The effects of concurrent cannabis use among ecstasy users: Neuroprotective or neurotoxic?

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Running head: concurrent cannabis use among ecstasy users.

Keywords: ecstasy, cannabis, cognitive functioning

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Abstract

The research evidence regarding the potential effects of ecstasy suggests that it may be neurotoxic and that its use is associated with cognitive impairment. In recent years evidence has emerged suggesting that cannabinoids, the active ingredients in cannabis, can be neuroprotective under certain conditions. Given that many ecstasy users also consume cannabis at the same time, the possibility emerges that these individuals might be less susceptible to ecstasy-related impairment. The present paper reanalyses the data from a number of previous studies, contrasting the performance of those individuals who generally consume cannabis and ecstasy at the same time with those who generally consume ecstasy on its own. The two ecstasy-using groups are compared with non-ecstasy users on a range of measures including processing speed, random letter generation, verbal and visuo-spatial working memory span, reasoning and associative learning. The two ecstasy user groups did not differ significantly from each other on any of the measures. Both user groups were significantly worse than non-ecstasy users on measures of associative learning, verbal and visuo-spatial working memory, and reasoning. The results suggest that consuming cannabis at the same time as ecstasy does not reduce the likelihood of cognitive impairment.

There is abundant evidence that ecstasy (MDMA) is neurotoxic, disrupting serotonergic systems in diverse brain regions. There is also a considerable body of evidence that cannabis can have neuroprotective as well as neurotoxic properties. Given that most ecstasy users are also cannabis users (Morgan, 2000) the question arises as to whether concurrent use of cannabis by ecstasy users might make them less susceptible to MDMA related neurotoxicity. The present paper is intended to investigate this issue.

Although there is abundant evidence that MDMA is neurotoxic in a range of animal species, evidence of neurotoxicity in humans is less extensive and sometimes controversial (Curran, 2000). A review of the neuroimaging evidence can be found in Reneman et al (2006). A number of studies have found evidence of neurotoxicity among ecstasy users. For example, using PET neuroimaging, McCann, et al (1998), investigated 5-HT neural damage in the brains of ecstasy users. Regions of interest included the frontal cortex, pariental cortex, temporal cortex, occipital cortex and cingulate cortex, as well as the caudate, putamen, thalamus, mid-brain, pons, hypothalamus and cerebellum. The results showed that, compared to a control group, ecstasy users had significantly lower densities of 5HT transporter sites in all brain regions. Further, the reductions observed were correlated with the extent of ecstasy use.

Reneman, et al (2002a) also assessed neural injury in ecstasy users using single-voxel (^{1}H) MR spectroscopy imagining. N-Acetylasportate (NAA)/Creatine (CR), NAA Choline (CHO), and Myoinositol (MI) CR ratios in ecstasy users were measured in grey matter in the frontal and occipital cortex and in white matter in the parietal cortex. The reason for focusing on NAA was that it is contained, almost

entirely, within neuron cell bodies as well as axons and that it serves as a marker for neuronal loss or dysfunction. Thus the objective of the study was to evaluate whether ecstasy leads to alterations in metabolite ratios in NAA\Cr and NAA\Cho. The results revealed that ecstasy users exhibited a reduction in NAA/Cr and NAA/Cho ratios in the frontal cortex compared with a control group. No significant differences between groups were found in the occipital and parietal cortex. Furthermore, a significant correlation was obtained between the extent of ecstasy use and NAA/Cr and NAA/Cho ratios in the frontal cortex.

While most research evidence tends to concentrate on pre-synaptic 5-HT neurons, Reneman, et al (2002b) investigated post-synaptic 5-HT_{2a} receptor densities in the cerebral cortex of human ecstasy users using single photon emission computed tomography (SPECT). Current ecstasy users had significantly lower binding ratios when compared to previous ecstasy users and nonusers in all brain regions studied (frontal, parietal, and occipital cortex). Previous users showed significantly higher binding ratios in the occipital cortex when compared with nonusers. This raises the possibility that there may be a compensatory up-regulation of post-synaptic 5-HT_{2a} receptors due to low synaptic 5-HT levels in the occipital cortex of previous ecstasy users.

In light of the findings reported above, it appears that ecstasy does have the potential to cause neurological toxicity to the serotonergic system in humans. This in turn appears to adversely affect cognitive functioning in users of this drug (Morgan, 2000). The question emerges as to whether those ecstasy users who use cannabis concurrently with ecstasy are at reduced risk of harm and are less susceptible to cognitive deficits. While there has been abundant evidence that cannabis may

adversely affect cognitive functioning, in recent years it has emerged that cannabis may possess neuroprotective properties.

Cannabinoids, the active ingredients in cannabis (marijuana), have been found to be primarily neurosuppressive, reducing neuronal activity by inhibiting voltage dependent calcium channels and modulating potassium channels. Chronic use of cannabis has been shown to suppress motor activity, reduce body temperature and impair cognitive processes (Sarne & Keren, 2004). With regard to the last of these cannabis use has been shown to adversely affect the maintenance of attention, short term memory and executive functions (Hall & Solowij, 1998; Pope & Yurgelun-Todd, 1996; Pope et al 2001). Animal studies have revealed that chronic administration of the cannabinoid THC causes hippocampal damage and impairs maze learning in rats (Fehr et al, 1976; Lawston et al 2000).

However, the anti-inflammatory and anti-oxidative properties of cannabinoids have also raised the possibility that they may have beneficial effects in limiting neurological damage (Carter et al 2004; Grundy, 2002). For example, the inhibitory effects of cannabinoids on the excitotoxic neurotransmitter glutamate (Drysdale & Platt, 2003) and their capacity to counter the oxidative damage to dopaminergic neurones has raised the possibility that they may be of value in the treatment of Parkinson's disease (Croxford, 2003). In terms of their effects on cell survival, human and animal studies have revealed that cannabinoids can be either neurotoxic or neuroprotective (Guzman et al 2001). With regard to their neuroprotective properties, studies have revealed that hippocampal neurones were protected from synaptically mediated excitotoxity by cannabinoid agonists acting through CB1 receptors. Furthermore as noted above, through the inhibition of voltage dependent calcium channels, cannabinoid agonists have been shown to protect cortical neurones from

glutamatergic exitotoxity (Sarne & Keren, 2004). More generally various cannabinoids have been found to prevent neuronal cell death in experimental forms of acute neuronal injury such as cerebral ischaemia and traumatic brain injury (Grundy 2002). Indeed it has been proposed that the endogenous cannabinoid system may serve a neuroprotective function in the brain (Sarne & Keren, 2004).

Contrasting with these findings cannabinoids have been shown to have stimulatory properties inducing increased motor activity, elevated body temperature, and aggressive tendencies (Sarne et al, 2005). Whether cannabinoids produce stimulatory or inhibitory effects may depend on their concentration, the timing of delivery and the cell type (Guzman et al 2001). Sarne and co-workers note that while regular (high) concentrations of cannabinoids induced conventional (inhibitory) effects, low concentrations induced stimulatory effects (Sarne et al 2005; Sarne & Keren 2004).

At the neuronal level low doses of cannabinoids can elevate intracellular calcium levels and increase transmitter release(Sarne & Keren, 2004). Doble and co-workers note that intracellular calcium plays a key role in mediating neuronal cell death (Doble, 1999; Hubert & Doble, 1998). In turn these elevated levels of calcium are associated with the stimulation of numerous enzymes and the production of free radicals that attack DNA, mitochondria and the cell membrane (Sarne & Keren, 2004). Increased intracellular calcium also stimulates the release of glutamate and the activation of postsynaptic NMDA receptors, which in turn facilitates the entry of calcium into neighbouring cells thereby spreading the damage (Doble, 1999).

By way of contrast at higher doses cannabinoids appear to produce beneficial effects reducing intracellular calcium levels and the release of glutamate thereby acting as a neuroprotective agent. This beneficial effect might also be facilitated

through the action of cannibinoids on other calcium dependent mechanisms for example inhibiting NO synthesis and attenuating the release of pro-inflammatory agents (Sarne & Keren, 2004).

Exposure to low concentrations of cannabinoids over a prolonged period of time is likely to result in neurotoxic effects (Rubovitch et al 2004; Sarne & Keren, 2004; Sarne et al 2005) while an acute administration at high concentrations at the time of trauma may be neuroprotective. For at least a week following the ingestion of cannabis, THC and its metabolites are stored in small quantities in body fat, leaking out into the circulatory system. Thus regular cannabis users may have continuous exposure to low concentrations of cannabinoids giving rise to neurotoxic effects.

The implications of these dual effects for ecstasy/cannabis users are potentially complex. Sarne and Keren (2004) have shown that the level of THC immediately following cannabis ingestion is sufficient to produce neuroprotective effects and thus might serve to counter the neuronal damage associated with administration of MDMA. On the other hand, as THC concentrations decline in the week following cannabis administration, cannabis-related neurotoxic effects might emerge.

At a more indirect level, it is well documented that the neurotoxic effects of MDMA are exacerbated by increases in core body temperature (Malberg et al, 1996) and ambient temperature (Malberg and Seiden, 1998) such that temperature is an important factor in determining the extent of serotonin neurotoxicity. As cannabis (more specifically CB1 cannabinoid receptors) is known to decrease core body temperature (e.g. Azad et al, 2001; Rawls et al, 2002), then it is possible that the neurotoxic potential of MDMA is further attenuated in ecstasy/cannabis users. According to Sarne and co-workers whether this temperature reduction occurs may be

dose dependent with small infrequent doses of cannabinoids resulting in elevated body temperature and larger doses having the opposite effect (Sarne & Keren, 2004; Sarne et al 2005).

Individuals who usually consume ecstasy on its own would not benefit from the neuroprotective effects of cannabis and would therefore be more likely to sustain MDMA related neuronal damage. On the other hand they would not be susceptible to the neurotoxic effects of cannabis. In reality most ecstasy user also consume cannabis, if not at the same time as ecstasy then at other times. Thus what potentially distinguishes the two groups is susceptibility to MDMA related damage. Relative to individuals who use ecstasy on its own, it might be reasonable to expect that combined ecstasy/cannabis users would be less susceptible to neurotoxic damage and therefore less likely to exhibit cognitive deficits.

Previous research from our laboratory has revealed a range of cognitive deficits in ecstasy users (e.g., Fisk et al 2005; Montgomery et al 2005b; Wareing et al. 2005). However, we have not previously discriminated between individuals who consume ecstasy on its own and those who routinely take the drug with cannabis. Fortuitously, since our research commenced, we have asked ecstasy users to indicate whether they typically take ecstasy on its own or with other drugs. Thus it is possible for us to divide the ecstasy user group between those who seldom used cannabis at the same time as ecstasy and those who frequently used cannabis at the same time. Thus we have reanalysed the existing data collected by our laboratory comparing the performance of these two groups with each other and with a non-ecstasy user control group. Assuming that cannabis may exhibit neuroprotective properties when taken with ecstasy, it is expected that those users who generally do not consume cannabis at

the same time as taking ecstasy will show more evidence of impairment relative to those who consume ecstasy and cannabis together.

METHOD

Participants.

Participants were recruited through direct approach to university students at Edge Hill College of Higher Education and Liverpool John Moores University. Following this, additional participants were forthcoming via the "snowball technique" (Solowij et al, 1992). Sample sizes for each analysis may be found in Table 1. In all cases it is apparent that females predominate in the nonuser group, accounting for approximately two-thirds of the sample in each case, while in the two user groups the gender split is more equal. With regard to information processing speed, the data were originally collected by Wareing (2005); the random letter generation data were originally collected by Wareing et al (2002) and Fisk et al (2004); the reading span. data by Wareing et al (2004); the computation span data by Wareing et al (2004), Fisk et al (2004), and Montgomery et al (2005b); the spatial working memory data by Wareing et al (2005); the associative learning data from Montgomery et al (2005a); and the syllogistic reasoning data from Montgomery et al (2005c) and Fisk et al (2005).

<insert Table 1 about here>

Materials.

Information Processing Speed. Two measures of processing speed were obtained following the procedure devised by Fisk and Warr (1996). The first involved a letter comparison speed task in which participants were presented with two rows of letters on a computer screen. They were asked to classify these as quickly as possible

by pressing the "/" key if the two rows were the same, and the "z" key if they were different. The two rows of letters were identical in half of the trials but differed (by one letter only) in the other half. In each trial, the letters were randomly chosen from the set of consonants and the position of the non-identical letter within the string was randomised. For the first 30 seconds, each presented row consisted of three letters, for the next 30 seconds each row contained six letters, and for the third 30 seconds each row consisted of nine letters. For each level of complexity (three, six, or nine letters), the computer kept a record of the number of correct responses. This task was repeated three times.

The pattern comparison speed task was structured in exactly the same way as the letter comparison task. However, the stimulus was a matrix potentially consisting of a basic grid of nine cells (three across and three down). Line segments defined the borders of each cell and the targets were made up of three, six, or nine such line segments randomly selected from the basic grid. Two patterns were displayed, one in the top and one in the bottom half of the screen. As in the letter task, the objective was to classify as many pairs as "the same" or "different" within a fixed time period. For the first 30 seconds, patterns consisted of three line segments, for the next 30 seconds they comprised six line segments, and for the third 30 seconds they were made up of nine line segments.

Reading Span involved two elements, firstly participants were required to process a sentence by answering a simple multiple choice comprehension question; and secondly they were asked to recall the final word of that sentence. As the task proceeded, the number of sentences that had to be processed, while recalling the last word of each, gradually increased. Once all of the sentences in a given set had been processed, the participant was asked to recall all of the final words in the order in

which they occurred. The task commenced with three trials containing just a single sentence, this was followed by three trials with two sentences presented consecutively, and then three trials with three consecutive sentences, and so on. Span was defined as the maximum number of end words successfully recalled in serial order. This level had to be achieved in at least two of the three relevant trials and the corresponding multiple-choice questions had to be answered correctly.

Computation Span. This task is analogous to reading span, but uses arithmetic processing rather than sentence comprehension. With the computation span task simple arithmetic problems were presented, for example, 7+3 = ?, and the individual attempted to solve the problem while recalling the second digit of each presented problem. As with the reading span task, computation span commenced with three trials with one arithmetic problem and increased by one problem to two, three etc. Span was defined in a similar manner to reading span.

Spatial Working Memory Task. This task was developed by Fisk (2004) and is similar to Miyake et al's (2001) spatial working memory measure. Participants were presented with a four-by-four matrix containing five highlighted cells on a computer monitor for three seconds. The task commenced with three trials with one matrix being displayed. On the next three trials two matrices were presented sequentially, and the number increased by one matrix at a time up to a maximum of six. In each matrix, one of the highlighted cells was filled with 00000's and the participant had to remember the position of that cell while at the same time indicating (by pointing) whether the number of cells highlighted was greater at the top of the matrix or at the bottom. After all of the matrices in a particular set had been presented, the participant was required to indicate, on a blank grid, the position of the '00000' marked cells in the order in which they had occurred. The task generated a span score

corresponding to the maximum number of '00000' marked cells recalled in the order presented. This level had to be achieved in at least two out of the three trials at a given level. The task is analogous to global working memory measures such as computation span and reading span in that it requires the concurrent processing and storage of information. However, it is not reliant on the phonological aspect of working memory.

Associative Learning. This was assessed via a verbal paired-associates task. Participants were presented sequentially with the same eight word pairs (see Montgomery et al 2005a) on a computer screen. For example,

DOOR	CASE
YEAR	PAGE

After each presentation, the participant was prompted with the first member of each pair and required to recall the second member. Eight such trials were administered. The order of presentation was randomised and changed for each trial. Measures included the number of correct responses in trial 1 (a measure of initial learning), forgetting, the number of trials required to learn all associations, and the number of perseverative errors (giving the same incorrect answer in consecutive trials).

Random letter generation task. Participants were asked to speak aloud a letter each time they heard an auditory signal. They were asked to avoid generating alphabetical sequences and repeat sequences such as AB or BBC. They were also asked to try and produce each letter with the same overall frequency. Each participant produced three sets of 100 letters, at the rate of one per second, one every two seconds and one every four seconds. The order in which the sets were produced was randomised for each participant. The experimenter recorded participants' responses.

This task yields four separate measures for each generation rate. These are the total number of letters produced, the number of alphabetically ordered pairs, the number of times that any given letter pair is repeated, and redundancy, which is a measure of the extent to which each letter of the alphabet is produced equally often. Sequences containing relatively few letters that are repeated often, produce high redundancy. For each of these measures, the scores were standardised and averaged over the three generation rates thereby producing mean standardised scores for alphabetical sequences, repeat sequences, redundancy, and the total number of letters generated. For the first three of these a high score is associated with poor performance, for total number of letters a high score is indicative of efficient performance.

Syllogistic reasoning. Syllogistic reasoning requires a participant to draw valid inferences from a set of premises. For Example,

Given that:	Some A are B,
	and
	No B are C
It follows that:	Some A are not C.

Johnson-Laird (1983) maintains that reasoning involves constructing mental models of the premises and testing conclusions against these models. Constructing a single model may solve some problems, others may require up to three models. The more complex the problem, the greater number of models required and the greater is the load on working memory and executive resources. The syllogisms were presented in abstract form as in the example set out above. Participants attempted to generate solutions for four one-model syllogisms, four three-model syllogisms, and four syllogisms for which there was no valid conclusion (NVC). The syllogisms were the

same as those used by Fisk and Sharp (2002). Scores were based on the number of correct solutions, or in the case of the NVC syllogisms, a response was deemed correct when the participant indicated that no valid conclusions were possible. According to Johnson-Laird (1983), NVC syllogisms require either two or three mental models in order to derive the correct solution. In the present study, two of the NVC syllogisms were two-model and two were three-model. Therefore, in terms of the number of models required, three-model and NVC syllogisms were the hardest, and one-model the easiest. The syllogisms used in the study were presented in random order. The test was administered following the procedure outlined by Fisk and Sharp (2002).

Procedure.

The procedures varied across the different studies and details may be found in the original papers. All studies were conducted in accordance with the ethical guidelines of the British Psychological Society. Approval was obtained from the Ethics Committee of Liverpool John Moores University. With regard to distinguishing between the ecstasy/cannabis group and the 'ecstasy-only' group, in all studies ecstasy users were asked to indicate which drugs they used at the same time as using ecstasy and further to indicate the frequency of concurrent use on a four point scale: never, occasionally, frequently, always. Thus it was possible to identify those ecstasy users who said that they never or occasionally used cannabis when using ecstasy. These are described below as 'ecstasy-only' users. We were also able to identify those ecstasy users who indicated that they frequently or always used cannabis when using ecstasy. These are described as ecstasy/cannabis users. Clearly most of the former group, the 'ecstasy-only' users, do in fact consume cannabis but this is generally not at the same time as using ecstasy.

Design

Information processing speed. A mixed design was employed with type of task (letters versus patterns), trial (with three levels) and stimulus complexity (low, medium and high) within participants and group (nonusers, 'ecstasy-only' users, ecstasy/cannabis users) between participants. Dependent variables were the number of correct responses and the number of errors.

Random letter generation. A between participant design was employed with group (nonusers, 'ecstasy-only' users, ecstasy/cannabis users) between participants. Dependent variables were the number of alphabetical and repeat sequences, redundancy and the number of letters produced.

Reading span, computation span, and spatial working memory. In each case, a between participant design was employed with group (nonusers, 'ecstasy only' users, ecstasy/cannabis users) between participants. The dependent variables were the respective span scores.

Associative learning. A between participant design was employed with group (nonusers, 'ecstasy only' users, ecstasy/cannabis users) between participants. The dependent variables were trials to completion, the number of correct responses on trial one, total number of previously learned responses subsequently forgotten, and the number of perseverative errors.

Syllogistic reasoning. A mixed design was used with level of difficulty (easy and hard) within participants and group (nonusers, 'ecstasy-only' users, ecstasy/cannabis users) between participants.

Post-hoc Tests. In all cases, with regard to group differences, pairwise comparisons were made using Tukey's HSD test.

RESULTS

Background Variables.

Life time ecstasy dose. Inspection of Table 2 reveals that ecstasy/cannabis users generally had a higher lifetime dose compared with the ecstasy/non cannabis users. The difference was statistically significant for the processing speed sample, $t(50.15) = 2.08$, $p<.05$ but not for any of the other samples[1].

<insert Table 2 about here>

Age. For the samples completing the processing speed, random generation and learning tasks there were no significant age differences, $F < 1$; $F(2,133) = 2.20$; and $F(2,92) = 1.36$ respectively, $p>.05$ in all cases. Significant differences or differences approaching significance were obtained for the samples completing the reading, computation, spatial working memory span and syllogistic reasoning tasks; $F(2,94) = 3.64$; $F(2,186) = 3.22$; $F(2,76) = 2.90$, $p = .061$; and $F(2,100) = 5.44$ respectively; $p<.05$ unless otherwise noted. In each of these analyses, only one pairwise comparison was statistically significant at $p<.05$: in all cases the ecstasy/cannabis users were significantly younger than 'ecstasy-only' users.

Years of Education. Years of full time education differed significantly for the processing speed sample, $F(2,121) = 6.80$, $p<.01$. Pairwise comparisons revealed that ecstasy/cannabis users had significantly fewer years of education compared to the other groups, $p<.01$ in both cases. Significant differences were also obtained for the samples completing the random generation, reading span and spatial working memory tasks, $F(2,132) = 4.24$, $p<.05$; $F(2,93) = 4.17$, $p<.05$.; and $F(2,76) = 3.42$, $p<.05$ respectively. In each of these three cases, only one of the pairwise comparisons was significant, ecstasy/cannabis users having significantly fewer years of education compared to nonusers, $p<.05$ in all cases. For those participants completing the

computation span task, although years of education differed significantly, $F(2,186) = 3.48$, $p<.05$, none of the pairwise comparisons were statistically significant, $p>.05$ in all cases. Furthermore, years of education did not differ significantly for those samples completing the learning and syllogistic reasoning tasks, $F< 1$ and $F(2,100) = 1.05$, $p>.05$ respectively.

Intelligence. For the samples completing the processing speed, random generation, reading, computation, and spatial working memory span tasks, intelligence was measured utilising Ravens progressive matrices, sets D and E only. Those participants completing the learning and syllogistic reasoning tasks, undertook the complete Ravens test (Sets A through to E) (Raven et al, 1998). In five of the seven samples no significant differences between the groups were obtained[2]. Among those completing the processing speed task, for Ravens Set E the overall effect was just short of significance, $F(2,117) = 2.89$, $p = .059$,. However, pairwise comparisons revealed that ecstasy/cannabis users scored significantly lower than 'ecstasy-only' users, $p<.05$. There was no significant group difference in relation to Set D, $F < 1$. For the sample completing the computation span task, again the overall group differences were non significant. $F = 3.04$, $p = .050$ for Set D, and $F = 3.01$, $p = .052$ for Set E, both with $df = 2, 182$. However, two of the pairwise comparisons were statistically significant. For Set D ecstasy/cannabis users scored significantly lower than nonusers, and for Set E ecstasy/cannabis users scored significantly lower than 'ecstasy-only' users, $p< .05$ in both cases.

Main Results

The number of errors on the processing speed task yielded a significant group effect, $F(2,122) = 3.83$, $p<.05$. The ecstasy/cannabis group made more errors

compared to the 'ecstasy-only' group and compared to nonusers (Table 3). Of the pairwise comparisons, only the nonuser versus ecstasy/cannabis user difference was significant, $p<.05$. None of the interactions containing user group were statistically significant, $F<1.65$ in all cases.

<insert Table 3 about here>

In relation to the number of correct responses on the processing speed task there was a significant interaction between user group and type of task, $F(2,122) = 4.01$, $p<.05$. Compared to the other two groups, ecstasy/cannabis users were generally faster when processing patterns but slower when processing the letter stimuli. With this exception, neither the main effect of user group nor any of the interactions containing this variable were statistically significant, $F<1.08$ in all cases.

No group differences were observed on three of the random generation measures, specifically for alphabetic sequences and redundancy, $F < 1$ in both cases and for repeat sequences, $F(2,133) = 1.93$, $p>.05$. There was a significant group difference in the number of letters generated, $F(2,133) = 5.88$, $p<.01$. Inspection of Table 3 reveals that ecstasy/cannabis users produced significantly fewer letters compared to nonusers, $p<.01$. None of the other pairwise comparisons were significant.

Although both user groups had lower reading span scores compared to nonusers, the difference was not statistically significant, $F(2,94) = 1.07$, $p > .05$. However, on the computation span measure there was a significant overall group difference, $F(2,186) = 14.77$, $p<.001$. Pairwise comparisons revealed that ecstasy/cannabis scored significantly lower than non users, $p<.001$ as did 'ecstasy-only' users, $p<.05$. The two user groups did not differ significantly from each other. With regard to spatial working memory, a significant overall group difference

emerged, $F(2,76) = 8.86$, $p<.001$. Pairwise comparisons revealed that both user groups achieved significantly lower scores compared to nonusers, $p<.05$ for 'ecstasy-only' users, and $p<.001$ for ecstasy/cannabis users. As with the computation span measure, the two user groups did not differ significantly from each other.

All of the learning measures yielded significant overall group differences. For initial learning, perseverative responses, total forgetting, and trials to completion, F values were respectively, 6.90, $p<.01$; 5.23, $p< 01$; 4.77, $p<.05$; and 10.92, $p<.001$. Pairwise comparisons revealed that for initial learning, ecstasy/cannabis users scored significantly lower than non users, $p<.05$. For perseverative responses, 'ecstasy-only' users did significantly worse than nonusers, $p<.01$. In relation to forgetting ecstasy/cannabis users forgot more previously learned responses compared to nonusers, $p<.05$. With regard to trials to completion, both users groups did worse than nonusers, $p<.01$ in both cases. None of the other pairwise comparisons were statistically significant and the two users groups did not differ significantly on any of the learning measures.

In relation to performance on the syllogistic reasoning task, mixed ANOVA with group between participants and problem difficulty (with two levels easy and difficult) within participants yielded a significant interaction, $F(2,100) = 3.40$, $p<.05$. Users performed worse than nonusers on the easy problems while on the more difficult problems all participants performed at little better than chance. Subsequent one-way ANOVAs revealed that the overall group difference was significant for the easy problems, $F(2,100) = 9.90$, $p<.001$ with ecstasy/cannabis users performing worse than nonusers, $p<.01$ and ecstasy-only users also performing worse than nonusers, $p<.001$. The two user groups did not differ significantly from each other. On the more difficult problems there was no significant group difference, $F < 1$.

Use of other drugs.

Inspection of Table 4 reveals that there was occasional use of cocaine and amphetamine by both ecstasy user groups. Non ecstasy users had used neither of these two drugs during the three months prior to testing. It is also worthy of note that ecstasy/cannabis users consumed cannabis more frequently during the previous three months than either of the other two groups. Cannabis use among non-ecstasy users was infrequent with the majority of non-ecstasy users not using cannabis during the three months prior to testing. In terms of the median responses, all groups indicated that there use of alcohol during the previous three months was frequent or very frequent.

<insert Table 4 about here>

DISCUSSION

It had been predicted that 'ecstasy-only' users would perform worse on all of the measures. However, in terms of the means, it was ecstasy/cannabis users who were most impaired on the majority of measures. Tukey's post hoc comparisons failed to reveal any significant differences between the two ecstasy user groups on any of the measures. Relative to non-ecstasy users, ecstasy/cannabis users were significantly impaired on processing speed errors, the number of letters produced in the random generation task, computation span, and spatial working memory. Ecstasy/cannabis users also performed significantly worse on the associative learning measures. Compared to non-ecstasy users, they exhibited poorer initial learning, forgot more previously learned responses, and required more trials to learn the paired associates. With regard to the syllogistic reasoning measure, ecstasy/cannabis users registered significantly fewer correct responses compared to non-ecstasy users.

Switching the focus to the 'ecstasy-only' users, Tukey's post hoc analyses revealed that they were significantly worse than non-ecstasy users on the computation span and spatial working memory measures. They also made significantly more perseverative responses and required more trials to learn the paired associates. In addition, they achieved significantly fewer correct responses on the one-model syllogistic reasoning problems compared to non-ecstasy users.

It is worthy of note that for the analyses reported above, for the most part, the 'ecstasy-only' group had consumed fewer ecstasy tablets in total compared to the ecstasy/cannabis group. This might have resulted in any beneficial effects of concurrent cannabis consumption being outweighed by the greater exposure to ecstasy. However, only in one case was the difference statistically significant. In other instances the difference was well short of statistical significance. Also noteworthy was the fact that in all of the analyses reported above, the ecstasy/cannabis group consumed cannabis more frequently than the 'ecstasy-only' group. While some difference might have been expected (given the manner in which the two groups are defined), the discrepancy is nonetheless considerable. While in most cases 'ecstasy-only' users reported that they used cannabis 'occasionally', ecstasy/cannabis users indicated that their frequency of use was 'frequently' or 'always'. Thus it is possible that concurrent cannabis use does provide protection from the effects of MDMA, but that the higher incidence of cannabis use among ecstasy/cannabis users produces neurotoxic effects, which cancel out the benefits from reduced MDMA-related neurotoxicity.

However, while this possibility cannot be ignored, an alternative argument can be posed. Sarne and Keren (2004) have argued that cannabis is likely to produce neurotoxic effects when individuals are exposed to small concentrations over

prolonged periods. Higher concentrations are associated with neuroprotective properties. Recent studies from our own laboratory have revealed that ecstasy users consume cannabis three times a week on average (e.g., Montgomery et al 2005b). Thus it seems probable that concentrations of THC are unlikely to decline to a level that has been associated with neurotoxicity. On the other hand ecstasy-only users, with their infrequent pattern of use, are likely to experience low concentrations that may give rise to neurotoxic effects. It is perhaps unrealistic and paradoxical to assume that frequent use of cannabis may actually have less potential for neurotoxicty than occasional use but what does seem reasonable is that both frequent and occasional cannabis users may be subject to cannabis-related neurotoxicity.

With regard to future research it might be desirable to balance cannabis consumption between the two ecstasy users groups by restricting the sample. However, the results of the present study suggest that at least among the population of ecstasy users sampled here, those individuals who do usually take cannabis concurrently with ecstasy also tend to consume cannabis more frequently compared with 'ecstasy-only' users. Thus even if future research were to demonstrate that cannabis was neuroprotective in some restricted sample of ecstasy users, this finding would be of limited practical importance if it proves to be the case that the present sample is more represenative of the typical ecstasy user.

The present study is not the first to examine whether cannabis used in conjunction with another illicit drug might have neuroprotective properties. Gonzalez et al (2004) found that a combined methamphetamine-cannabis using group showed less impairment than methamphetamine-only users on a range of cognitive measures. Although the differences between the two groups were nonsignificant, the methamphetamine only users scored significantly worse than a control drug naïve

group while the combined methemphetamine-cannabis users did not differ significantly from controls. While Gonzalez et al concede that their results do not imply that cannabis is neuroprotective, they note that cannabis did not exacerbate the methamphetamine related deficits. In the present study again there is little evidence to suggest that cannabis is neuroprotective and while concurrent cannabis use did not significantly exacerbate the ecstasy-related deficit it is noteworthy that ecstasy/cannabis users generally performed worse than 'ecstasy-only' users.

A number of limitations were evident in the present paper, for example, we were reliant on individuals being willing and able to provide an accurate account of their previous drug use. Indeed in defining the two ecstasy user groups, we needed users to specify the typical context in which they had taken ecstasy and our classification is limited by the veracity and consistency of these judgements. Furthermore, because of limited resources, we were unable to use urine, saliva, or hair samples to confirm recent patterns of drug use. However, by way of mitigation, it is noteworthy that most of the published studies that have probed cognitive deficits among ecstasy users have not resorted to urine, hair, or saliva testing (e.g., Fox et al, 2002; Morgan, 1998; Morgan, 1999; Parrott & Lasky, 1998; Rodgers, 2000). The importance of not over generalising from the present findings must also be stressed. For example, given that word of mouth referral was used as the primary means of recruiting participants, our ecstasy-user groups may not be entirely representative of all ecstasy users, especially those who consume the drug in settings that are unlike those frequented by those individuals included in the present paper. It is also important to note that a number of participants contributed data to more than one study so the participant details set out in Table 1 mask a certain degree of overlap in the different samples. Inspection of Table 1 also reveals that in some cases the sample

sizes within particular cells were limited thereby reducing statistical power in some of the analyses.

Finally, it must be acknowledged that the present paper is the product of an opportunistic exercise involving reanalysing existing data reported elsewhere and combining the results of a number of different studies. Clearly the present findings need to be replicated in an appropriately designed study in which new participants are recruited in a carefully balanced manner so that the effects of potentially confounding variables are minimised.

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Table 1 Sample Sizes for each of the Analyses

	Nonuser		Ecstasy 'Only' User		Ecstasy/Cannabis User	
	Total	Males	Total	Males	Total	Males
Processing Speed	71	23	20	10	34	17
Random Generation	58	20	25	13	53	32
Reading Span	34	12	17	9	46	24
Computation Span	95	30	34	17	60	33
Spatial Working Memory	31	12	17	8	31	16
Associative Learning	62	18	16	8	16	10
Syllogistic Reasoning	52	16	22	10	29	18

Table 2

Background Variables for each of the Analyses

	Nonuser		Ecstasy 'Only' User		Ecstasy/Cannabis User	
	Mean	SD	Mean	SD	Mean	SD
Processing Speed:						
Ecstasy, total number of tablets consumed	-	-	292.20	268.61	516.80	515.23*
Age	22.45	4.54	23.15	4.l1	21.82	2.35
Years of Education	15.66	1.94	16.35	1.76	14.38	2.46**
Ravens Set D (maximum 12)	9.74	1.65	9.50	1.54	9.38	2.12
Ravens Set E (maximum 12)	6.03	2.94	7.50	2.80	5.44	3.39
Random Generation (standardised scores)						
Ecstasy, total number of tablets consumed	-	-	405.08	446.63	525.27	622.76
Age	22.47	4.98	24.24	5.12	22.06	3.08
Years of Education	15.73	1.89	15.64	2.33	14.58	2.43*
Ravens Set D (maximum 12)	9.85	1.44	8.96	1.77	9.12	2.33
Ravens Set E (maximum 12)	5.84	2.96	6.72	2.94	5.43	3.42
Reading Span						
Ecstasy, total number of tablets consumed	-	-	471.25	508.48	497.74	639.95
Age	23.21	6.23	25.41	5.82	21.85	2.38*
Years of Education	15.62	1.84	15.41	2.76	14.08	2.81*
Ravens Set D (maximum 12)	9.71	1.72	8.53	1.91	8.95	2.17
Ravens Set E (maximum 12)	6.10	2.99	5.94	2.90	5.17	3.33
Computation Span						
Ecstasy, total number of tablets consumed	-	-	355.09	393.99	480.50	590.97
Age	21.98	4.06	23.68	4.59	21.77	2.16*
Years of Education	15.47	2.03	15.71	2.59	14.63	2.36*
Ravens Set D (maximum 12)	9.84	1.63	9.32	1.72	9.11	2.23
Ravens Set E (maximum 12)	6.13	2.84	7.18	2.67	5.61	3.25

Spatial Working Memory						
Ecstasy, total number of tablets consumed	-	-	471.25	508.48	597.26	728.46
Age	23.39	6.47	25.41	5.82	21.77	2.09
Years of Education	15.66	1.88	15.41	2.76	14.05	2.98*
Ravens Set D (maximum 12)	9.63	1.69	8.53	1.91	9.07	2.16
Ravens Set E (maximum 12)	6.03	3.02	5.94	2.90	5.40	3.33
Associative Learning						
Ecstasy, total number of tablets consumed	-	-	260.75	201.47	402.50	433.57
Age	21.30	1.79	22.06	1.77	21.19	1.56
Years of Education	15.37	2.12	16.00	2.53	15.44	1.15
Ravens Total (maximum 60)	48.13	5.27	50.81	3.78	48.63	5.10
Syllogistic Reasoning, Correct responses						
Ecstasy, total number of tablets consumed	-	-	336.86	439.13	336.43	339.12
Age	21.12	1.55	23.05	4.26	21.28	1.44**
Years of Education	15.54	1.99	15.50	2.77	14.76	2.84
Ravens Total (maximum 60)	47.94	5.55	47.27	6.69	47.83	6.20

Table 3

Performance Measures on each of the Tasks for Non Ecstasy Users, 'Ecstasy-Only' Users, and Ecstasy/Cannabis Users

	Nonuser		Ecstasy 'Only' User		Ecstasy/Cannabis User	
	Mean	SD	Mean	SD	Mean	SD
Processing Speed:						
Total Errors	1.05	0.72	1.15	0.73	1.51	1.00*
Correct Responses, Letters	17.60	3.27	17.01	3.12	16.65	2.45
Correct Responses, Patterns	15.81	3.45	15.43	2.64	16.30	2.79
Random Generation (standardised scores)						
Alphabetic Sequences	-0.01	0.75	-0.03	0.54	-0.04	0.93
Repeat Sequences	-0.04	0.51	-0.18	0.44	0.16	1.07
Redundancy	-0.04	0.69	-0.07	0.77	0.12	0.84
Number of Letters	0.18	0.44	0.09	0.42	-0.16	0.64**
Working Memory Span						
Reading Span	3.06	1.13	2.71	0.85	2.72	1.17
Computation Span	4.56	1.62	3.62	1.81	3.10	1.66***
Spatial Working Memory	4.16	1.19	3.06	1.30	2.87	1.34***
Associative Learning						
Initial Learning	4.32	2.01	3.69	2.18	2.25	1.77**
Perseverative Responses	0.16	0.66	0.94	1.57	0.38	0.50**
Total Forgotten	0.48	0.94	1.13	1.20	1.38	1.78*
Trials to Completion	4.32	1.46	5.94	1.81	6.00	2.00***
Syllogistic Reasoning, Correct responses						
One model (easy)	4.90	1.85	2.91	1.87	3.55	2.10***
Two/Three model (difficult)	1.75	1.61	1.32	2.01	1.34	1.88

*** p<.001; ** p<.01; * p<.05

Table 4

Median Use of Other Drugs Among each of the Samples

Study/Measure	Nonuser	Ecstasy 'Only' User	Ecstasy/Cannabis User
Processing Speed			
Alcohol	3	3	4
Amphetamine	1	1	1
Cannabis	1	2	4
Cocaine	1	1.5	1
Random Generation			
Alcohol	3	4	4
Amphetamine	1	1	1
Cannabis	1	2	4
Cocaine	1	2	2
Reading Span			
Alcohol	3	4	4
Amphetamine	1	1	1
Cannabis	1	2	4
Cocaine	1	1	1
Computation span			
Alcohol	3	4	4
Amphetamine	1	1	1
Cannabis	1	2	3.5
Cocaine	1	1	1.5
Spatial Working Memory			
Alcohol	3	4	4
Amphetamine	1	1	1
Cannabis	1	2	4
Cocaine	1	1	2
Associative Learning			
Alcohol	3	3.5	4
Amphetamine	1	1	1
Cannabis	1	2	3
Cocaine	1	1.5	2
Syllogistic Reasoning			
Alcohol	3	4	4
Amphetamine	1	1	1
Cannabis	1	2	3
Cocaine	1	1	2

1 = never; 2 = occasionally; 3 = frequently; 4 = always

[1] T values were 0.85, 0.15, -1.09, -0.62, -1.19, and 0.00 for random generation, reading, computation, and spatial working memory span, learning, and syllogistic reasoning respectively.

[2] For the sample completing the random generation task, F values were 2.80 and 1.40, for sets D and E respectively, df= 2, 126. For the reading span sample, $F(2,87) = 2.28$ and $F< 1$ for sets D and E respectively. For the spatial working memory sample, $F(2,74) = 1.83$ and $F< 1$ for sets D and E respectively. For the associative learning and syllogistic reasoning samples completing the total Ravens measure, $F(2,92) =1.82$ and $F < 1$ respectively. For all of these analyses, $p>.05$.