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ORIGINAL INVESTIGATION

Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study

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Abstract
Rationale There is important preclinical evidence of the long-lasting neurotoxic and selective effects of ecstasy (MDMA) on serotonin systems in nonhuman primates. In humans, long-term recreational use of ecstasy has been mainly associated with memory impairment.
Objective The first aim of our study was to evaluate the cognitive and electrophysiological long-term alterations associated with lifetime ecstasy use within a sample of ecstasy polydrug users along a 1-year follow-up. Our second aim was to explore the relationship between specific cognitive functions and P300 (P3) event-related potentials (ERPs) in ecstasy users.
Materials and methods We conducted auditory P3 latency and amplitude and administered a battery of cognitive tests to three groups of subjects: 14 current ecstasy polydrug users, 13 current cannabis users, and 22 controls free of illicit drugs in two evaluations during 1 year.
Results We found significant differences between ecstasy users and controls on cognitive measures of word fluency, processing speed, and memory recognition after 1-year follow-up. We found no significant differences between ecstasy and cannabis users or cannabis users and controls

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on cognitive tests. Lifetime ecstasy use was associated with poorer memory recognition. No group differences were shown on P3 latency or amplitude. Significant correlations emerged between P3 latency and cannabis lifetime use (higher cannabis use was related to faster latency, showing a paradoxical effect) but not with ecstasy exposure.
Conclusions Our findings provide evidence of mild long-term cognitive deficits among ecstasy polydrug users. Both ecstasy use and the dynamic interaction between ecstasy and cannabis effects may account for these deficits. No significant P3 alterations were found in ecstasy users.

Keywords Cognitive impairment · Cannabis · Ecstasy · MDMA · P300 · Event-related potentials · ERP

Introduction

Ecstasy or 3,4-methylenedioxymethamphetamine (MDMA) is a ring-substituted amphetamine derivative, structurally related to the hallucinogenic compound mescaline, which has been tentatively classified as entactogen drug for its main psychoactive profile that distinguishes it from classical hallucinogens and stimulants (Green et al. 2003). Ecstasy and other amphetamine type stimulants are nowadays the second most commonly used illicit drugs after cannabis (OEDT Annual Report 2007; UNODC 2007). Epidemiological surveys refer that almost 8.6 million people have taken ecstasy at least once in their life with Europe accounting approximately for 36% of all ecstasy users worldwide (UNODC 2007). The popularity of ecstasy use may be explained by its highly desirable psychological and behavioral effects, which include loss of inhibitions, euphoric state, reduced anxiety, and emotional openness and empathy (Morgan 2000). Frequent long-term effects related to prolonged ingestion are the development of tolerance, impaired concentration, depression, and increased openness to others (Verheyden et al. 2003).

MDMA affects peripheral and central nervous system functions acting mainly on the serotonergic system, blocking 5-TH reuptake, inducing 5-TH release, and to lesser extent, also causing DA and NE release (Lyles and Cadet 2003). Animal studies evidence that MDMA is neurotoxic (Green et al. 2003) and can induce persistent alterations in the brain serotonin system when given in high doses. In nonhuman primates, sensitivity to its neurotoxic effects has shown to be more pronounced, resulting in higher rates of 5-HT depletion with smaller doses of MDMA, lower 5-HT levels, reduced serotonergic axon density, and persisting abnormal reinnervation patterns for as long as 7 years posttreatment (Hatzidimitriou et al. 1999; Scheffel et al. 1998). Up to date, the generation of free radicals by MDMA metabolites, in addition to the associated oxidative stress and membrane damage, has been pointed as the possible causal agents for long-term MDMA-induced neurodegeneration (Green et al. 2003). Considering the important limitations of the applicability of animal studies to humans (de la Torre and Farre 2004), a relevant question is whether similar changes may occur in humans and their potential impact on cognition. There is growing consensus that MDMA might be selectively neurotoxic to serotonergic modulation in humans (Morgan 2000; Parrott 2006): studies have shown reduced cerebrospinal fluid 5-HIAA levels, significant decrease in 5-HT binding, and altered cerebral glucose metabolism in MDMA users compared to nonusers (Green et al. 2003; Lyles and Cadet 2003; McCann et al. 2005), and there is limited evidence of partial recovery of these alterations (Thomasius et al. 2006).

Neuropsychological studies have revealed a broad range of cognitive deficits associated with MDMA use, including attention, learning, memory, and executive function alterations (Kalechstein et al. 2007; Lamers et al. 2006; Reneman et al. 2006; Zakzanis et al. 2007). Furthermore, most of these studies have demonstrated dose-related cumulative effects of lifetime ecstasy use on cognitive functioning (Morgan 2000; Parrott 2006). In an attempt to assess the durability of these alterations, recent longitudinal studies have observed that ecstasy use-related deficits are persistent but do not deteriorate further with time (Gouzoulis-Mayfrank et al. 2005; Reneman et al. 2006; Thomasius et al. 2006). Furthermore, there is mixed evidence of partial recovery or stability of deficits after prolonged ecstasy abstinence (i.e., the pattern is different across different cases), whereas continuation of ecstasy use is associated with further deterioration of memory functioning (Zakzanis and Campbell 2006).

The observed cognitive deficits are likely related to alterations in other neurobiological indices, such as electrophysiological activity. Several electrophysiological studies have been conducted in ecstasy users attempting to find sensitive measures of central serotonin dysfunction. Studies on dipole source analysis have reported that ecstasy users, compared to controls, have increased intensity dependence of the tangential N1/P2 source activity with higher stimulus intensity (Tuchtenhagen et al. 2000; Croft et al. 2001a). Furthermore, there is an association between the intensity dependence of the auditory-evoked potentials and several measures of ecstasy use (Croft et al. 2001a; Daumann et al. 2006), although it is unclear if this association is stable across time (Daumann et al. 2006). Other electrophysiological measures such as P300 (P3), which has been extensively studied in research on substance use could also be impaired. P3 is considered a measure of cortical activity on complex processing and is normally assessed by means of its two main components: amplitude (μV) and latency (ms), although other subcomponents have also been

proposed (Polich 2007). The P3 is believed to underlie the neural mechanisms required to switch the mental set to make appropriate responses to changing demands. In this complex process, attention and memory interaction seem to play a key role. P3 amplitude has been associated with memory function and with efficient allocation of attentional resources during information processing. On the other hand, P3 latency is considered a measure of stimulus evaluation speed and has been associated with mental processing speed (for review, see Linden 2005; Polich 2007). Research has linked a broad network of brain regions to the P3 generation (Horn et al. 2003; Linden 2005) and there is evidence that P3 components reflect indirect modulating effects from dopamine, acetylcholine, noradrenaline, or serotonin neuromodulators (Hansenne 2000; Polich and Criado 2006).

The P3 component has shown functional significance in a range of substance use disorders, and it has been proposed as a biological marker predisposing to substance use disorders and externalizing psychopathology during adolescence (Iacono et al. 2002; Iacano and McGue 2006; Yoon et al. 2006). However, to date, only few studies have attempted to assess the proposed neurotoxic effects of ecstasy use using P3 brain event-related potentials (Casco et al. 2005; Gamma et al. 2005; Mejias et al. 2005). Casco et al. (2005) found smaller P3 amplitude in heavy and moderate ecstasy users. Furthermore, Mejias et al. (2005) observed longer P3 latencies in MDMA heavy users when detecting target stimuli; the larger latencies were associated with lower levels of cognitive processing. In contrast with previous studies, Gamma et al. (2005) concluded that similar neuroelectric mechanisms were observed in ecstasy polydrug users compared to drug controls after adjusting for relevant confounds, failing to show disturbed brain functioning in MDMA users. Overall, the available evidence is mixed, tentatively suggesting that ecstasy use effects are associated with subtle but significant neuroelectric changes in humans. Nevertheless, these could reflect preexisting traits that might predispose to drug use (Gouzoulis-Mayfrank and Daumann 2006). In this study, we aimed to investigate if the P3 component is specifically associated with ecstasy use and with cognitive deficits linked to ecstasy use. We believe that the P3 may be specifically associated with ecstasy use in light of the evidence of the neuromodulatory effects of ecstasy on serotonin neural function and its dose-related association with memory and attention deficits (i.e., the main cognitive correlates of the P3).

This study compared current ecstasy polydrug users, current cannabis users (both with high–moderate drug use), and drug-naïve controls on cognitive performance and ERP P3 over a period of 12 months. The cannabis group was included because MDMA users very frequently coabuse cannabis, which also have important effects on cognition and electrophysiological activity (Solowij et al. 1995). The neuropsychological battery included tests measuring attention, memory, executive function, and processing speed. P3 response was elicited using an auditory oddball paradigm and was assessed by means of its two main components: latency and amplitude. The aim of this study was to find neuropsychological and electrophysiological evidence related with recreational long-term ecstasy use over the course of 1 year. In addition, we attempted to explore the relationship between P3 main components with specific cognitive domains and lifetime MDMA consumption in the ecstasy group. Based on previous findings, we hypothesized that: (1) Ecstasy polydrug users would have poorer neurocognitive performance compared to cannabis users and drug-free controls; (2) Ecstasy polydrug users would have longer P3 latency and/or reduced P3 amplitude compared to cannabis users and drug-free controls; (3) Cognitive performance and P3 response within the ecstasy group would remain stable or deteriorate over the course of 1 year; (4) Significant associations would emerge between P3 indices and memory function in ecstasy polydrug users.

Materials and methods

Participants

Forty-nine participants were recruited: 14 ecstasy polydrug users, 13 cannabis users, and 22 drug-naïve controls. All subjects were selected randomly from an ongoing 2-year follow-up study whose results are reported elsewhere (de Sola et al., in press). 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 participants were screened in a telephone interview to determine drug history. Subjects with neurological, relevant medical disease, and current psychiatric histories were excluded.

Inclusion criteria for the ecstasy group were: current ecstasy use with a minimum intake of more than five occasions during lifetime and at least one occasion during the last year. For the cannabis group, inclusion criteria were daily cannabis use or having used cannabis more than 25 times during lifetime. A number of exclusion criteria were applied on the different groups. For the cannabis group, current history of regular use of other illegal psychotropic

drugs during the last year, as well as past use of illegal drugs for more than five occasions. For nonusers, 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 users with moderate use of other illicit drugs, being ecstasy the main psychostimulant drug abused.

Test procedure

This study was approved by and conducted in accordance with the local ethics committee (CEIC-IMAS) and with the ethical standards laid down in the Declaration of Helsinki. Upon arrival to the research center (Institut Municipal d'Investigació Mèdica [IMIM]), 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, neuropsychological, and neurophysiological assessments. After completing testing, all subjects were economically compensated with 150 euros for their participation. All participants underwent a neuropsychological assessment session of 90 min. They completed all tasks in a quiet comfortable room. Two neuropsychological evaluations were carried during the 12-month follow-up period: the baseline cognitive testing (t1) and a follow-up assessment 12 months later (t2). After completing the neuropsychological testing, participants got an appointment for the ERP assessment. The electrophysiological study included the following measures in addition to ERPs: blink reflex and accommodation, which will be reported elsewhere. In the current ERP study, two electrophysiological evaluations were carried during the 12-month follow-up period: baseline measures at ERP study onset (t1) and 12 months later (t2). Fifty-three subjects were initially recruited for the ERP study. All subjects had normal audition. From this initial sample, ERPs could not be recorded in two subjects (one from the ecstasy group and one from the cannabis group) due to capillary problems (dreadlocks hair style), whereas two controls were excluded from the first evaluation (t1) due to relevant clinical abnormalities in their somatosensory-evoked potentials. From the 49 subjects that started the ERP study (14 MDMA, 13 cannabis, and 22 drug-naïve controls), after 12 months, 41 participants remained in the study: 11 ecstasy polydrug users (three drop-outs), nine cannabis users (four drop-outs), and 21 nonusers (one drop-out). These eight subjects left the study because they lost their interest and missed the follow-up assessment. The loss of the follow-up examination of these participants is not expected to have a significant impact on cognitive and ERP results since the number of subjects lost to follow-up was small.

Abstinence period was not strictly delimitated, although all participants were requested to observe a minimum 72 h abstinence period. Due to this fact, urine drug screens were carried out by immunoassay (CEDIA, Microgenics) in all subjects prior to neurophysiological and neuropsychological testing in order to avoid acute effects. Drug classes screened included: cannabis, ecstasy, cocaine, and amphetamine/methamphetamine. Drug screens were performed also in hair samples by segmental analysis (last month and previous 6 months) for the same drug classes in order to verify self-reported drug consumption history following methods previously published (Pichini et al. 2006; Pujadas et al. 2003). This procedure allowed us to reliably classify participants into the different subgroups according to the pattern of drug use (ecstasy/cannabis vs. cannabis).

Neuropsychological tests

Premorbid intelligence estimation

Vocabulary subtest (from the WAIS-III, Spanish version; Wechsler 1997a) 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 preexisting 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 colored 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 and Hécaen 1970; Benton and Hamsher 1976) Subjects are asked to generate as many words as

possible in 1 min 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 s. 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. Then the subject must repeat as many words as remembered each time and is required a short-term recall after interference list in a free and cued recall trial. After 20 min, a free and cued recall is 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, 1959) This test involves a copy trial of a complex figure stimulus, followed by a 3-min immediate recall and a 30-min delayed recall where subjects are requested to redraw the memorized complex stimulus. Scores in immediate and delayed recalls provide a good measure of visuospatial memory performance.

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

Letter number sequencing subtest (from the Wechsler Memory Scale III, Wechsler 1997b) 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 afterwards 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.

ERP recordings, stimulation, and procedure

ERPs were recorded with 32 electrodes EEG International System mounted in an electrode Quick-Cap. Electrode placement followed the standard 10#20 International System locations and impedance was kept below 10 K. Recordings were made with a linked ear lobe reference. Amplification parameters were: gain of 30,000, band-pass of 0.1–100 Hz, and low pass filter of 30 Hz. Artifact rejection was performed. Subjects were seated in a comfortable upright chair in a dedicated room with a constant low level of illumination and environmental noise. P300 ERPs (or p3b component) were obtained by averaging the signal. Two grand average ERP P3 components were assessed: P3 latency and P3 amplitude (according to its maximum topographical peak amplitude, central or parietal). P300 component was not only manually identified mainly on the basis of its latency range but also according to its amplitude.

ERPs were evoked using an auditory oddball paradigm, which consisted of a simple discrimination task involving sustained attention by means of two different stimulus: a frequent standard tone and an infrequent "target" one (tone burst and tone pips, respectively) of 90 dB each. Both ears were simultaneously stimulated. Subjects had to memorize and count the infrequent stimuli (target) in two consecutive different runs with ERPs being recorded each time in order to obtain the best latency value from each participant.

Statistical analysis

The comparison of the three groups (ecstasy, cannabis, and control) with respect to the sociodemographic characteristics and drug consumption at baseline was carried out by means of one-way analysis of variance (F test) for continuous variables and Fisher's exact test for categorical variables. To check whether drug consumption at baseline and after 12 months differed significantly, the t test for paired observations was applied. To compare the neuropsychological test results and the P3 components (amplitude and latency) among these groups at baseline (t1), analysis of covariance (ANCOVA) models were used adjusting for gender and premorbid intelligence. Spearman's correlation coefficient was used to measure the association between lifetime drug consumption, neuropsychological test results, and P3 components.

Longitudinal analyses were performed for all tests scores using the linear mixed model, which accounted for the introduced dependency among the data due to repeated measures at baseline and after 12 months. Additionally to the variables considered in the ANCOVA models, the linear mixed models included the variable 'time of evaluation' (baseline and 12 months). In those cases where significant differences were found, post hoc pairwise comparisons between categories of drug consumption were carried out using the Tukey test for repeated measures.

Statistical analyses were performed using the statistical software packages SPSS, version 15.0, and R, in particular,

the R libraries 'nlme' (Pinheiro et al. 2007) and 'multcomp' (Hothorn et al. 2007). Test results were considered to be statistically significant if the resulting p value was less than 0.05. Due to the limited sample size, p values were not corrected for multiple comparisons.

No drug group segmentation in lifetime consumption categories was applied due to the small sample size of both ecstasy and cannabis group. This would have compromised the statistical power and hence the validity of any result. Even though we talk of the ecstasy, cannabis, and control group, we are aware of the fact that the subjects of the first group also consumed cannabis.

Results

Demographic and drug use data

Sociodemographics of the participants are provided in Table 1. No significant differences were observed regarding age or gender among the three groups. There were no significant differences concerning years of education, although the proportion of individuals with a university degree or studying at a university was significantly lower in the ecstasy group (71.4%) compared to the cannabis (75.0%) and control (100%) groups (p=0.015). Significant differences emerged for employment status (p=0.022) with ecstasy group showing a minor rate of students (14.3%) and a mayor percentage of employed (64.3%) and unemployed (21.7%) compared to the controls (with 63.6%, 27.3%, and 9.1%, respectively). Scores on the vocabulary test (WAIS-III) were worse in the ecstasy group (p=0.017) at baseline, although this group difference did not persist after 12 months (p=0.4).

Table 2 displays the drug use patterns from participants, including alcohol, tobacco, cannabis, and ecstasy consumption. At baseline, the ecstasy group showed a mean total ecstasy lifetime consumption of 207.4 tablets (SD=151.0) and of 7.0 (SD=2.4) in terms of years on average, having started first use at the age of 18.0 (SD=4.0). The mean frequency of consumption during the 6 months prior to baseline testing was 6.8 days (SD=3.7). Concerning alcohol consumption, on average, controls showed a significant less frequency of consumption prior to baseline evaluation (days of use in the last 6 months) in comparison to ecstasy users (p=0.019). Groups did not differ significantly in terms of age at onset of alcohol use or duration of use in years. As for smoking, there were more current smokers in the ecstasy group (p=0.005) and again ecstasy users showed an earlier age of onset of use at 14.3 years (SD=1.7; p=0.005) than the other two groups. Comparing ecstasy and cannabis users in terms of cannabis consumption, no significant differences emerged between the groups although the ecstasy group showed a longer duration of use in years and higher daily consumption. The age at onset of use was also very similar between both groups. Frequency of cannabis use in days during the last 6 months was borderline significant (p=0.057), despite ecstasy users showing a more frequent consumption of cannabis with 109.0 days (SD=78.6) than the cannabis group with an average of 44.6 days (SD=65.3).

The consumption of other drugs was recorded but not presented in Table 2. Among the 14 ecstasy users, previous to baseline evaluation, 8 (57.1%) subjects had used cocaine at least once, 8 (57.1%) speed, 2 (14.3%) LSD, 5 (35.7%) ketamine, 4 (28.6%) GHB, 2 (14.3%) sedatives, and 2 (14.3%) heroin. As for the cannabis and control groups, no one had used these drugs before.

No significant changes were observed in drug consumption patterns in both user groups after 12 months compared to baseline intake. That is, no statistical changes emerged in the 11 ecstasy users and nine cannabis users that remained

Table 1 Sociodemographic characteristics at baseline

	Ecstasy (n=14)	Cannabis (n=13)	Control (n=22)	F (df)[a]	p value
Age	25.2 (3.3)	25.1 (2.9)	24.3 (3.0)	0.458 (2)	0.636
Males, n (%)	6 (42.9)	5 (38.5)	7 (31.8)		0.808
Years of education	15.4 (3.1)	16.2 (2.1)	16.8 (2.0)	1.359 (2)	0.268
University degree[b], n (%)	10 (71.4)	9 (75.0)	22 (100)		0.015
Employment status, n (%)					0.022
Student	2 (14.3)	6 (50.0)	14 (63.6)		
Employed	9 (64.3)	6 (50.0)	6 (27.3)		
Unemployed	3 (21.7)		2 (9.1)		
Vocabulary WAIS-III (index score)	12.2 (2.3)	13.9 (2.7)	14.7 (2.3)	4.485 (2)	0.017[c]

Results are presented as the mean (standard deviation) for continuous variables and absolute frequency (relative frequency) for categorical variables. p values result from either F test (age, years of education, WAIS-III) or Fisher's exact test

[a] Value of F statistic (degrees of freedom); only in case of F test

[b] Including students

[c] Significant differences between MDMA users and control subjects

Table 2 Drug use characteristics at baseline

	Ecstasy (n=14)	Cannabis (n=13)	Control (n=22)	F (df)[a]	p value
Alcohol					
Age at onset of use	14.8 (3.5)	15.2 (1.2)	16.5 (1.4)	2.333 (2)	0.111
Duration of use (years)	10.2 (2.7)	8.6 (2.4)	7.9 (2.9)	2.608 (2)	0.087
Total use in the last 6 months (days)	63.0 (43.6)	41.0 (54.4)	22.2 (15.6)	4.438 (2)	0.019[b]
Tobacco					
Current smokers, n (%)	12 (85.7)	5 (38.5)	7 (31.8)		0.005
Age at onset of use	14.3 (1.7)	15.0 (2.2)	18.3 (1.0)	7.834 (2)	0.005 [c]
Duration of use (years)	9.4 (2.4)	10.3 (2.6)	7.3 (1.9)	1.805 (2)	0.201
Cigarettes per day	9.7 (7.7)	7.1 (8.1)	3.6 (3.2)	1.774 (2)	0.194
Cannabis					
Age at onset of use	16.2 (3.1)	17.0 (1.3)		0.577 (1)	0.457
Duration of use (years)	8.8 (2.0)	7.0 (2.6)		3.363 (1)	0.082
Total use in the last 6 months (days)	109.0 (78.6)	44.6 (65.3)		4.119 (1)	0.057
Joints per day	1.7 (1.1)	1.1 (1.1)		2.026 (1)	0.167
Ecstasy					
Age at onset of use	18.0 (4.0)				
Duration of use (years)	7.0 (2.4)				
Lifetime consumption (tablets)	207.4 (151.0)				
Total consumption in the last 6 months (days)	6.8 (3.7)				

Results are presented as the mean (standard deviation). p values result from either t or F test. Proportions of current smokers are compared by means of Fisher's exact test

[a] Value of F/t statistic (degrees of freedom); only in the case of F/t test

[b] Significant differences among ecstasy users and control subjects

[c] Age at onset significantly higher among control subjects

in the study concerning ecstasy, cannabis, tobacco, and alcohol consumption. Only the control group showed a significant change with an increase in the alcohol frequency of use (22.83 vs. 44.33 days during the past 6 months) between baseline and 12-month follow-up (p=0.05). At the 12-month follow-up, reported consumption of other drugs during the 1-year interval was the following: among the 11 ecstasy users, 6 (54.5%) subjects had used cocaine at least once, 6 (54.5%) speed, 1 (9.1%) LSD, 2 (18.2%) ketamine, 4 (36.4%) GHB, 1 (9.1%) sedatives, and 2 (18.2%) heroin. As for both other groups, no one had used these drugs during the 12 months.

Neurocognitive performance: cross-sectional and longitudinal analysis

The results of the neuropsychological tests for the groups are shown in Table 3. ANCOVA revealed no significant overall group differences at baseline with respect to neuropsychological performance. All three groups performed within the normal range at baseline according to published tests norms, although ecstasy users showed poorer results compared to cannabis and control groups in measures of attention, memory, and executive functions, but did not differ at a significant level.

The results of the longitudinal analysis are also shown in Table 3. After 1 year of follow-up, scores among all three groups remained within the normal range. However, an overall trend to poorer cognitive functioning is observed in ecstasy users. Linear mixed models revealed significant overall group differences in neuropsychological performance. Pairwise comparisons indicate that these differences are found between ecstasy users and controls but not between ecstasy and cannabis groups. Ecstasy users showed significantly poorer results than drug-naïve controls with respect to semantic word fluency (p=0.021), verbal memory recognition (p=0.018), and information processing speed (p=0.048). Differences were also observed in verbal memory delayed recall, although this variable failed to reach statistical significance (p=0.055).

Univariate correlation analyses were carried out between cognitive measures with ecstasy and cannabis intake (lifetime consumption and recent frequency of use) in order to explore a link between these variables. Only a negative correlation emerged between lifetime ecstasy use with performance in verbal memory recognition (p=0.027) but not with cannabis exposure, suggesting a poorer performance in verbal recognition associated to lifetime intake of ecstasy tablets.

Electrophysiological P3 measures: cross-sectional and longitudinal analysis

The regression models applied did not reveal significant overall group differences for P3 amplitude or P3 latency,

Table 3 Neuropsychological test scores as a function of drug consumption group

	Drug consumption group									
	Baseline evaluation					Follow-up evaluation				
	Ecstasy	Cannabis	Nonusers	F (df)[a]	p value	Ecstasy	Cannabis	Nonusers	F (df)[a]	p value
Attention										
CalCAP: simple RT	349.3 (59.3)	318.7 (51.2)	323.0 (50.2)	0.591 (2)	0.559	345.5 (72.2)	331.4 (45.2)	336.6 (49.2)	0.787 (2)	0.462
CalCAP: choice RT-digits	421.9 (53.9)	389.8 (32.1)	396.5 (39.6)	1.862 (2)	0.169	414.8 (52.9)	387.0 (43.0)	402.4 (37.0)	1.669 (2)	0.201
CalCAP: sequential RT2	564.6 (90.3)	509.0 (116.3)	507.1 (95.0)	0.873 (2)	0.426	559.8 (82.8)	495.1 (98.4)	507.3 (118.8)	1.710 (2)	0.194
Working memory										
Corsi block visual span backwards	8.8 (0.8)	8.4 (1.2)	9.1 (1.5)	0.627 (2)	0.539	8.9 (1.1)	9.8 (1.8)	9.4 (1.3)	0.446 (2)	0.643
Letter number sequencing	12.8 (1.9)	12.2 (1.6)	12.7 (1.8)	0.362 (2)	0.698	13.5 (4.1)	12.1 (1.5)	13.2 (2.5)	0.377 (2)	0.688
Memory										
CVLT: total A1–A5	57.5 (7.7)	58.0 (8.7)	61.6 (7.1)	0.347 (2)	0.710	61.9 (6.9)	63.8 (5.8)	64.9 (6.6)	0.620 (2)	0.543
CVLT: immediate recall	13.4 (2.1)	13.7 (1.1)	13.8 (1.9)	0.026 (2)	0.974	13.4 (2.3)	15.3 (1.0)	14.9 (1.6)	1.369 (2)	0.266
CVLT: delayed recall	11.9 (4.8)	14.2 (1.4)	14.3 (1.5)	1.887 (2)	0.168	14.2 (2.3)	15.6 (0.5)	15.2 (1.4)	3.122 (2)	0.055
CVLT: total recognition	15.2 (1.0)	15.1 (1.4)	15.7 (0.7)	1.018 (2)	0.372	15.0 (1.2)	15.8 (0.5)	15.9 (0.2)	4.431 (2)	0.018[b]
ROCFT: immediate recall	24.2 (5.4)	25.4 (4.7)	28.1 (4.2)	1.319 (2)	0.279	25.7 (3.4)	28.5 (2.2)	27.2 (4.6)	1.657 (2)	0.204
ROCFT: delayed recall	23.9 (5.6)	26.9 (4.4)	27.1 (3.8)	0.797 (2)	0.458	25.2 (2.4)	28.3 (4.1)	26.8 (5.0)	2.086 (2)	0.138
Executive functions										
Semantic word fluency	23.9 (6.2)	27.3 (5.4)	27.7 (5.5)	0.958 (2)	0.393	22.8 (4.8)	24.9 (5.0)	28.6 (5.2)	4.259 (2)	0.021[b]
ToL: total movements	66.3 (7.1)	74.9 (9.3)	70.6 (11.1)	2.128 (2)	0.133	64.6 (6.5)	64.0 (5.7)	64.9 (9.9)	2.222 (2)	0.122
ToL: initiation time	53.0 (25.4)	49.4 (26.2)	52.4 (24.2)	0.122 (2)	0.886	79.8 (29.0)	72.0 (28.7)	58.7 (34.1)	0.079 (2)	0.924
Mental processing speed										
SDMT: total correct	64.8 (12.8)	70.6 (13.1)	72.3 (8.6)	0.253 (2)	0.778	64.5 (8.9)	71.4 (13.9)	75.0 (8.3)	3.287 (2)	0.048[b]
SDMT: total incorrect	0.8 (1.1)	0.7 (1.3)	0.5 (1.1)	0.078 (2)	0.925	1.0 (1.2)	0.8 (1.2)	0.4 (0.7)	1.022 (2)	0.369
P300										
LP300	306.8 (18.8)	306.3 (20.5)	301.4 (18.7)	0.928 (2)	0.404	311.6 (15.0)	308.8 (20.4)	306.0 (20.4)	0.353 (2)	0.705
AP300	8.1 (2.4)	9.5 (2.7)	10.3 (2.5)	1.155 (2)	0.325	8.8 (2.7)	10.1 (2.8)	9.9 (3.1)	0.755 (2)	0.477

Results are presented as the mean (standard deviation). p values result from ANCOVA models (baseline evaluation) adjusting for gender and premorbid intelligence and linear mixed models (baseline until follow-up) adjusting for gender, evaluation time (baseline, follow-up), and premorbid intelligence, respectively

[a] Value of F statistic (degrees of freedom)

[b] Significant differences between ecstasy users and control subjects (p=0.008 [CVLT: total recognition]; p=0.01 [semantic word fluency] and p=0.05 [SDMT]); differences between the cannabis group and both MDMA users and controls are not significant (p>0.25 in all cases)

neither at baseline nor after 12 months of follow-up study. In accordance with the neuropsychological findings, all three groups had indices within the normal range for both P3 components.

Correlation of electrophysiological measures with neurocognitive measures: baseline and follow-up

First, univariate correlation analyses were carried out within ecstasy users to assess the relationship between the P3 main components and neurocognitive functions in this group. Second, we conducted correlation analyses between the P3 main components and ecstasy and cannabis lifetime intake to explore the link between these variables. Here, we used the ecstasy group for the ecstasy use–P3 correlations and both the ecstasy and cannabis groups for the cannabis use–P3 correlations.

Analyses between P3 main components and cognitive functions in ecstasy users revealed significant links with P3 latency but not with amplitude. Quite strong associations were found at baseline between P3 latency and verbal working memory, word fluency, divided attention, and verbal memory recognition. Negative correlations emerged between P3 latency and verbal working memory (r=−0.674, p=0.016) and semantic word fluency (r=-0.629, p=0.028), whereas positive associations were found with divided attention (r=0.732, p=0.007) and memory recognition for verbal information (r=0.657, p=0.039), both in the unexpected direction. Therefore, improved neural processing speed would be related to a higher achievement in executive functions, whereas increased processing timing would be associated with higher efficiency in divided attention and memory recognition. After 12 months of follow-up, no significant correlations were found.

Univariate correlation analyses carried out between drug use and P3 response failed to reveal significant associations between ecstasy consumption and P3 main components at baseline or after 12 months. Despite this fact, significant associations were found for lifetime cannabis use and P3 latency at baseline (r=−0.464, p=0.003) and with borderline significance for the follow-up period (r=−0.322, p=0.052). These associations emerged with an unexpected trend, relating greater long-term cannabis exposure with improved neural processing speed. Nonetheless, a marginally significant correlation between P3 amplitude and cannabis use was also observed at baseline (r=−0.301, p=0.059), linking higher lifetime cannabis use with lower P3 amplitude.

Discussion

The aims of the study were (1) to assess changes in cognition and P3 response in current ecstasy polydrug users, current cannabis users, and drug-naïve controls over the course of 1 year and (2) to explore the associations between P3 indices, cognitive performance, and lifetime ecstasy use. Results showed significant differences between ecstasy users and drug-free controls on neurocognitive measures of semantic word fluency, processing speed, and verbal memory recognition at 1-year follow-up. These results remained significant after statistically controlling for gender and premorbid intelligence. Furthermore, lifetime ecstasy use was negatively correlated with performance in verbal memory recognition. However, we found no significant differences between the ecstasy and cannabis groups, so that the observed effects cannot be entirely attributed to ecstasy use. Ecstasy polydrug users showed longer P3 latency and reduced P3 amplitude than both other groups, remaining stable along the whole study, but these differences were negligible and nonsignificant. According to the second aim of the study, significant correlations were found within the ecstasy group for P3 latency with working memory, memory recognition, word fluency, and divided attention. We found no correlations between P3 amplitude and cognition in ecstasy users. P3 main components were related to cannabis cumulative use but not to ecstasy consumption.

These results are consistent with extensive evidence of poorer cognitive performance in tests of processing speed, memory, and executive functions associated with heavy ecstasy use. Impaired recognition and delayed recall are among the more common memory deficits reported in ecstasy users (Quednow et al. 2006) with lifetime use being significantly associated with poorer verbal memory performance (Parrott 2006). Moreover, long-term prospective memory problems are also self-reported by heavy and moderate ecstasy users related with the extent of ecstasy use (Rodgers et al. 2003) and with nondrug factors such as prolonged dancing or overheat self-perception (Parrott et al. 2006). In addition, word fluency and syllogistic reasoning deficits indicate that ecstasy polydrug use is associated with impaired higher-order executive functioning, particularly related to poorer access to long-term memory (Fox et al. 2002; Montgomery et al. 2005) and working memory processes (Fisk et al. 2005), respectively. Slower processing speed in ecstasy users has been also reported in previous studies (Croft et al. 2001b; Wareing et al. 2007) with negative implications over several executive functions. This latter deficit has been more closely related to MDMA use than cannabis intake (Croft et al. 2001b). The fact that no significant group effect was found at baseline (t1) may well respond to the reduced sample size, since our previous study in a larger sample of 94 participants (de Sola et al., in press) showed fluency deficits in ecstasy users at baseline. In this previous study, we also showed that ecstasy users performed poorer than controls on tests of word fluency,

working memory, and processing speed at 2-year follow-up. Furthermore, there was a significant association between ecstasy lifetime use and episodic memory, which was also observed in the present study. Although we are aware that the limited sample size is an important limitation of this study, results from both studies agree to demonstrate subtle cognitive deficits in ecstasy users that remain static or further deteriorate with time. The fact that cognitive alterations were observable after 1 and 2 years in our two studies is consistent with previous findings, indicating that cognitive alterations tend to persist (Gouzoulis-Mayfrank et al. 2005; Reneman et al. 2006; Thomasius et al. 2006) or further deteriorate across time (Zakzanis and Young 2001; Zakzanis and Campbell 2006). However, we should note that these alterations were subtle and subclinical, since ecstasy users performed all tests within the normal range.

P3 ERPs elicited in all three groups fell within the normal range across the whole study, although ecstasy polydrug users showed a nonsignificant pattern of reduced P3 amplitude and increased latency when compared with the control groups. Thus, the present findings failed to reflect neurotoxic changes induced by prolonged recreational ecstasy use on this neurophysiological index. These results are consistent with those of Gamma et al. (2005) who failed to show significant P3 differences between ecstasy users and drug-free controls after covariating for relevant confounding variables (age, education, and cannabis use), which were also controlled in the present study. However, our results stand in contrast with those of Casco et al. (2005) who found reduced P3 amplitude in ecstasy users and Mejias et al. (2005) who found delayed latencies for the P3b component in their ecstasy group. Several differences related to the ecstasy group characteristics and task design could account for discrepancies between both studies. Noteworthy, Casco et al. examined ecstasy users abstinent for at least 6 months, whereas Mejías et al. assessed a mixed group including participants that were actually taking the drug and participants abstinent for an undetermined period of time. In contrast, the present study analyzed performance in current users with minimum controlled abstinence duration of 72 h. Furthermore, we tried to account for polydrug use incorporating a cannabis control group and to carefully assess cooccurring drug use using detailed toxicological analyses, which is an asset contributing to supply more reliable data about the role of ecstasy use. Thus, our results are more representative of nonacute residual or long-term effects of ecstasy polydrug use. Furthermore, the type of task used was markedly different among these three studies. Casco et al. used a visual attention discrimination task and found robust effects for the frontal and especially the occipital waves, which were not recorded in the present study. In contrast, Mejias et al. used a more ecologically sound visual test containing emotional facial expressions, which may introduce factors related to emotional appraisal in the P3 evaluation. Nonetheless, more studies are warranted to consistently establish the electrophysiological correlates of ecstasy use. Specifically, although the oddball task is a sound index of attentional orientation, it would be interesting to further explore ERP components during memory or executive function tasks that are impaired at the cognitive level.

Another related aim of the study was to explore the relationship between P3 cortical activity and specific cognitive domains in ecstasy users. Significant associations emerged between P3 latency and working memory, verbal memory recognition, word fluency, and attention with a quite strong power of association. No association was found with P3 amplitude. Several studies support the negative relationship between P3 latency and cognitive performance, reporting faster P3 latency in the prefrontal cortex related to better working memory (Hansell et al. 2005) or increasing P3 latency linked to normal ageing and slow down of cognitive processing (Knott et al. 2004). Therefore, P3 latency as a measure of cognitive efficiency and mental processing speed (Polich and Criado 2006; Polich 2007) would improve memory subprocesses such as short maintenance and updating and may account for a major efficiency in this domain. This notion could certainly be made extensive to the association relating P3 latency with word fluency due to the finding that probably faster neural processing timing (required to evaluate a target stimuli) may enhance other interconnected processes such as access to long-term memory storage. Consistent with this view, working memory, semantic word fluency, and P3 latency would be related measures. In contrast, association between P3 latency with memory recognition emerged but not with the expected trend (faster latency was associated with poorer recognition). This finding is counterintuitive and may reflect a statistical artifact. Otherwise, this could tentatively explain the poorer memory recognition of the ecstasy group. In that case, it would reflect poorer cognitive efficiency associated with increased neural processing speed that leads to inaccurate endorsement of false alarms (a "lure" effect). Divided attention was also found to be positively associated with increased processing timing in ecstasy group. Again, this finding could respond to the engagement of compensatory attentional processes that could slow down mental processing speed. Overall, the relationships shown between P3 latency, memory, attention, and executive functions could partly respond to the widespread distribution of brain areas involved both in P3 generation (Wager and Smith 2003; Nebel et al. 2005; Baldo et al. 2006) and these cognitive abilities. As such, the latter associations may tentatively suggest that these specific cognitive domains and P3 ERPs could be mediated by common neural substrates.

We found no correlation between the P3 main components and lifetime ecstasy use, similar to Gamma et al. (2005). In contrast, correlation analyses highlighted the contribution of cannabis long-term cumulative consumption (number of joints) to P3 latency, although the direction of the relationship was unexpected: higher use, faster latency. This finding indicates that cannabis use is not an overriding negative factor for P3 integrity in this sample of ecstasy and cannabis users. In fact, previous studies indicate that the couse of cannabis and ecstasy may result on dynamic or synergistic effects of both drugs. It has been suggested that cannabis couse may attenuate ecstasy-related neurotoxicity due to cannabinoids' antioxidant and hypothermic properties. This hypothesis is supported by the fact that the degree of "neurotoxicity" observed in ecstasy polydrug users in PET and SPECT studies is often weaker to that predicted by animal studies with pure MDMA treatment (Parrott et al. 2007). Nevertheless, neuroprotective effects appear to be only partial; protective doses seem much higher than recreational doses and protective effects are still unknown in cannabinoid-tolerant animals and, therefore, in frequent cannabis users (Sala and Braida 2005). Turning back to cognition, the majority of studies report that couse of both drugs contribute to cognitive impairment, although the nature of this association remains unclear (Parrott et al. 2007). More research is thus warranted to clarify this issue.

Besides the mentioned methodological limitations, there are further factors inherent to this field of research in humans which allow alternative explanations of our findings, such as inaccurate retrospective self-reports of ecstasy use or uncertainties related to the precise chemical composition of ecstasy tablets. Reduced arousal and restlessness associated with ecstasy user's lifestyle and heavy cannabis use withdrawal can also affect cognitive and ERP measures. In this sense, the 72-h abstinence period could have not, being in certain cases, long enough to rule out residual effects of the substances used. Moreover, our study is retrospective, therefore, we cannot rule out the possibility of premorbid group differences in intellectual skills or cognitive and brain functioning. However, IQ cannot explain the poorer cognitive performance reported in ecstasy users, since differences with healthy controls were not clinically relevant and became nonsignificant at the end of the study, and group differences remained significant after adjusting for this variable. Possible directions for future research on long-term ecstasy effects could focus on prospective designs with large cohorts of young nonusers belonging to risk groups of drug abuse, during wide life periods (Gouzoulis-Mayfrank and Daumann 2006). This kind of study would supply more reliable data on several key issues: the neurotoxic impact on developmental stages, behavioral and cognitive changes associated to drug history, drug interactions, probable trend of chronic impairment or reversibility in case of abstinence, and functional impact on every daily life.

In conclusion, our results demonstrate several cognitive subclinical deficits in chronic ecstasy polydrug users than drug-naive controls after 1 year relating to memory, executive functions, and information processing speed. Findings remain significant after adjusting for gender and IQ. Cognitive deficits show a stable but not progressive trend after 12 months in ecstasy users. The three groups did no differ significantly in P3 response, suggesting no impairment in neuroelectric brain activation in ecstasy users. This finding was further supported by the fact that P3 response remained stable and within the normal range along the whole study period, although ecstasy users showed consistently poorer latency and amplitude. Ecstasy cumulative use was related to lower performance in memory recognition whereas cannabis consumption was linked to P3 latency. The overall findings may be explained by ecstasy or ecstasy/cannabis-induced neurotoxic impairment on cognitive function, but not in brain activation, although preexisting cognitive differences cannot be ruled out. The present group differences seem to have limited consequences insofar as poorer cognitive performance by ecstasy users suggests subclinical impairment due to the fact that the results keep within standard norms and because neuroelectric brain activation is similar in all three groups with measures standing within the normal range.

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Conflict of interests The authors declare the absence of conflicts of interest.

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