

Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study

Journal of Psychopharmacology
22(5) (2008) 498–510
© 2008 British Association
for Psychopharmacology
ISSN 0269-8811
SAGE Publications
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881107081545

S de Sola Llopis *Behavioral Neurology and Dementia Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

M Miguelez-Pan *Behavioral Neurology and Dementia Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

J Peña-Casanova *Behavioral Neurology and Dementia Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

S Poudevida *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

M Farré *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona (UDIMAS), Barcelona, Spain.*

R Pacifici *Drug Control and Evaluation Department, Istituto Superiore di Sanità, Rome, Italy.*

P Böhm *Behavioral Neurology and Dementia Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

S Abanades *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, and Universitat Autònoma de Barcelona (UDIMAS), Barcelona, Spain.*

A Verdejo García *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, Barcelona, Spain.*

K Langohr *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, and Universitat Politècnica de Catalunya (UPC), Barcelona, Spain.*

P Zuccaro *Drug Control and Evaluation Department, Istituto Superiore di Sanità, Rome, Italy.*

R de la Torre *Human Pharmacology and Clinical Neurosciences Research Group, Neuropsychopharmacology Program, IMIM-Hospital del Mar, and Universitat Pompeu Fabra (CEXS-UPF), Barcelona, Spain.*

Abstract

There is important preclinical evidence of long lasting neurotoxic and selective effects of ecstasy MDMA on serotonin systems in non-human primates. In humans long-term recreational use of ecstasy has been mainly associated with learning and memory impairments. The aim of the present study was to investigate the neuropsychological profile associated with ecstasy use within recreational polydrug users, and describe the cognitive changes related to maintained or variable ecstasy use along a two years period. We administered cognitive measures of attention, executive functions, memory and learning to three groups of participants: 37 current polydrug users with regular consumption of ecstasy and cannabis, 23 current cannabis users and 34 non-users free of illicit drugs. Four cognitive assessments were conducted during two years. At baseline, ecstasy polydrug users showed significantly poorer performance than cannabis users and non-drug using controls in a

measure of semantic word fluency. When ecstasy users were classified according to lifetime use of ecstasy, the more severe users (more than 100 tablets) showed additional deficits on episodic memory. After two years ecstasy users showed persistent deficits on verbal fluency, working memory and processing speed. These findings should be interpreted with caution, since the possibility of premorbid group differences cannot be entirely excluded. Our findings support that ecstasy use, or ecstasy/cannabis synergic effects, are responsible for the sub-clinical deficits observed in ecstasy polydrug users, and provides additional evidence for long-term cognitive impairment owing to ecstasy consumption in the context of polydrug use.

Keywords

cognitive impairment, cannabis, ecstasy, MDMA

Introduction

MDMA (3,4-methylenedioxymethamphetamine) or ecstasy is a ring-substituted amphetamine and currently one of the most popular recreational synthetic drugs in Europe and the USA (Parrott, 2001). The word 'ecstasy' rather than MDMA has been adopted throughout the manuscript when referring both to acute and long lasting effects, as the latter term implies the administration of a pharmaceutically pure drug when in fact subjects are consuming street ecstasy that may or may not contain any MDMA. Ecstasy has a distinct pharmacological profile from classical hallucinogens and stimulants that led some researchers to propose ecstasy as a probe of a new drug class: entactogens. These drugs have specifically the ability to induce empathy (Morgan, 2000). Acute psychological positive effects induced by ecstasy include euphoria, feelings of intimacy, heightened arousal, self-confidence, increased sensory sensitivity and openness to new ideas (Cami, 2000). Onset of rebound effects appears within 24–48h after ingestion and includes fatigue, anhedonia, irritability, low mood, rebound midweek depression, concentration and memory difficulties (Morgan, 2000). In comparison to other illicit drugs, ecstasy shows few indications of physical dependence or drug craving (Parrott, 2001).

There is preclinical evidence of the neurotoxic and selective effects induced by ecstasy on serotonin systems in a great variety of mammalian species (Green *et al.*, 2003). These consist in a long-lasting degeneration of serotonergic axons, and decreases in brain 5-HT and 5-HIAA concentrations in several regions of the forebrain, including neocortex, hippocampus, caudate nucleus, putamen and thalamic nuclei. Because there is empirical evidence for neural damage after high and repeated dosing in animals (Ricaurte *et al.*, 2000), there is concern that the cumulative doses ingested by moderate recreational users over a long period of time could induce similar neurotoxic effects. Accordingly, initial studies in humans have demonstrated that ecstasy use is associated with selective decrements in 5-HIAA concentration (Bolla *et al.*, 1998) and serotonin transporters (SERT) availability (Buchert *et al.*, 2003; Reneman *et al.*, 2000; Semple *et al.*, 1999; Thomasius *et al.*, 2003) and with blunted neuroendocrine response to 5HT-agonist challenges (Verkes *et al.*, 2001). However, a recent study has shown that the reduced SERT can be restored in abstinence (Thomasius *et al.*, 2006) and more research is needed to set this issue.

The neurodegeneration of the serotonergic system may have subtle but important long-term effects on cognition and mood. In agreement with this notion, several studies have revealed residual neurocognitive deficits in recreational and long-term users of ecstasy. Available evidence indicates that long-term ecstasy use is mainly associated with deficits in memory and executive functions. On the one hand, several studies have detected a relatively selective profile of memory impairment (sparing other cognitive functions) in current and abstinent users of ecstasy (Bolla *et al.*, 1998; Morgan *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2000, 2003; Rodgers J 2000; Fox *et al.*, 2002; McCardle *et al.*, 2004; Medina *et al.*, 2005). Furthermore, most of these studies have shown dose-related cumulative effects of lifetime ecstasy exposure on memory performance. Therefore, it has been proposed that ecstasy use is associated with specific damage to the medial temporal lobes and the hippocampus

(Fox *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2003). On the other hand, a number of studies have pointed out specific effects of ecstasy use on executive functions. However, executive functions are not a unitary construct (Miyake *et al.*, 2000) and recent evidence indicates that ecstasy use can be associated with impairment of some executive processes, while others remain unaffected. Specifically, long-term users of ecstasy usually present prominent deficits in the processes of working memory (Verkes *et al.*, 2001; Fisk *et al.*, 2004; Wareing *et al.*, 2000, 2004a, 2004b; Montgomery *et al.*, 2005; Reay *et al.*, 2006), categorization and organization of mnemonic material (Fisk *et al.*, 2005; Quednow *et al.*, 2006a) and verbal fluency (Bhattachary and Powell, 2001; Hefferman *et al.*, 2001; Fox *et al.*, 2002; Montgomery *et al.*, 2005). These deficits have been associated with prefrontal cortex dysfunction. To a lesser extent, deficits of attention and speed of processing have been as well associated with long-term ecstasy use (Croft *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2001; Hanson and Luciana 2004). Thus, delimitation of the neurocognitive correlates of ecstasy use is still an open question with relevant implications for the clinical and social impact of these deficits.

Moreover, little is known about the persistence of ecstasy induced neurocognitive deficits in the long-term, to the point that at present we cannot predict the extent of the impact of regular use of ecstasy on the middle-age of the average ecstasy user. Cross-sectional studies indicate that memory and executive functions deficits are persistent even after abstinence periods ranging from three to 11 months (Morgan 1998; Gouzoulis-Mayfrank *et al.*, 2000, 2003; Wareing *et al.*, 2000, 2004a, 2004b). However, longitudinal designs are more appropriate to grasp the evolving nature of these deficits in groups of ecstasy users who continue or discontinue drug use. Along these lines, Zakzanis and Young (2001) demonstrated a significant decline of memory functioning after one year follow-up in ecstasy users who continued using the drug. In contrast, Thomasius *et al.*, (2006) found that memory disturbances remained stable (failed to improve but they did not deteriorate either) despite recovery of SERT availability in both current and former ecstasy users after more than two years' follow-up. Similarly, Gouzoulis-Mayfrank *et al.* (2005) compared two groups of ecstasy users who continued versus stopped using the drug over the course of 18 months and found that memory deficits were quite stable in both groups. Despite stability of behavioural measures, a recent neuroimaging study revealed that ecstasy users who continue consumption tend to present abnormal patterns of parietal activation (when compared with ecstasy users who quitted) during performance on a working memory task (Daumann *et al.*, 2004a). In view of conflicting results, more research is needed to clarify this issue.

Another relevant challenge in the investigation of the neurocognitive correlates of ecstasy use is that of delimitation of the effects associated with other co-abused substances, mainly cannabis. Because the majority of ecstasy users are also heavy users of cannabis, both substances could have interactive effects (aggregated or protective) on neurocognitive performance (Gouzoulis-Mayfrank and Daumann, 2006). Along these lines, several studies have investigated the differential effects of both substances by comparing groups of combined ecstasy/cannabis users with cannabis users and drug-naïve controls. These studies have yielded conflicting outcomes.

On the one hand, several studies have proposed that the neurocognitive deficits of ecstasy polysubstance users are mainly associated with concurrent cannabis use (Croft *et al.*, 2001; Simon and Mattick 2002; Dafters *et al.*, 2004; Lamers *et al.*, 2006). On the other hand, recent studies have revealed greater neurocognitive impairment in memory and executive functions in ecstasy/cannabis users when compared with cannabis users (Gouzoulis-Mayfrank *et al.*, 2000; Rodgers 2000; McCardle *et al.*, 2004; Quednow *et al.*, 2006b). The latter finding clearly point to ecstasy induced selective impairments after controlling for cannabis co-abuse. Several factors associated with history of drug use and patterns of consumption may be associated with variability of results. Ecstasy studies are subject to numerous methodological problems: inadequate sampling and verification of drug histories, varying degrees of control for the possible influence of other illicit drugs and lack of baseline data concerning premorbid levels of functioning (Morgan 2000). Most previous studies have failed to fully control for these variables.

The main aims of this study were: (i) to examine the neurocognitive profile associated with long-term use of ecstasy in a sample of Spanish recreational polysubstance users; (ii) to examine differential effects of combined ecstasy/cannabis use, with regard to cannabis use alone on neurocognitive performance; and (iii) to assess changes in neurocognitive performance in ecstasy users due to variability of drug use over the course of two years. According to existing evidence, we hypothesize that: (i) ecstasy/cannabis polysubstance users will present a neurocognitive profile consistent with fronto-temporal dysfunction; (ii) ecstasy/cannabis polysubstance users will present greater neurocognitive deficits than cannabis users and drug naive controls; and (iii) neurocognitive deficits will remain stable or decline over the course of two years in the ecstasy polysubstance users.

Methods

Participants

One-hundred seventeen participants were recruited, of whom 37 were ecstasy polydrug users, 23 were cannabis users and 34 were non-users. Other 23 participants were excluded from the present study because their drug use patterns did not match inclusion criteria. All participants were healthy, self-reporting an adequate functioning within their social and professional context, and were comparable in terms of years of education and socioeconomic status. As for drug users, subjects were not seeking for drug abuse treatment. Participants were recruited through several sources: 'word of mouth' notices in the local area, advertisement in the local university and advertisement in a local NGO (Energy Control) specialized in providing harm reduction guidelines among drug users. All were screened in a telephone interview to determine drug history. Subjects with neurological, relevant medical disease and current psychiatric histories were excluded.

As for the different groups, other exclusion criteria were applied: for cannabis group, current history of regular use of other illegal psychotropic drugs with the exception of cannabis during last year, as well as past use of illegal drugs for more than five occasions; and for non-users current history of use of any illegal drugs

during the past year and past use of illegal drugs in more than five occasions. Alcohol and nicotine were allowed. As for the ecstasy group, because it was impossible to recruit exclusive ecstasy users, it was decided to include ecstasy consumers with moderate use of other illicit drugs, being ecstasy the main psychostimulant drugs abused.

Test procedure

This study was approved by and conducted in accordance with the local ethics committee (CEIC-IMAS). Upon arrival to the research centre (IMIM, Institut Municipal d'Investigació Mèdica), subjects were informed of the ensuing protocol and gave their written informed consent before participating in the study.

Testing consisted of drug history, medical checking, drug screens, biochemical analyses, psychiatric and neuropsychological assessments. After completing testing, all subjects were economically compensated for their participation. All participants underwent a neuropsychological assessment session of 90 minutes. They completed all tasks in a quiet comfortable room. Several evaluations were carried out during two years: baseline measures at study onset, and after 6, 12 and 24 months. For the aims of this study, we will mainly report results obtained at baseline (t1) and after 24 months (t4). During this time period, subjects were reclassified among the three groups according to changes in their pattern of drug use. From the 94 subjects that started the study, after 24 months 60 participants remained in the study: 22 ecstasy polydrug users, 13 cannabis users and 25 non-users. Other 25 subjects left the study. No statistically significant age, gender, level of education and pattern of drug use differences were found between subjects who finished the follow-up period and those that dropped-out within each group.

Abstinence period was not strictly delimited, although all participants were requested to observe a 72 h abstinence period. Owing to this fact, urine drug screens were carried out by immunoassay (CEDIA, Microgenics) in all subjects prior to neuropsychological testing in order to avoid acute effects. Drug classes screened for included: cannabis, ecstasy, cocaine and amphetamine/methamphetamine. Drug screens were performed also in hair samples by segmental analysis (last month, previous six months and last year) for the same drug classes in order to verify self-reported drug consumption history. This procedure allowed us to reliably classify participants into the different subgroups according to the pattern of drug use (ecstasy/cannabis versus cannabis).

Neuropsychological tests

Premorbid intelligence estimation *Vocabulary subtest* (from the WAIS-III, Spanish version, Wechsler, 1997). Subjects are required to provide definitions to 33 words with increasing difficulty. The accuracy of word knowledge provides a good estimation of premorbid IQ and the test was used to control for pre-existing differences in general cognitive capacity between groups, which could be clinically relevant.

Attention measures *California Computerized Assessment Package CALCAP* (Miller, 1990). We used a selection of subtests included in the standard version, which consisted of a series of

simple and choice reaction time measures administered by a computer. All tasks are designed to be self-explanatory. Several cognitive domains were assessed: basal measure of reaction time (simple RT), recognition memory (choice RT-digits) and divided attention (sequential RT2).

Executive functions *Tower of London (TOL)*. (Shallice, 1982). This test requires the movement of three different coloured balls across three different size pegs in order to duplicate a goal configuration. Movements must follow strict rules. Scores for planning time (latency), solution time and total number of moves needed to complete the configuration are obtained, providing a good measure of planning ability.

Word fluency (Ramier, 1970, 1977; Benton and Hamsher, 1983). Subjects are asked to generate as many words as possible in one minute belonging to the specified category of 'animals'. High scores indicate greater verbal fluency.

Symbol Digit Modalities Test (Smith, 1973). This task involves the conversion of meaningless geometric designs into written Arabic number responses within 90 seconds. Answers must follow the correspondence shown in a visual key. The test involves the integration of visual, motor and executive functions and provides a good measure of processing speed.

Memory and learning *California Verbal Learning Test II* (Delis *et al.*, 2000). The test consists on a list of 16 words, which is read out to the examinee in five occasions. Following, the subject must repeat as many words as remembered each time. Following, the subject is required a short-term recall after interference list in a free and cued recall trial. After 20 minutes a free and cued recall are requested again. Last task consists in the recognition of the original list among another extensive list words. Measures of total learning, immediate and delayed recall and recognition are obtained.

Rey complex figure test (Rey, 1941). This test involves a copy trial of a complex figure stimulus, followed by a three minute immediate recall and a 30 minute delayed recall, where subjects are requested to redraw the memorized complex stimulus. Scores in immediate and delayed recalls provide a good measure of visuo-spatial memory performance.

Corsi block tapping subtest (from the WAIS-III, Wechsler, 1997). Subjects must memorize and reproduce a sequence of spatial locations demonstrated by the examiner. Examinee has to touch the prearranged wooden blocks first in the same order, and backwards later on. Length of the sequence increases with the subject's success. Direct sequence measures attention span, whereas backward sequence is predominantly a measure of visual working memory span.

Letter number sequencing subtest (from the Wechsler Memory Scale III, Wechsler, 1997). Subjects are required to listen to a series of numbers and letters with randomized presentation, then repeat them back, giving numbers first following numerical order and after letters alphabetically arranged. The length of the series increases with the subject's success. Higher scores provide a good measure of verbal working memory span.

Statistical analyses

The comparison of the three groups (Ecstasy, Cannabis and Control) with respect to socio-demographic characteristics and drug consumption at baseline was carried out by means of one-way ANOVA (*F*-test) for continuous variables and the χ^2 -test for categorical variables, respectively. The *t*-test for paired observations was applied in order to check whether drug consumption habits changed significantly between baseline and the last evaluation after 24 months within each group. To compare the neuropsychological test results among the three groups at baseline, ANCOVA models were used adjusting for gender and premorbid intelligence.

Given the fact that neuropsychological test scores at baseline did not differ significantly between the cannabis group and controls, longitudinal analyses for these variables were carried out for ecstasy users and controls only. The linear mixed models used adjusted for sex, premorbid intelligence and evaluation month (baseline, 6, 12 and 24 months) treating the latter variable as a factor. A possible group per time interaction was considered in order to check for possible differences in time trends between the two groups. Whenever this interaction was non-significant, it was removed from the model in order to reduce the number of the model parameters. Longitudinal analyses included only those ecstasy/cannabis and control subjects who showed up at all four evaluations, and diagonal matrices were chosen to model the covariance structure of the repeated measures. The same type of model was used to examine the effect of age at first cannabis consumption (15 years and younger/ older than 15 years). For this aim, models included all subjects from the ecstasy/cannabis and cannabis group.

At baseline, we also had a closer look at the importance of lifetime consumption of ecstasy. Pearson's correlation coefficient was used to measure the linear association between lifetime ecstasy consumption (measured in tablets) and neuropsychological test results. At a multivariate level, three groups were compared: controls, moderate users (1 through 100 ecstasy tablets), and heavy users (more than 100 tablets). The ANCOVA models applied included gender and premorbid intelligence as further covariates.

Results were considered statistically significant whenever $P < 0.05$. In all ANCOVA models, post hoc pairwise comparisons between categories of drug consumption were carried out using the Sidak adjustment for multiple comparisons (Hochberg and Tamhane, 1987).

Even though we talk of the ecstasy, cannabis, and control group, we are aware of the fact that subjects of the first group did also consume cannabis.

Results

Demographic and drug use data

Sociodemographics of the participants are provided in Table 1. No significant differences were observed regarding years of education and employment status. Mean age in the ecstasy group was significantly higher ($P = 0.029$) than in the other two groups (23.6 versus 22 years). The proportion of individuals with a university degree or

Table 1 Sociodemographic characteristics at baseline

	Ecstasy (<i>n</i> = 37)	Cannabis (<i>n</i> = 23)	Control (<i>n</i> = 34)	<i>P</i> -value
Age	23.6 (3.5)	22.0 (1.9)	22.0 (2.6)	0.029
Males	19 (51.4%)	8 (34.8%)	9 (26.5%)	0.091
Years of education	14.7 (2.8)	14.3 (2.6)	15.2 (1.7)	0.406
University degree ^a	25 (67.6%)	20 (87%)	33 (97.1%)	0.004
Employment status				0.244
Student	23 (62.2%)	18 (78.3%)	29 (85.3%)	
Employed	10 (27%)	4 (17.3%)	4 (11.8%)	
Unemployed	4 (10.8%)	1 (4.4%)	1 (2.9%)	
Vocabulary WAIS-III (Index score)				
Baseline	11.1 (2.2) ^b	12.4 (2.3) ^b	12.6 (2.3) ^b	0.017
After 24 months ^c	12.5 (2.6)	13.5 (2.0)	14.6 (2.1)	0.007

Results are presented as mean (standard deviation) for continuous variables and absolute frequency (relative frequency) for categorical variables.

P-values result from either *F*-test (continuous variables) or χ^2 -test.

^aIncluding students.

^bScores among subjects with follow-up to 24 months: ecstasy, 12.0 (1.9); cannabis, 12.4 (2.4); control, 12.2 (1.7); *P*-value (*F*-test): 0.849.

^c*n* = 20 (ecstasy); *n* = 13 (cannabis); *n* = 26 (control).

studying at university was lower in the ecstasy group (67.6%) than in the control (97.1%) and cannabis (87%) groups ($P = 0.004$). Scores on the Vocabulary test (WAIS III index score) were worse in the ecstasy group ($P = 0.017$) at baseline and this group difference persisted after 24 months. Concerning gender, the proportion of males was higher in the ecstasy group (19 out of 37); however, there were no significant differences between groups.

In Table 2, drug use patterns are shown, considering alcohol, tobacco, cannabis and ecstasy consumption. At baseline, the ecstasy group shows a mean total ecstasy lifetime consumption of 206 tablets ($SD = 228.3$) over 5.5 years on average ($SD = 3.4$), having started first use at the age of 18.1 ($SD = 3.5$). Mean frequency of consumption during the six months prior to testing was 10.5 days ($SD = 10.8$). Concerning alcohol consumption, on average, controls were significantly older ($P < 0.001$) at onset of alcohol use, in comparison to subjects from both other groups. In addition, frequency of consumption (days of use during the last six months prior to the evaluation) was lower ($P < 0.001$). There were more smokers in the ecstasy group ($P < 0.001$), the age of onset of use was younger ($P < 0.006$) and the number of cigarettes smoked higher ($P < 0.04$) when compared with the other two groups. Comparing ecstasy and cannabis groups in terms of cannabis consumption, a higher use was observed in the ecstasy group during the last six months ($P = 0.006$). The age at onset of use was very similar ($P = 0.26$) between both groups, but since the mean age in ecstasy users was higher, a longer mean lifetime consumption of cannabis was observed in ecstasy users at baseline ($P < 0.01$). In addition, ecstasy users showed a more frequent consumption of cannabis, which is translated in a higher mean number of joints

during lifetime than the cannabis group ($P = 0.01$). In addition, among ecstasy users, consumption of other drugs was recorded (but is not presented in Table 2): 34 (91.9%) subjects had used at least once cocaine; 27 (73.0%) speed; 26 (70.3%) LSD; 8 (21.6%) ketamine; 5 (13.5%) GHB and one (2.7%) heroin. Among the cannabis and control group, no one had used these drugs before.

Drug consumption over time

After 24 months, the 20 ecstasy users left in the study showed a decrease in the ecstasy frequency of use (5.7 versus 12.4 days during the past six months, $P = 0.02$), and similar patterns of cannabis ($P = 0.82$), tobacco ($P = 0.60$) and alcohol consumption ($P = 0.46$). Concerning tobacco and alcohol consumption, the same was observed among the subjects in the cannabis and control group ($P > 0.2$ in all cases), whereas the decrease of cannabis consumption among the cannabis group (56.0 versus 75.0 days during the past six months) was borderline significant ($P = 0.057$).

Neurocognitive performance: cross sectional analysis at baseline

The results of the neuropsychological tests at baseline in the three groups are shown in Table 3. All groups performed within the normal range in baseline scores according to published tests norms. However, ANCOVA models revealed significant overall group differences with respect to semantic word fluency ($P = 0.014$). Post hoc analyses in this measure revealed that the ecstasy group performed at a significant lower level than non-users.

Table 2 Drug use characteristics at baseline

	Ecstasy (<i>n</i> = 37)	Cannabis (<i>n</i> = 23)	Control (<i>n</i> = 34)	<i>P</i> -value
Alcohol				
Age at onset of use	14.5 (2.2)	15.1 (1.3)	16.4 (1.4)	<0.001
Duration of use (years)	9.0 (3.1)	6.6 (1.7)	5.3 (2.4)	<0.001
Total use in the last 6 months (days)	46.9 (40.8)	46.7 (38.3)	19.9 (14.7)	0.004
Tobacco				
Current smokers	27 (73.0%)	12 (52.2%)	8 (23.5%)	<0.001
Age at onset of use	14.8 (1.7)	16.8 (3.1)	17.0 (1.6)	0.006
Duration of use (years)	7.9 (3.6)	5.5 (2.8)	4.8 (1.6)	0.017
Cigarettes per day	11.7 (6.1)	7.3 (6.5)	6.8 (4.5)	0.043
Cannabis				
Age at onset of use	16 (2.2)	16.6 (1.8)		0.26
Duration of use (years)	7.4 (2.7)	5.6 (2.7)		0.02
Total lifetime use (joints)	4368 (4510)	1670 (2845)		0.01
Total use in the last 6 months (days)	128.7 (68.5)	76 (69.8)		0.006
Ecstasy				
Age at onset of use	18.1 (3.5)			
Duration of use (years)	5.5 (3.4)			
Total lifetime consumption (tablets)	206 (228.3)			
Total consumption in the last 6 months (days)	10.5 (10.8)			

Results are presented as mean (standard deviation).

P-values result from either *t*-or *F*-test. Proportions of current smokers are compared with the χ^2 -test.

Table 3 Neuropsychological test scores at baseline

	Ecstasy (<i>n</i> = 37)	Cannabis (<i>n</i> = 23)	Control (<i>n</i> = 34)	<i>P</i> -value
Attention				
CalCAP: simple RT	328.6 (58.7)	334.6 (73.5)	350.2 (93.2)	0.516
CalCAP: choice RT –Digits	385.6 (42.4)	386.9 (46.9)	395.6 (33.0)	0.581
CalCAP: sequential RT2	545.8 (94.9)	549.2 (110.7)	568.4 (91.4)	0.731
Working Memory				
Corsi Block Visual Span Backwards	8.4 (1.9)	9.4 (1.5)	9.3 (1.1)	0.082
Letter Number sequencing	12.2 (2.7)	11.7 (1.8)	12.6 (2.4)	0.243
Memory				
CVLT: Total A1-A5	54.7 (9.4)	59.3 (7.6)	57.9 (8.6)	0.571
CVLT: Immediate recall	12 (2.9)	12.7 (2.8)	12.8 (2.4)	0.995
CVLT: Delayed recall	12.5 (2.4)	13.4 (2.7)	13.2 (2.5)	0.848
CVLT: Total Recognition	15.4 (0.9)	15 (1.2)	15 (1.2)	0.155
ROCFT: Immediate recall	22.1 (5.7)	23.9 (4.7)	23.3 (4.5)	0.620
ROCFT: Delayed recall	22.2 (5.5)	23.7 (4.5)	22.6 (3.7)	0.640
Executive functions				
Semantic word fluency	23.2 (3.5)	26.2 (6.4)	27.2 (5.6)	0.014 ^a
ToL: Total Movements	88 (17.7)	78.9 (11.1)	83.5 (15.4)	0.175
ToL: Initiation Time	33.8 (15.3)	40.1 (18.1)	36.1 (20.0)	0.596
Mental processing speed				
SDMT: Total correct	57.8 (11.7)	64.5 (10.3)	63.9 (10.7)	0.146

Results are presented as mean (standard deviation).

P-values result from ANCOVA models adjusting for gender and premorbid intelligence.

^aSignificant differences between ecstasy and control group.

Univariate correlation analyses (Pearson) revealed a significant association between lifetime ecstasy use and performance on measures of working memory, visual memory, information processing speed as well as planning. That is, the higher lifetime ecstasy consumption, the lower achievement in the mentioned cognitive results. In particular, significant negative correlations were found for immediate visual memory ($r = -0.430$, $P = 0.008$) and delayed recall ($r = -0.517$, $P = 0.001$), working memory for visual ($r = -0.352$, $P = 0.033$) and verbal information ($r = -0.393$, $P = 0.016$) and for information processing speed ($r = -0.375$, $P = 0.022$). Furthermore, a significant positive association was found for planning ability and ecstasy use (ToL: total number of movements $r = 0.428$, $P = 0.008$).

Moreover, the baseline scores of heavy and moderate ecstasy users as well as controls were compared, adjusting for gender and premorbid intelligence. This analysis not only confirmed the difference between controls and ecstasy users with respect to Semantic Word Fluency described before, but also showed the following differences (not presented in tables): Concerning working memory (Corsi blocks) and mental processing speed (SDMT: total correct), results were significantly worse in heavy ecstasy users compared with non-users ($P = 0.024$ and $P = 0.033$, respectively); regarding the Rey Complex Figure Test, heavy ecstasy users obtained

significantly worse results than both other groups with respect to immediate recall ($P < 0.001$), as well as significantly worse results than moderate ecstasy users with respect to delayed recall ($P < 0.001$).

Longitudinal analysis: from baseline to 24 months

The results of the longitudinal analysis are shown in Table 4. After two years of follow-up, scores among all three groups remained within the normal range. A global improvement over time was observed in several functions: attention (Choice reaction time and sequential reaction time), processing speed (SDMT: total of correct answers), planning ability (Tower of London), and memory variables (Rey Complex Figure Test).

In addition, the differences between the control group and ecstasy users with respect to working memory (Corsi Blocks; $P = 0.017$), Semantic Word Fluency ($P = 0.018$) and processing speed (Total of correct answers; $P = 0.043$) persisted over time and were found to be statistically significant; Figure 1 shows the evolution over time in both groups for each of these three variables. In both groups, comparisons of baseline test results between the ones lost to follow-up and those who remained in the study did not show any significant differences.

Table 4 Neuropsychological test scores over time in MDMA consumers and Controls

	Baseline evaluation		After 24 months		P-value ^a
	Ecstasy (<i>n</i> = 20)	Control (<i>n</i> = 26)	Ecstasy (<i>n</i> = 20)	Control (<i>n</i> = 26)	
Attention					
CalCAP: Simple RT	330.2 (59.3)	346.1 (87.3)	355.9 (63.9)	319.7 (49.6)	0.189
CalCAP: Choice RT –Digits	385.5 (36.2)	390.2 (31.7)	417.3 (50.3)	399.0 (42.7)	0.774
CalCAP: Sequential RT2	543.7 (94.0)	579.0 (89.3)	542.4 (103.6)	510.9 (98.9)	0.383
Working Memory					
Corsi Block Visual Span Backwards	8.6 (1.6)	9.3 (1.1)	8.3 (1.1)	8.9 (1.6)	0.017
Letter Number Sequencing	12.4 (2.4)	12.7 (2.3)	12.4 (2.4)	12.7 (1.9)	0.496
Memory					
CVLT: Total A1-A5	56.8 (8.2)	57.3 (8.4)	55.2 (9.6)	61.0 (8.3)	0.211
CVLT: Immediate recall	12.7 (2.7)	12.8 (2.3)	13.2 (2.6)	13.7 (2.2)	0.560
CVLT: Delayed recall	13.3 (2.0)	13.0 (2.6)	12.6 (3.9)	14.2 (2.0)	0.764
CVLT: Total Recognition	15.4 (1.0)	15.0 (1.1)	14.8 (1.5)	15.6 (0.8)	0.375
ROCFT: Immediate recall	23.1 (3.4)	22.9 (4.7)	26.0 (4.1)	27.5 (4.7)	0.481
ROCFT: Delayed recall	23.6 (3.7)	22.6 (3.9)	25.3 (4.7)	26.5 (4.0)	0.822
Executive Functions					
Semantic Word Fluency	23.7 (3.6)	27.7 (5.9)	25.0 (5.0)	27.6 (5.6)	0.018
ToL: Total Movements	86.6 (17.7)	84.6 (16.5)	72.6 (14.0)	71.9 (12.4)	0.995
ToL: Initiation Time	33.2 (14.4)	36.4 (18.4)	45.2 (20.9)	50.2 (23.2)	0.393
Mental processing speed					
SDMT: Total correct	57.7 (11.5)	63.5 (11.2)	64.5 (14.4)	70.4 (10.0)	0.043

Results are presented as mean (standard deviation).

^aP-values are obtained from linear mixed models including all data from baseline until the 4th evaluation, and adjusting for gender and premorbid intelligence.

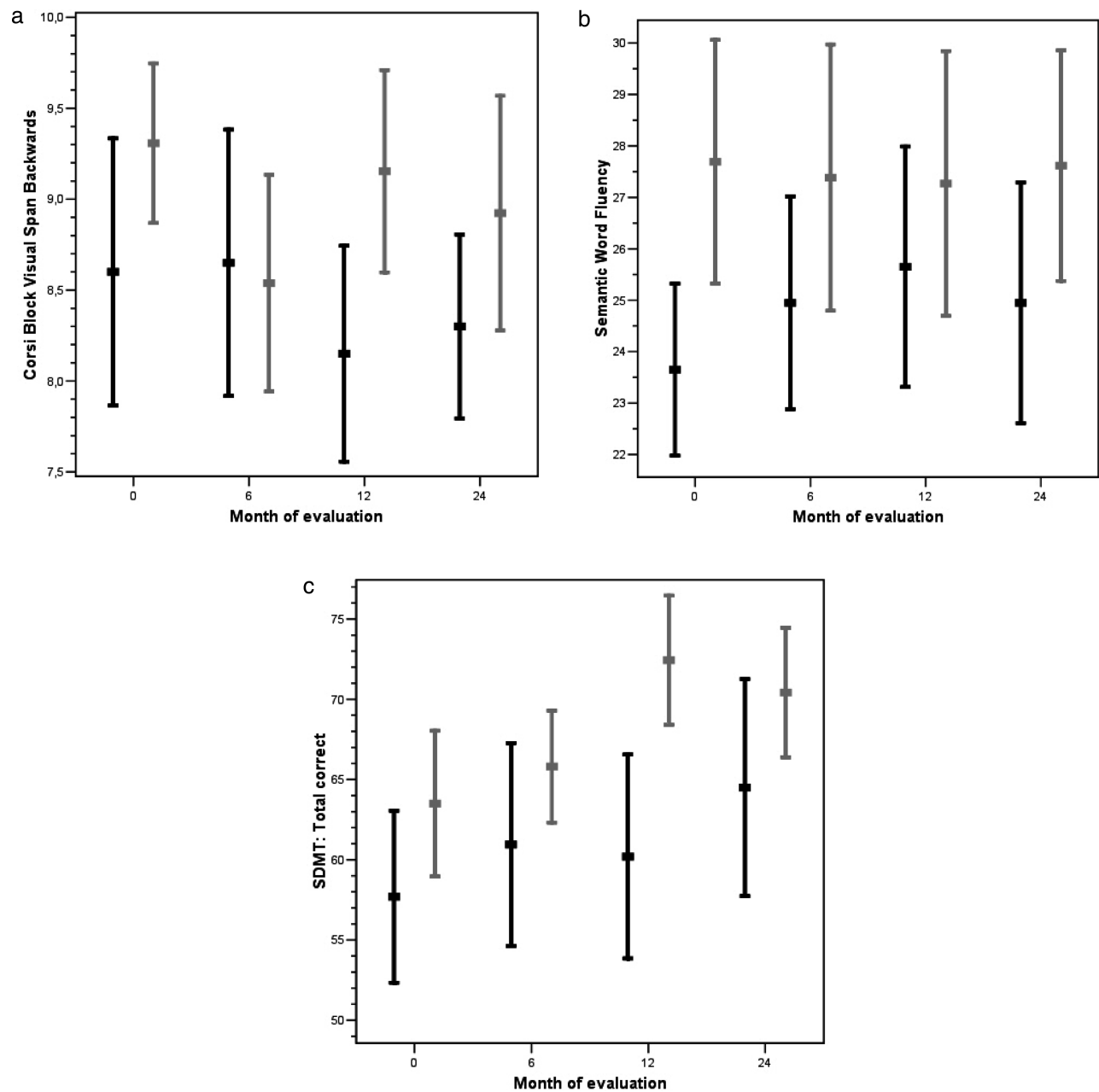


Figure 1 Longitudinal analysis of ecstasy users and control group for working memory, executive functions, and processing speed: a) Corsi Block Visual Span Backwards. b) Semantic Word Fluency, and c) SDMT: Total correct. Figures show 95% confidence intervals of the mean scores at each evaluation. Grey lines: control group; black lines: ecstasy group.

The longitudinal models to check the effect of age at onset of cannabis consumption, revealed worse performance of those with age of onset less or equal to 15 years with respect to working memory (Corsi blocks; $P = 0.032$); the worse results regarding attention (simple reaction time) of the same group were borderline significant ($P = 0.076$); results are not shown in tables.

Discussion

The main aims of this study were: (1) to examine the neurocognitive profile associated with long-term use of ecstasy in current users of this substance, as compared with cannabis users and non-drug using controls; and (2) to investigate the long-term effects of

continued use of ecstasy on cognition over a period of two years. At baseline assessment, ecstasy/cannabis users showed specific deficits in the domain of semantic word fluency. When we classified ecstasy polydrug users according to their lifetime consumption of ecstasy, we found additional deficits of visual episodic memory, visual working memory and processing speed in the more severe users (more than 100 tablets). Furthermore, lifetime ecstasy use was negatively correlated with performance on tests of working memory, episodic memory, planning and processing speed, thus the heavier use the poorer cognition. Although ecstasy/cannabis users presented lower estimated premorbid intelligence, group differences remained significant after adjusting for this variable. At two years follow-up assessment, ecstasy polydrug users showed significantly poorer performance than non-drug using controls on measures of word fluency, working memory, and processing speed. Although both ecstasy polydrug users and controls showed improved performance after two years (probably reflecting learning effects), ecstasy polydrug users performed consistently worse than controls in these domains across the four assessments.

Overall, results from cross-sectional, correlational and longitudinal analyses in this sample are consistent with extensive evidence that indicates that ecstasy use is associated with deficits on memory and executive functions. Previous studies had demonstrated that ecstasy users tend to present poorer performance on several measures of verbal and visual episodic memory (Gouzoulis-Mayfrank *et al.*, 2000; Rodgers, 2000; Fox *et al.*, 2002; Thomasius *et al.*, 2003). Additionally, several studies have shown that extent of lifetime use of ecstasy is specifically related to memory performance and not to other cognitive processes (Gouzoulis-Mayfrank *et al.*, 2003). These studies are consistent with our findings that demonstrated that the more severe users of ecstasy showed specific impairments in immediate and delayed episodic memory retrieval. These behavioural results are further supported by neuroimaging findings. For example, one recent MR spectroscopy study showed decreased levels of the neuronal marker N-acetylaspartate in the hippocampus (but not the neocortex) in ecstasy users (Daumann *et al.*, 2004b); and one functional imaging study using specific 5HT-binding radioligands detected decreased levels of SERT also in the hippocampus (McCann *et al.*, 2005). Along the same lines, in a functional imaging study, Daumann *et al.* (2005) detected significant reductions in the hippocampal activity of ecstasy users during the retrieval phase of an episodic memory task.

Additionally, results showed impaired performance of ecstasy users on different aspects of executive functions. At baseline evaluation, ecstasy users showed specific deficits on semantic word fluency. In addition, the more severe users also showed impaired performance on measures of visual episodic memory, visual working memory and processing speed. Furthermore, longitudinal analyses demonstrated persistent deficits of fluency, visual working memory and speed. A number of previous studies had observed similar deficits on verbal and visual working memory (Wareing *et al.*, 2000, 2004a, 2004b; Verkes *et al.*, 2001; Fisk *et al.*, 2004) and fluency (Bhattachary and Powell, 2001; Heffernan *et al.*, 2001; Fox *et al.*, 2002; Montgomery *et al.*, 2005) in samples of ecstasy users. Furthermore, dose-related cumulative use of ecstasy has been related to poorer working memory performance in polysubstance

users (Verdejo-García *et al.*, 2005). Recent investigations using structural equation models have proposed that executive functions can be fractionated into four relatively independent components: updating (working memory), access (ability to temporarily activate information from long-term memory), inhibition (ability to suppress prepotent responses) and shifting (related to mental flexibility and set shifting skills) (Miyake *et al.*, 2000; Fisk and Sharp, 2004). It has been proposed that ecstasy use is specifically associated with impaired performance on tests, which tax the updating, and access components, but not on tests of inhibition or shifting. For example, Montgomery *et al.* (2005) observed that ecstasy users were selectively impaired on low-level tasks of working memory and verbal fluency, but not on tasks of inhibition and shifting. Our results provide further support to this notion. Brain lesion and imaging studies have shown that an important neural correlate of both working memory and fluency skills is the dorsolateral prefrontal cortex (DLPFC) (Wendt and Risberg, 2001; Collette and Van der Linden, 2002; Bor *et al.*, 2006). Interestingly, imaging studies have detected significant reductions of serotonin transporter availability at the level of the DLPFC in ecstasy users (McCann *et al.*, 2005). Additionally, functional imaging studies have detected abnormal activation of the DLPFC and the superior frontal gyrus in ecstasy users during performance on a specific task of working memory (Moeller *et al.*, 2004). Interestingly, our results seem to suggest asymmetrical effects of ecstasy on visual versus verbal memory, whereas most previous studies had reported verbal deficits. This effect may be related to sub-acute effects of ecstasy use (as opposed to abstinence-related effects on verbal memory), or to a higher exposure to ecstasy in the users included in our sample. Nonetheless, deficits in visuo-spatial working memory had been as well previously reported in ecstasy users (Verkes *et al.*, 2001; Wareing *et al.*, 2004a, 2005).

Thus, according to our results, the neurocognitive profile of this group of polysubstance ecstasy users is consistent with alterations in the DLPFC, medial temporal lobes and the hippocampus. These are neural regions richly interconnected, and they probably interact in the execution of complex processes, such as working memory, access and retrieval of contents from long-term memory and the organization/ categorization of mnemonic material (Montgomery *et al.*, 2005; Quednow *et al.*, 2006a). Additionally, recent studies in frontal lesion patients indicate that processing speed can be importantly involved in the operations of these and other related executive processes (Stuss *et al.*, 2005).

A related aim of our study was to examine the differential contributions of ecstasy and cannabis to neurocognitive performance in ecstasy polysubstance users. Our results showed that performance of ecstasy/cannabis users only differed significantly from that of cannabis users on a measure of verbal fluency. However, correlational analyses also showed dose-related effects of ecstasy use on memory, working-memory and planning skills. Therefore, our results provide partial support to previous evidence showing that ecstasy misuse contributes to cognitive impairment even after controlling for cannabis co-abuse (Gouzoulis-Mayfrank *et al.*, 2000; Rodgers, 2000; Fisk *et al.*, 2004; McCardle *et al.*, 2004; Wareing *et al.*, 2004ab). Similar to our results, most of these studies have shown that specific deficits of working memory, long-term episodic

memory (delayed recall) and executive functions in combined ecstasy/cannabis users are closely related to ecstasy and not cannabis use. However, an important contribution of cannabis consumption to the sub-clinical impairment observed in our ecstasy sample is the age at onset of use. The effects of cannabis use before 15 years old seem to be persistent over lifetime, specifically on measures of attention and verbal working memory. This enhancing effect of early exposure on neurotoxicity had been previously observed in cannabis users (Ehrenreich *et al.*, 1999; Pope *et al.*, 2003). Therefore, negative effects of an early start at cannabis use raise an important concern for its possible contribution to future impairment in young users, in addition to the effects of concomitant use of other illicit drugs.

However, our findings do not fully agree with previous evidence indicating that cannabis use can account for the bulk of the neurocognitive deficits revealed in ecstasy polysubstance users (Croft *et al.*, 2001; Simon and Mattick, 2002; Lamers *et al.*, 2006). In light of our findings, the poorer performance of severe ecstasy users, as compared with cannabis users and non-drug using controls, supports the notion that ecstasy or ecstasy/cannabis combined effects (but not cannabis alone) are responsible for the observed deficits. Moreover, the close correspondence between ecstasy lifetime use and poorer performance in the domains of memory and executive function support this notion. Several variables can account for discrepancy of findings between this and the above-mentioned studies. One relevant variable is severity of ecstasy use. Overall, studies, which have reported prominent neurocognitive effects of cannabis, have been conducted in samples of relatively mild ecstasy users, as opposed to the severe pattern of use that characterized ecstasy polysubstance users in this sample. A second relevant variable is a strict assignment and matching of participants included in the subgroups of ecstasy/cannabis and cannabis users. In this study, we were able to confirm self-reported information about drug use with biochemical analyses able to precisely detect this use. This has not been a common practice among studies of ecstasy neurocognitive deficits, and thus constitutes a relevant methodological tool to better classify users according to their pattern of consumption, providing more reliable findings. Our findings neither supports the hypothesis that cannabis use may attenuate substantially the effects produced by ecstasy itself (i.e., protective effects) (Croft *et al.*, 2001; Gonzalez *et al.*, 2004).

A third aim of this study was to investigate persistence or change in neurocognitive deficits over a period of two years of continued substance use. Results at two years follow-up showed that ecstasy polydrug users still performed poorer than controls in several cognitive measures including working memory, fluency and processing speed. It is important to note that time related analyses (repeated-measures comparisons between baseline and follow-up) showed overall improvement in all three groups after 24 months. This improved performance can be partly explained owing to learning effects, as participants underwent four assessment sessions during this period. In future studies, we plan to use parallel versions of neurocognitive measures to control for these effects. However, despite improved performance, ecstasy polydrug consistently showed decreased performance in several measures across the four assessments. We also assessed the possible relationship between the

decrease of ecstasy use and the reversibility of the negative effects. An average decrease in recent ecstasy consumption (last six months before testing) is noticed after two years ($P = 0.02$). This is a common incidental finding in longitudinal studies of ecstasy recreational users (Gouzoulis-Mayfrank *et al.*, 2005; Thomasius *et al.*, 2006). Previous longitudinal studies had reported absence of significant neurocognitive changes over time (Gouzoulis-Mayfrank *et al.*, 2005; Thomasius *et al.*, 2006) or modest declines (Zakzanis and Young, 2001). Persistence of working memory, fluency and speed deficits in our study also points in the direction of ecstasy long-lasting stable but subtle deficits. Unfortunately, the lack of other significant differences between groups could respond to reduced statistical power owing to a smaller ecstasy sample after 24 months. Therefore, we cannot conclude that a decrease in ecstasy use can contribute to partial improvement of the overall cognitive function, but we can state that sub-clinical impairment is still persistent after two years. Nonetheless, alternative explanations such as pre-existing differences between the groups cannot be completely ruled out in spite of the longitudinal design. In any case, this persisting impairment may have increasing negative impact as a function of aging. It is likely that young current users of ecstasy may well compensate for these subtle deficits, but stability of these deficits over the years may compromise daily functioning in the long-term. For example, a recent study has shown that despite minimal executive function deterioration, ecstasy users manifest relevant deficits in social and emotional aspects of daily life (Reay *et al.*, 2006).

There are a number of methodological problems in the present study which apply to all ecstasy research in humans. Objective doses, frequency of use or lifelong consumption were retrospectively self-reported by the participants. No clear cut off point in the abstinence period was another important weakness. An average minimum period of 72h since last intake of any illicit drug is unlikely to have avoided residual effects; nevertheless, both user groups experienced similar abstinence periods. Another drawback of this study is that we could not completely exclude possible pre-existing group differences in the areas of semantic word fluency, information processing speed, memory and working memory. Polydrug use also contributes to confound ecstasy effects on cognitive performance. Another main problem with polydrug users is that pattern of drug consumption evolves very quickly along the study, which means a change of the experimental drug use characteristics. That makes it even more difficult to conclude causality and affects statistical significance owing to a smaller sample size if inclusion criteria for the ecstasy group are very restrictive. An additional limitation was that healthy controls and cannabis users had higher IQ compared with ecstasy users. However, these pre-existing differences were not clinically relevant and thus non-sufficient to explain the poorer performance of the ecstasy group. In support of this, all participants performed between high (cannabis and non-users) and high-normal (ecstasy group) IQ ranges. Plus, contribution of ecstasy use to cognitive performance remained significant when IQ was statistically controlled. Possible directions for future research on long-term ecstasy effects could focus on older participants with extensive histories of ecstasy use. Longitudinal studies could include wider follow-up periods with current ecstasy users who intend to become abstinent, in order to compare in the future

abstinent subjects with consumers who have not succeeded in quitting drug use (see Gouzoulis-Mayfrank *et al.*, 2005). This design could contribute to clarify worsening, persistency or reversibility of long-term chronic effects. Another interesting direction for future research would be to assess, in addition to the neuropsychological data, the socioeconomic implications of ecstasy (unemployment rates and costs, educational achievement, etc.) in subjects with cognitive impairment due to ecstasy/polydrug use.

Acknowledgements

Funding/Support: This study was supported in part by Fondo de Investigaciones Sanitarias (FIS-00/00777) and Plan Nacional Sobre Drogas (INT/2012/2002) Spain. The project "Neurotossicità a Lungo Termine dell'Ecstasy" from Istituto Superiore di Sanità, Rome, Italy, and Generalitat de Catalunya (2001SGR00407, SGR 2005).

References

- Benton A L, Hamsher K, Sivan A B (1983) Multilingual aphasia examination. third edition, Iowa City, IA: AJA Associates
- Bhattachary S, Powell J H (2001) Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or "ecstasy": evidence for cognitive impairment. *Psychol Med* 31: 647–658
- Bolla K I, McCann U D, Ricaurte G A (1998) Memory impairment in abstinent MDMA ("MDMA") users. *Neurology* 51: 1532–1537
- Bor D, Duncan J, Lee A C, Parr A, Owen A M (2006) Frontal lobe involvement in spatial span: converging studies of normal and impaired function. *Neuropsychologia* 44: 229–237
- Buchert R, Thomasius R, Nebeling B, Petersen K, Obrocki J, Jenicke L, Wilke F, Wartberg L, Zapletalova P, Clausen M (2003) Long-term effects of "ecstasy" use on serotonin transporters of the brain investigated by PET. *J Nucl Med* 44: 375–384
- Cami J, Farre M, Mas M, Roset P N, Poudevida S, Mas A, San L, de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *J Clin Psychopharmacol* 20: 455–466
- Collette F, Van der Linden M (2002) Brain imaging of the central executive component of working memory. *Neurosci Biobehav Rev* 26: 105–125
- Commins D L, Vosmer G, Virus R M, Woolverton W L, Schuster C R, Seiden L S (1987) Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. *J Pharmacol Exp Ther* 241: 338–345
- Croft R J, Mackay A J, Mills A T D, Gruzeller J G H (2001) The relative contribution of MDMA and cannabis to cognitive impairment. *Psychopharmacology* 153: 373–379
- Dafters R I, Hoshi R, Talbot A C (2004) Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. *Psychopharmacology* 173: 405–410
- Daumann J, Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E (2004) Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. *Biol Psychiatry* 56: 349–355
- Daumann J, Fischermann T, Pilatus U, Thron A, Moeller-Hartman W, Gouzoulis-Mayfrank E (2004) Proton magnetic resonance spectroscopy in ecstasy (MDMA) users. *Neurosci Lett* 362: 113–116
- Daumann J, Fischermann T, Heekeren K, Henke K, Thron A, Gouzoulis-Mayfrank E (2005) Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. *Psychopharmacology* 180: 607–611
- Ehrenreich H, Rinn T, Kunert H J, Moeller M R, Poser W, Schilling L, Gigerenzer G, Hoehe M R (1999) Specific attentional disfunction in adults following early start of cannabis use. *Psychopharmacology* 142: 295–301
- Fisk J E, Sharp C A (2004) Age-related impairments in executive functioning: updating, inhibition, shifting and access. *J Clin Exp Neuropsychol* 26: 874–890
- Fisk J E, Montgomery C, Murphy P, Wareing M (2004) Evidence for executive deficits among users of MDMA (Ecstasy). *Br J Psychol* 95: 457–466
- Fisk J E, Montgomery C, Wareing M, Murphy P (2005) Reasoning deficits in ecstasy (MDMA) polydrug users. *Psychopharmacology* 181: 550–559
- Fox H C, McLean A, Turner J J, Parrott A C, Rodgers R, Sahakian B J (2002) Neuropsychological evidence of a relatively selective profile of temporal dysfunction drug-free MDMA ("MDMA") polydrug users. *Psychopharmacology* 162: 203–214
- Gonzalez R, Vassileva J, Bechara A, Grbesic S, Sworowski L, Novak R M, Nunnally G, Martin E M (2004) Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. *Drug Alcohol Depend* 76: 181–190
- Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert H-J, Fimm B, Sass H (2000) Impaired cognitive performance in drug-free recreational MDMA (MDMA) users. *J Neurol Neurosurg Psychiatry* 68: 719–725
- Gouzoulis-Mayfrank (2000)
- Gouzoulis-Mayfrank E, Thimm B, Rezk M, Hensen G, Daumann J (2003) Memory impairment suggests hippocampal dysfunction in abstinent MDMA users. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 27: 819–827
- Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J (2005) Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. *Drug Alcohol Depend* 78: 317–323
- Gouzoulis-Mayfrank E, Daumann J (2006) The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. *J Psychopharmacol* 20: 188–193
- Green A R, Mechan A O, Elliott J M, O'Shea E, Colado M I (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "MDMA"). *Pharmacol Rev* 55: 463–508
- Hanson K L, Luciana M (2004) Neurocognitive function in users of MDMA: the importance of clinically significant patterns of use. *Psychol Med* 34: 229–246
- Hatzidimitriou G, McCann U D, Ricaurte G A (1999) Altered serotonin innervation patterns in the forebrain of monkeys treated with ($\pm$) 3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 19: 5096–5107
- Heffernan T M, Jarvis H, Rodgers J, Scholey A B, Ling J (2001) Prospective memory, everyday cognitive failure and central executive function in recreational users of ecstasy. *Hum Psychopharmacol* 16: 607–612
- Hochberg Y, Tamhane A (1987) Multiple Comparison Procedures. John Wiley and Sons

- Lamers C T J, Bechara A, Rizzo M, Ramaekers J G (2006) Cognitive function and mood in MDMA/THC users, TJC users and non-drug using controls. *J Psychopharmacol* 20: 302–311
- McCann U D, Szabo Z, Seckin E, Rosenblatt P, Mathews W B, Ravert H T, Dannals R F, Ricaurte G A (2005) Quantitative PET studies of the serotonin transporter in MDMA users and controls using [¹¹C]McN5652 and [¹¹C]DASB. *Neuropsychopharmacology* 30: 1741–1750
- McCardle K, Luebbers S, Carter J D, Croft R J, Stough C (2004) Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology* 173: 434–439
- Medina K L, Shear P K, Corcoran K (2005) Ecstasy (MDMA) exposure and neuropsychological functioning: a polydrug perspective. *J Int Neuropsychol Soc* 11: 753–765
- Miller J (1990) Discreteness and continuity in models of human information processing. *Acta Psychol (Amst)* 74: 297–318
- Miyake A, Friedman N P, Emerson M J, Witzky A H, Howerther A (2000) The unity and diversity of executive function and their contribution to complex frontal lobe tasks: a latent variable analysis. *Cognit Psychol* 41: 49–100
- Moeller, Steinberg J L, Dougherty D M, Narayana P A, Kramer L A, Renshaw P F (2004) Functional MRI study of working memory in MDMA users. *Psychopharmacology* 177: 185–194
- Montgomery C, Fisk J E, Newcombe R, Murphy P N (2005) The differential effects of ecstasy/polydrug use on executive components: shifting, inhibition, updating and access to semantic memory. *Psychopharmacology* 182: 262–276
- Morgan M J (1998) Recreational use of MDMA (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* 19: 252–264
- Morgan M J, McFie L, Fleetwood L H, Robinson J A (2002) Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology (Berl)* 159: 294–303
- Morgan M J (2000) MDMA (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology* 141: 30–36
- Otto M W, Bruder G E, Fava M, Delis D C, Quitkin F M, Rosenbaum J F (1994) Norms for depressed patients for the California verbal learning test: associations with depression severity and self-report of cognitive difficulties. *Arch Clin Neuropsychol* 9: 81–88
- Parrott A C (2001) Human psychopharmacology of MDMA (MDMA): a review of 15 years empirical research. *Hum Psychopharmacol Clin Exp* 16: 557–577
- Pope H G, Gruber A J, Hudson J I, Cohane G, Huestis M A, Yurgelun-Todd D (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? *Drug Alcohol Depend* 69: 303–310
- Quednow B B, Jessen F, Kuhn K U, Maier W, Daum I, Wagner M (2006) (a) Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. *J Psychopharmacol* 20: 373–384
- Quednow B B, Kuhn K U, Hoppe C, Westheide J, Maier W, Wagner M (2006) (b) Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA (“Ecstasy”). *Psychopharmacology* 20: 1–14
- Ramier A M, Hecaen H (1970) Respective roles of frontal lesions and lesion lateralization in “verbal fluency” deficiencies. *Rev Neurol* 123: 17–22
- Ramier A M, Hecaen H (1977) Deficits in the “verbal fluency” test in left-handed subject with unilateral hemispheric lesions. *Rev Neurol* 133: 571–574
- Reay J L, Hamilton C, Kennedy D O, Scholey A B (2006) MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgment processes. *J Psychopharmacol* 20: 385–388
- Reneman L, Booij J, Schmand B, Van den Brink W, Gunning B (2000) Memory disturbances in ecstasy users are correlated with an altered brain serotonin neurotransmission. *Psychopharmacology* 148: 322–324
- Ricaurte G A, Forno L S, Wilson M A, DeLanney L E, Irwin I, Moliver M E, Langston J W (1988) (±) 3,4-Methylenedioxymethamphetamine selectively damages central serotonergic neurons in nonhuman primates. *JAMA* 260: 51–55
- Ricaurte G A, Yuan J, McCann U D (2000) (±)-3,4-methylenedioxymethamphetamine (MDMA, “MDMA”)-induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology* 42: 5–10
- Rodgers J (2000) Cognitive performance amongst recreational users of MDMA. *Psychopharmacology* 151: 19–24
- Semple D M, Ebmeier K P, Glabus M F, Ó Carroll R F, Johnsone F C (1999) Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA (“ecstasy”) users. *Br J Psychiatry* 175: 63–69
- Shallice T (1982) Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci* 25: 298: 199–209
- Simon N G, Mattick R P (2002) The impact of regular ecstasy use on memory function. *Addiction* 97: 1523–1529
- Smith R A (1982) Symbol Digit Modalities Test (SDMT): manual (revised). Los Angeles: Western Psychological Services
- Stuss D T, Alexander M P, Shallice T, Picton T W, Binns M A, Macdonald R, Borowiec A, Katz D I (2005) Multiple frontal systems controlling response speed. *Neuropsychologia* 43: 396–417
- Thomasius R, Peterson K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoldt A (2003) Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology* 167: 85–96
- Thomasius R, Zapletalova P, Petersen K, Buchert R, Andresen B, Wartberg L, Nebeling B, Schmoldt A (2006) Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users: the longitudinal perspective. *J Psychopharmacol* 20: 211–225
- Twitchell G R, Davis M R, Kalechstein A D, Newton T F (2001) Neurocognitive impairment in MDMA users [Abstract]. MDMA/Ecstasy research: advances, challenges and future directions. Bethesda, MD
- Verbaten M N (2003) Specific memory deficits in ecstasy users? The results of a meta-analysis. *Hum Psychopharmacol* 18: 281–290
- Verdejo-García A J, Lopez-Tordecillas F, Aguilar de Arcos F, Perez García M (2005) Differential effects of MDMA, cocaine and cannabis use severity on distinctive components of the executive functions in poly-substance users: a multiple regression analysis. *Addict Behav* 30: 89–101
- Verkes R J, Gijsman H J, Pieters M S M, Schoemaker R C, Visser S, Kuijpers M, Pennings J M, Bruin D, Van de Wijngaart G, Van Gerven J M A, Cohen A F (2001) Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology* 153: 196–202
- von Geusau N A, Staelenhoef P, Huizinga M, Snel J, Ridderinkhof K R (2004) Impaired executive function in male MDMA (“MDMA”) users. *Psychopharmacology* 175: 331–341
- Wareing M, Fisk J E, Murphy P N (2000) Working memory deficits in current and previous users of MDMA (“MDMA”). *Br J Psychol* 91: 181–188
- Wareing M, Fisk J E, Murphy P N, Montgomery C (2004) Verbal working memory deficits in current and previous users of MDMA. *Human Psychopharmacol* 19: 225–234 (a)
- Wareing M, Murphy P N, Fisk J E (2004) Visuospatial memory impairments in users of MDMA (“MDMA”). *Psychopharmacology* 173: 391–397 (b)

- Wareing M, Fisk J E, Murphy P N, Montgomery C (2005) Visuo-spatial working memory deficits in current and former users of MDMA ("ecstasy"). *Hum Psychopharmacol* 20: 115–123
- Wechsler D (1997) WAIS-III & WMS-III technical manual. San Antonio: The Psychological Corporation
- Wendt P E, Risberg J (2001) Ethanol reduces rCFB activation of left dorsolateral prefrontal cortex during a verbal fluency task. *Brain Lang* 77: 197–215
- Zakzanis K K, Young D A (2001) Executive function in abstinent MDMA ("ecstasy") users. *Med Sci Monit* 7: 1292–1298