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ORIGINAL INVESTIGATION

Event related potential (ERP) evidence for selective impairment of verbal recollection in abstinent recreational methylenedioxymethamphetamine ("Ecstasy")/polydrug users

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Abstract
Objectives Ecstasy is a recreational drug whose active ingredient, 3,4-methylenedioxymethamphetamine (MDMA), acts predominantly on the serotonergic system. Although MDMA is known to be neurotoxic in animals, the long-term effects of recreational Ecstasy use in humans remain controversial but one commonly reported consequence is mild cognitive impairment particularly affecting verbal episodic memory. Although event-related potentials (ERPs) have made significant contributions to our understanding of human memory processes, until now they have not been applied to study the long-term effects of Ecstasy. The aim of this study was to examine the effects of past Ecstasy use on recognition memory for both verbal and non-verbal stimuli using ERPs.
Methods We compared the ERPs of 15 Ecstasy/polydrug users with those of 14 cannabis users and 13 non-illicit drug users as controls.
Results Despite equivalent memory performance, Ecstasy/polydrug users showed an attenuated late positivity over left parietal scalp sites, a component associated with the specific memory process of recollection.
Conlusions This effect was only found in the word recognition task which is consistent with evidence that left hemisphere cognitive functions are disproportionately affected by Ecstasy, probably because the serotonergic system is laterally asymmetrical. Experimentally, decreasing central serotonergic activity through acute tryptophan depletion also selectively impairs recollection, and this too suggests the importance of the serotonergic system. Overall, our results suggest that Ecstasy users, who also use a wide range of other drugs, show a durable abnormality in a specific ERP component thought to be associated with recollection.

Keywords MDMA · Ecstasy · Memory · Event-related potentials · Serotonin

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Introduction

Ecstasy is the popular name for a synthetic recreational drug whose putative active constituent, 3,4-methylenedioxymethamphetamine (MDMA), is closely related to amphetamine and mescaline. MDMA acts as a releasing agent for the monoamines but, unlike most other psychostimulants, its effects are predominantly serotonergic rather than dopaminergic. It is toxic to serotonergic neurons in animals (Hatzidimitriou et al. 1999; Green et al. 2003) and has adverse long-term health effects on human users including increased rates of neuropsychological impairment (Rogers et al. 2009).

Ecstasy/polydrug users report higher rates of memory problems than Ecstasy-naive controls (Parrott et al. 2002). Users complain of prospective rather than retrospective memory problems (Rodgers et al. 2006) hence they may forget to carry out future intentions, such as meeting someone at a prearranged time or fail to post a letter. These subjective complaints have been confirmed by objective

neuropsychological testing and several quantitative reviews of the literature have all concluded that Ecstasy/polydrug users have poorer episodic memories than Ecstasy-naive controls or Ecstasy-naive polydrug users (Kalechstein et al. 2007; Laws and Kokkalis 2007; Zakzanis et al. 2007; Rogers et al. 2009; Nulsen et al. 2010).

Despite this, relatively little is known about which specific aspects of memory are most affected. One way to determine this would be to use neurophysiological measures of brain function such as event-related potentials (ERPs) that are useful in fractionating cognitive processes. However, although the effects of Ecstasy have been investigated frequently using ERPs, most studies have focused on simple visual or auditory stimuli (Croft et al. 2001). This is surprising because memory, particularly verbal recognition memory, has been studied extremely extensively using ERPs. For example, ERPs have been used to confirm Mandler's (1980) speculation that recognition memory consists of at least two different processes: familiarity and recollection. Familiarity is the experience you have when on meeting someone, you have the strong feeling that you have met them before, but are unable to recollect who they are or where you met them. Recollection is the experience you have when you remember all those contextual details. Familiarity and recollection have distinctive correlates in the ERP that have been experimentally dissociated (Rugg and Curran 2007). For verbal material, familiarity is associated with greater positivity for repeated words over frontal scalp sites between 350-500 ms whereas recollection is associated with greater positivity over left parietal sites from 400–800 ms. Familiarity appears to consist of multiple processes, including priming, but recollection appears to be a relatively 'pure' cognitive process. Based on evidence from behavioural studies, we hypothesised that Ecstasy/polydrug users would show attenuation in their memory-related ERPs but we did not have a clear expectation as to whether the recollection or familiarity components, or both, would be affected. The aim of this study, therefore, was to characterize the nature of the effects of Ecstasy on recognition memory using ERPs to determine whether it affects both recollection and familiarity and verbal and non-verbal material.

Method

Participants

The study design was approved by the Swansea University Department of Psychology Ethical Committee and all participants gave their written informed consent. Participants were recruited from the university's subject pool by advertisement and by snowball sampling referral. Recruitment was categorized into three groups: a control group, a cannabis group, and an Ecstasy/polydrug group. The control group was naive to Ecstasy use and had not used any other drug more than ten times. The cannabis group consisted of individuals who had used cannabis more than 50 times but had not used Ecstasy more than ten times. The Ecstasy/polydrug group had used cannabis and Ecstasy more than 50 times each. All participants reported having been abstinent from illicit recreational drug use for at least 10 days prior to testing. Participants were requested not to drink in the 24 h before testing. Smoking was permitted on the day of testing but was not allowed during the assessment period.

Materials

The drug use history of each participant was measured using the University of East London Recreational Drug Use Questionnaire (UEL–RDUQ) (Parrott et al. 2001) that listed the most commonly used illicit drugs and asked participants to indicate whether they had ever taken that particular substance and if so, how many times they had taken it. Subjective measures of well-being and cognitive function were measured using the Uplifts, Hassles, Stressors, Cognitive Failures, and Memory Problems Questionnaire (UHSCMQ) (Parrott and Kaye 1999), the Prospective and Retrospective Memory Questionnaire (PRMQ) (Smith et al. 2000), and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983). Memory performance was measured using a continuous recognition test for words and faces (Burgess and Gruzelier 2000). The two recognition memory tasks were identical except for the different type of stimuli, verbal (words) and non-verbal (faces), and were designed to preferentially activate the left and right hemispheres, respectively (Burgess and Gruzelier 1997) (Fig. 1). Performance was measured using Cohen's kappa to give a percentage correct score, adjusted for guessing.

Equipment

Electroencephalography (EEG) was recorded using a 128-channel BioSemi dense array EEG system with active electrodes and a virtual reference. Sampling rate was 512 Hz and recordings were made with a high-pass filter of 0.1 Hz and a low-pass filter of 100 Hz.

Procedure

Once participants had given their written informed consent, they were seated in a quiet, dimly lit room and instructed to relax, avoid movement, and to keep alert. The EEG

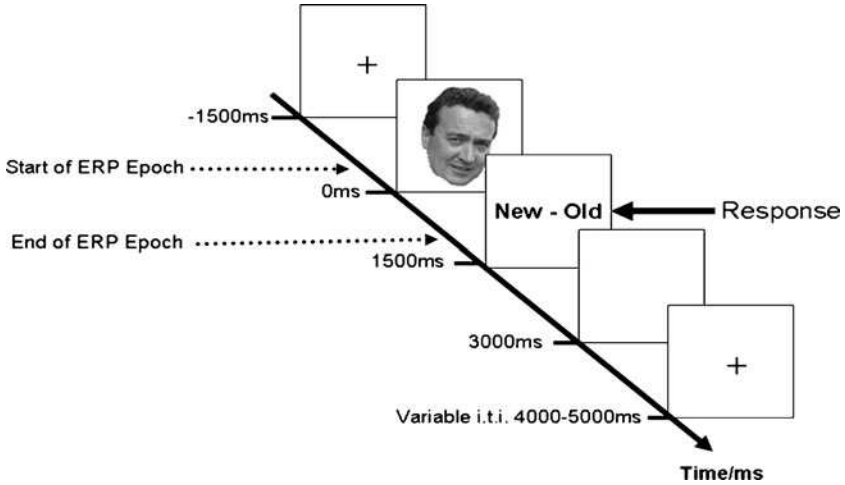

Fig. 1 The sequence of events for the continuous recognition memory tasks for words and faces. Each memory test consisted of 90 trials in which the participants were required to indicate whether they had seen the stimulus (word or face) for the first time in the sequence (i.e., 'New') or whether it was a repeat (i.e., 'Old'). There was an average delay of ten trials (~60 s) between presentations, within a range of 8–12 trials. The test included 40 stimuli that were repeated and ten filler items that were shown only once. Each trial consisted of three phases: a baseline fixation point, a memory stimulus and a response cue, each being presented for 1,500 ms. The response cue consisted of the words 'New–Old' or 'Old–New', randomly varied between trials. Participants were required to press either the left or the right key to correspond with the side on which the 'New' or 'Old' cue was presented. The inter-trial interval varied between 1,000 and 2,000 ms and consisted of a blank screen. ERPs were based on the average EEG recorded from 50 ms before to 1,200 ms after the onset of the stimulus before the participant made any motor response

equipment was attached to the participant's scalp, while they completed the UEL–RDUQ. Initial EEG recording commenced with 2 min of recording in a passive resting state with the eyes open followed by a further 2 min with the eyes closed. This was followed by the administration of the HADS before the first of the memory tests, the order of which was randomized between participants. After the first memory test, participants completed the UHSCMQ before starting the second memory test. After both memory tests, participants completed the PRMQ and EEG recording concluded with a further 2 min of eyes open and eyes closed at rest.

EEG preparation

EEG was analyzed using BESA v5.1.8. All recordings were visually analyzed and any channels judged to be bad were replaced by nearest neighbour interpolation and all data were EOG-corrected using the standard BESA PCA-based algorithm. EEG was segmented into epochs from −50 to +1,200 ms from the time of the stimulus onset, and all epochs were baseline corrected −50 ms to 0 ms. Any epochs that included values outside the range ±120 μV were excluded and all data were converted to common average reference. Epochs were time-averaged by stimulus type so that ERPs for correctly identified new stimuli ('true new') and correctly identified repeats ('true old') for both words and faces were generated for each individual. ERPs based on fewer than ten epochs were not included in the subsequent analysis.

Statistical analysis

Comparison between groups on continuous measures with a near-normal distribution was by ANOVA with post hoc comparisons made using Tukey's honestly significant difference test (Tukey's HSD). Where the data deviated substantially from the normal, the nonparametric Kruskal–Wallis or Mann–Whitney *U* tests were used instead.

ERPs for the 'true new' and 'true old' stimuli were analyzed using Partial Least Squares analysis (PLS) (Lobaugh et al. 2001). PLS is a method for determining whether the values of a multivariate dataset are systematically affected by the experimental manipulation, in this case, repetition of the stimuli, i.e., 'true new' vs. 'true old'. It does this by identifying the linear combination of data (i.e., a latent variable) that maximally co-varies with each component of the experimental design and then determines if this effect is greater than would be expected by chance. PLS can be used to establish: (a) whether there is a significant latent variable (i.e., does the experimental manipulation have an effect?), (b) what the contribution of each part of the data set to determine the effect is (i.e., a weighting, in the case of ERPs, for each channel and each time point, referred to as 'saliences'), and (c) what contribution each individual subject makes to the latent variable (i.e., latent variable scores). PLS is ideally suited to the statistical analysis of ERP data because it can be used without restricting the analysis to predetermined areas/times of interest. It uses

all the data in the time series and controls for the type 1 error. The statistical significance of the latent variables was estimated using permutation testing with 1,000 permutations, and the reliability of the saliences (i.e., where and when the latent variable was significantly greater than zero) was established using bootstrapping with 1,000 resamplings.

Although PLS will readily identify ERP differences between experimental conditions, where there is more than one factor at play (e.g., familiarity and recollection), these will not be separately identified but combined into a single latent variable. Therefore, in order to separate the familiarity and recollection components, the saliences of the latent variable were subjected to multivariate decomposition using singular value decomposition (SVD) followed by rotation of the extracted components to Promax criteria. For each component extracted, there was a component topography indicating the contribution of each channel, a component time series that showed how it changed over time and component scores that showed each individual subject's contribution to that component.

Results

Participants

Sixteen participants were recruited to each of three groups: drug-naive controls, cannabis users, and Ecstasy/polydrug users. Three participants were excluded because insufficient artifact-free EEG was obtained and two (both controls) because they scored at chance levels on the memory tests. One member of the cannabis group, who reported having used amphetamines more than 100 times, was excluded. All subsequent data are reported for this reduced sample that consisted of 13 controls (seven women), 14 cannabis users (seven women), and 15 Ecstasy/polydrug users (eight women). All participants were aged between 19 and 31 and there were no statistically significant differences in age between the groups (Table 1).

Recreational drug use

The lifetime use and frequency of use of the most common recreational drugs for the three groups is given in Table 2. The cannabis and the Ecstasy/polydrug groups did not differ significantly in their cannabis use (Mann–Whitney, z=-1.34, p<0.18). The groups differed in their alcohol consumption (Kruskal–Wallis $\chi^2_{df=2}$=7.10, p<0.029) with the control group drinking significantly less than the cannabis group (post hoc Mann–Whitney, z=−2.99, p< 0.002). The control group was largely drug-naive and the cannabis group too reported only infrequent uses of drugs other than cannabis. However, the Ecstasy users could be accurately described as polydrug users and the majority reported multiple uses of amphetamine, cocaine, magic mushrooms, poppers, ketamine, lysergic acid diethylamide (LSD), and benzodiazepines or barbiturates.

Well-being and cognitive functioning

There were no differences between the groups on any of the self-report measures of well-being or cognitive functioning. Nor were there any difference between groups in objective

Table 1 Age, questionnaire scores and recognition memory performance by group

		Controls (n=13) Mean (s.d.)	Cannabis (n=14) Mean (s.d.)	Ecstasy/ polydrug (n=15) Mean (s.d.)	ANOVA	
					$F_{(2,39)}$	p value
Age	22.3 (3.7)	21.9 (3.1)	24.1 (3.6)	1.73	0.19	
HADS	Anxiety	6.5 (3.2)	7.4 (3.3)	7.3 (4.6)	0.21	0.81
	Depression	2.6 (1.9)	2.4 (2.2)	3.3 (3.4)	0.41	0.67
UHSCMQ	Uplifts	11.8 (1.8)	11.4 (2.7)	1.2.2 (1.9)	0.45	0.64
	Hassles	7.6 (2.5)	7.4 (2.8)	7.4 (2.9)	0.003	0.97
	Stress	7.2 (3.1)	6.4 (3.5)	5.9 (3.2)	0.55	0.58
	Cognitive failures	7.8 (3.3)	7.4 (3.3)	7.7 (3.0)	0.07	0.93
	Memory problems	6.2 (2.8)	7.4 (3.0)	7.8 (3.5)	0.94	0.40
PRMQ	Prospective memory problems	19.9 (4.0)	22.1 (5.8)	24.6 (6.3)	2.53	0.09
	Retrospective memory problems	18.6 (3.2)	17.9 (4.0)	19.8 (5.2)	0.76	0.47
Recognition memory (% adjusted for guessing)	Faces	61.1 (13.8)	65.7 (10.6)	55.4 (20.1)	1.61	0.21
	Words	69.5 (14.5)	73.1 (12.3)	65.7 (18.8)	0.83	0.44

ANOVA analysis of variance, *HADS* Hospital Anxiety and Depression Scale, *UHSCMQ* Uplifts, Hassles, Stressors, Cognitive Failures, and Memory Problems Questionnaire, *PRMQ* Prospective and Retrospective Memory Questionnaire

Table 2 Recreational drug use by group

	Controls			Cannabis			Ecstasy/polydrug		
	No. of users	No. of lifetime uses		No. of users	No. of lifetime uses		No. of users	No. of lifetime uses	
		Mean (s.d.)	Range		Mean (s.d.)	Range		Mean (s.d.)	Range
Alcohol/units per week[d]	13	13.7 (9.5)	1–40	12	27.4 (18.3)	15–60	15	17.7 (11)	2–40
Tobacco/cigarettes per day[a]	0	–	–	6	9.3 (5.8)	3.5–17.5	6	8.9 (5.1)	1–15
Cannabis[a]	6	5.3 (3.1)	2–10	14	439 (486)	50–1,500	15	1,057 (1,558)	50–5,475
Ecstasy[b,e]	0	–	–	6	2.7 (2.9)	1–8	15	138 (119)	50–500
Cocaine[b,e]	0	–	–	3	2.0 (1.7)	1–4	14	87.2 (147.1)	1–576
Magic mushrooms[c,e]	0	–	–	5	1.8 (0.8)	1–3	14	17.3 (21.8)	1–70
Amphetamine[b,e]	1	1	–	2	1.5 (0.7)	1–2	13	51.6 (53.6)	3–200
Poppers[c]	1	3	–	6	10.7 (16.3)	1–40	13	19.0 (16.2)	2–60
Ketamine[b]	0	–	–	1	3	–	12	28.6 (55.9)	1–200
LSD[b]	0	–	–	1	15	–	11	14.9 (28.7)	1–100
Barbiturates/benzodiazepines[b]	0	–	–	2	1.5 (0.7)	1–2	9	66.9 (163.1)	1–500
Solvents[b]	0	–	–	0	–	–	4	6.8 (9.0)	1–20
Opiates	0	–	–	2	–	1–4	4	2.0 (1.2)	1–3
Prozac	0	–	–	2	275 (385)	1–547	3	155 (188)	1–365
Anabolic steroids	0	–	–	0	–	–	1	1	–

LSD lysergic acid diethylamide

[a] Proportion of users by group: controls<cannabis=Ecstasy/polydrug

[b] Proportion of users by group: controls=cannabis<Ecstasy/polydrug

[c] Proportion of users by group: controls<cannabis<Ecstasy/polydrug;

[d] Mean no. units per week: controls<cannabis group

[e] Mean no. lifetime: cannabis<Ecstasy/polydrug group

measures of their cognitive performance on the recognition memory tests (Table 1).

Event-related potentials

Word recognition memory

The grand average ERPs for word recognition memory at a representative subset of channels for all groups combined are shown in Fig. 2. Partial least squares identified a single latent variable that discriminated between the ERPs to 'true new' and 'true old' words. That is, there was a significant repetition effect (permutation test, $p<0.001$) that involved a more positive-going ERP for repeated words centred on the left parietal area that lasted from 200-800 ms but was maximal in the 500-700 ms interval. There was a significant difference in latent variable scores between groups ($F_{2,39}=4.829$, $p<0.013$) and post hoc analysis showed that although there was no significant difference between the controls and the cannabis users (Tukey's HSD, mean difference=22.5, s.e.=28.6, $p<0.715$), the Ecstasy/polydrug users differed from the controls (Tukey's HSD, mean diff=-83.6 s.e.=28.2, $p<0.14$) and were close to differing significantly from the cannabis users (Tukey's HSD, mean difference =−61.2, s.e.=27.6, $p<0.081$). In each case, the scalp scores were lower for the Ecstasy/polydrug group showing that the amplitudes of the ERPs were reduced compared with the other groups.

As it is known that the repetition effect is a compound of at least two components, a left parietal recollection effect and a midline frontal familiarity effect, the latent variable was subject to SVD to extract the two components. Each component had a specific time course and topography. The first component's left parietal maximum (Fig. 3a) and the time course of its repetition effect, extending from 150-900 ms but maximal from 500-700 ms (Fig. 3b), identified it as the recollection effect (Fig. 3a, b). The second component had a central midline focus (Fig. 3c) which, although less frontal than is typically reported (e.g., Rugg and Curran 2007), had a repetition effect whose time course was greatest from 350–500 ms and which clearly identified it as the familiarity effect (Fig. 3d). For both components, repeated words elicited more positive-going ERPs than new words (Fig. 3b, c).

Component scores were calculated for each individual and each condition ('true new' vs. 'true old') and compared between groups. For the recollection component, there was a significant repetition effect ($F_{1,39}=33.56$, $p<0.001$) and a significant group effect ($F_{2,39}=5.8$, $p<0.007$; Fig. 4a). The group difference was most prominent from 400-700 ms (Fig. 4b) and showed an attenuated ERP for the Ecstasy/polydrug group (Fig. 4a). Post hoc analysis showed there

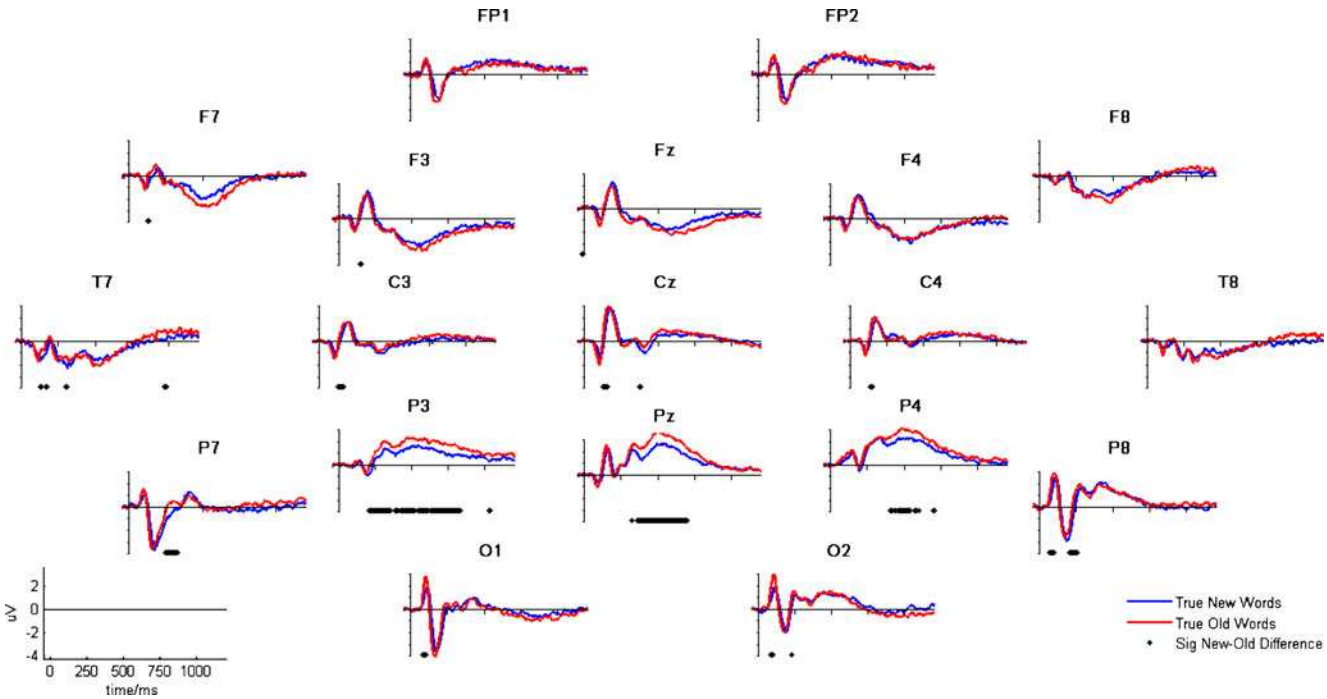

Fig. 2 The grand average event-related potentials at selected channels for the word recognition memory task ('true new' words vs. 'true old' words). PLS identified a significant latent variable (permutation testing, $p<0.001$) that corresponded to the difference between the ERPs to the 'true new' and 'true old' words. The *black dots* indicate the times and channels where the saliences of the latent variable were significantly greater than zero and the type 1 error rate was controlled by setting a p value with a false discovery rate of 0.05. The electrode channels shown are a sample of the 128 channels recorded that most closely approximated to the standard 10–20 electrode positions and are labeled following that nomenclature

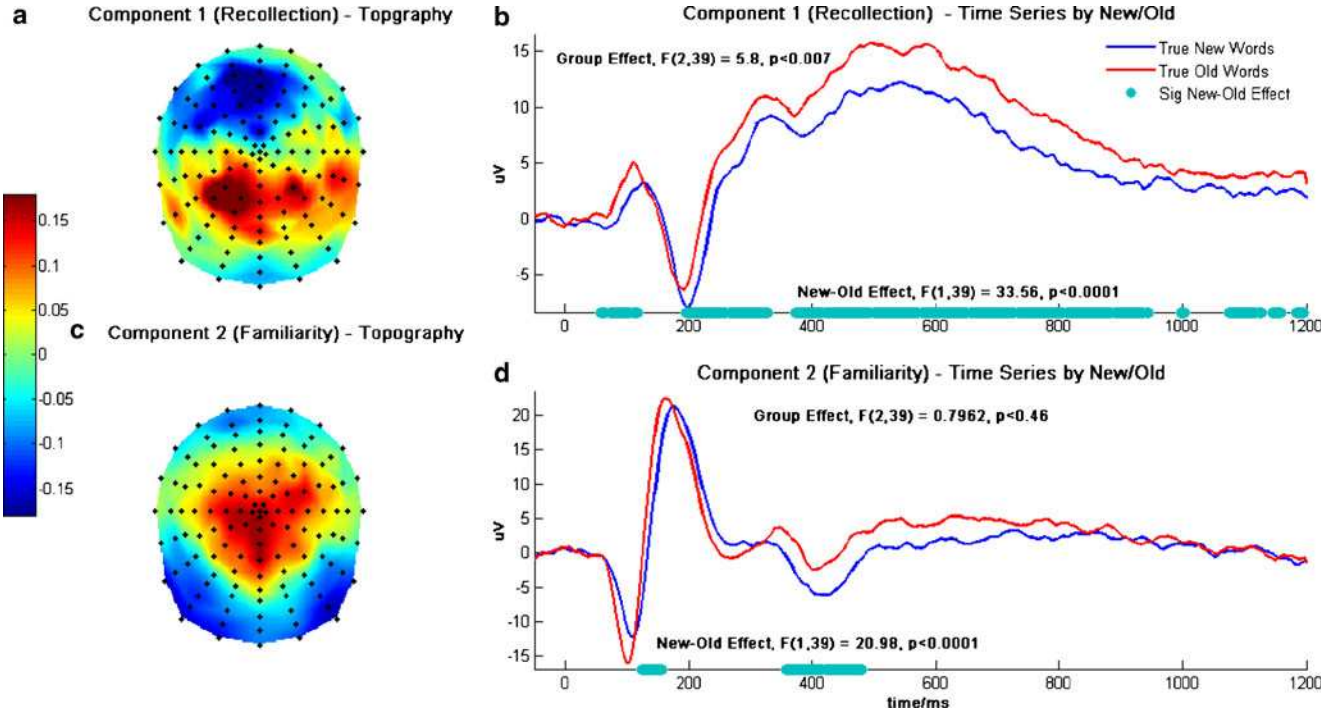

Fig. 3 Showing (**a**) the topography and (**b**) the time course of first component that was identified with the recollection component of the recognition memory ERP (see text). Note the left parietal focus and the late positivity showing a significantly more positive ERP for repeated words ('true old') particularly from 400–800 ms. Panel (**c**) shows the topography and (**d**) the time course of the second component which was identified as the familiarity component of the same ERP (see text). The topography is closer to the vertex than is commonly reported but the time course showing a more positive ERP for repeated words in the 350–500 ms interval is typical. *Green dots* indicate the times where the 'true new' and 'true old' time series differed significantly and the type 1 error rate was controlled by setting a p value with a false discovery rate of 0.05

was no significant difference between the controls and the cannabis groups (Tukey's HSD, mean difference=0.08, s.e.=0.12, $p<0.785$) but the Ecstasy/polydrug group differed from both (Ecstasy vs. controls: Tukey's HSD, mean difference=−0.38, s.e.=0.12, $p<0.008$; Ecstasy vs. cannabis: Tukey's HSD, mean difference=-0.30, s.e.=0.11, $p<0.037$). In each case, the Ecstasy/polydrug users showed a reduced late positive ERP at left parietal sites compared to the other groups (Fig. 4b). For the familiarity component, there was a significant repetition effect ($F_{1,39}=20.98$, $p<0.0001$) but no difference between the groups ($F_{2,\ 39}=0.80$, $p<0.46$; Fig. 4c). The analyses on the latent variable and the component scores were repeated, excluding those five participants who reported using selective serotonin reuptake inhibitors (SSRIs); this had little effect on the pattern of results, except that with this smaller sample size, the post hoc comparison between Ecstasy vs. cannabis users did not quite reach significance (Tukey's HSD, mean difference=-0.29, s.e.=0.13, $p<0.09$).

The relationship between the latent variable/component scores and the measures of well-being and cognitive functioning were examined with Spearman's rank-order correlation coefficient. The latent variable scores were significantly correlated with subjective measures of cognitive functioning (cognitive failures, memory problems, prospective memory problems, and retrospective memory problems) but not with objective memory performance (percentage correct for word and face recognition memory). In each case, the correlations were negative indicating that subjectively good cognitive and memory functioning (i.e., lower questionnaire scores) was associated with higher latent variable scores (i.e., higher amplitude ERP). Both the recollection and familiarity component scores were correlated with, or approached significant correlation with, self-reported memory problems (Table 3: recollection component, $\rho=-0.30$, $p<0.055$; familiarity component, $\rho=0.31$, $p<0.05$). However, there was a double dissociation between the component scores and the type of memory problems reported such that recollection was correlated with prospective memory but not retrospective memory whereas for the familiarity component, the relationship was with retrospective but not prospective memory. In each case, higher levels of subjective memory complaint were associated with lower amplitudes components. It is of note that objective memory performance was not significantly correlated with either the latent variable scores or the recollection component but was significantly correlated

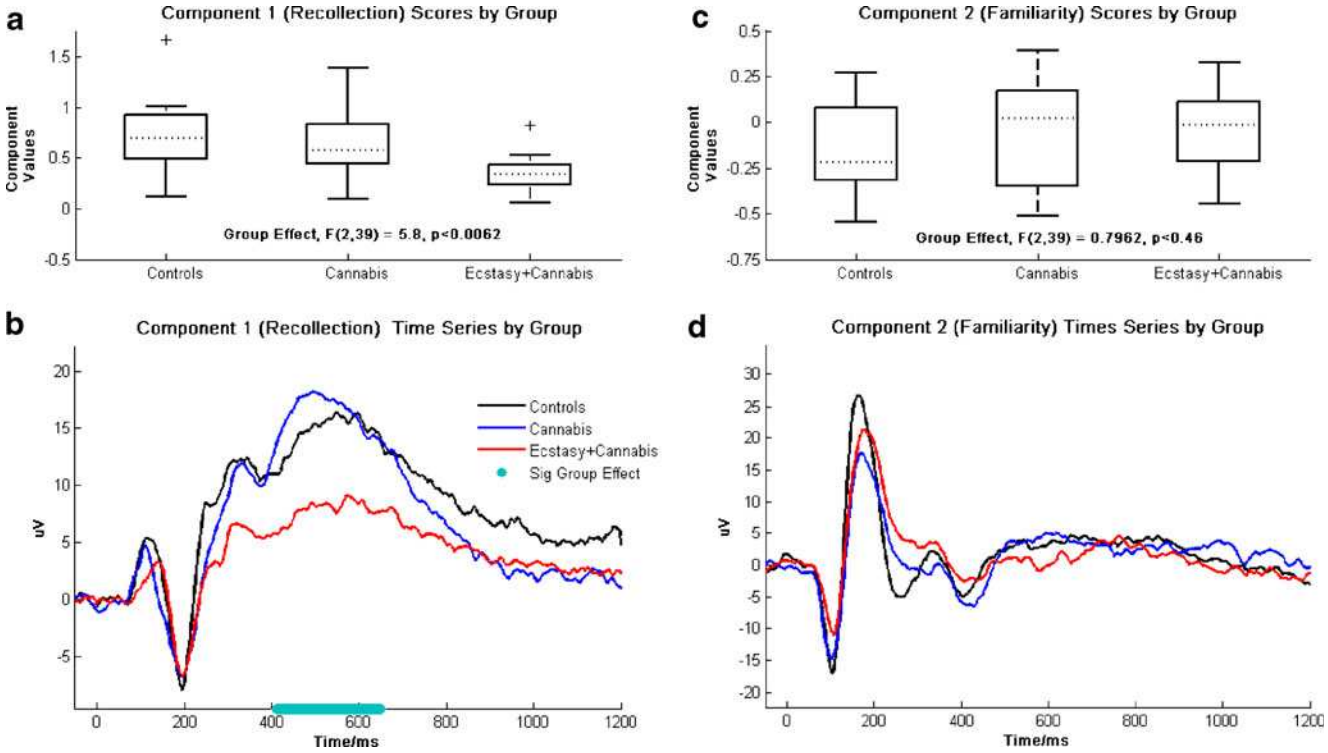

Fig. 4 Showing (**a**) the distribution of the subjects' first component scores (recollection) by group. Note that both the control and cannabis groups show significantly higher average components than the Ecstasy/polydrug group (see text). Panel (**b**) shows the time course of the first component by group. Note that both the group difference shown in (**a**) is maximal in the 400–700 ms interval. The *green dots* indicate the times where the group time series differed significantly and the type 1 error rate was controlled by setting a p value with a false discovery rate of 0.05. Panel (**c**) shows the distribution of the subjects' second component scores (familiarity) by group and (**d**) shows its time course. Note that there were no significant differences between groups on the second component

with the familiarity component such that better memory performance was associated with greater amplitude ERPs.

The relationship between the latent variable/component scores and drug use is reported in Table 4. None were significantly associated with either Ecstasy or cannabis use. However, the latent variable scores were negatively correlated with weekly alcohol consumption and lifetime popper use and positively correlated with lifetime use of LSD. Popper and barbiturate/benzodiazepine use were correlated with recollection and LSD with familiarity.

Table 3 Correlations between word recognition memory, event-related potential components, and self-report measures of mental health and cognitive performance

		Latent variable	Recollection component	Familiarity component
HADS	Anxiety	−0.29	−0.14	0.06
	Depression	−0.30	−0.17	0.14
UHSCMQ	Uplifts	0.15	0.01	−0.04
	Hassles	−0.29	0.04	0.32*
	Stress	−0.20	0.13	0.25
	Cognitive failures	−0.35*	−0.19	0.12
	Memory Problems	−0.52**	−0.30	0.31*
PRMQ	Prospective memory problems	−0.54**	−0.39*	0.25
	Retrospective memory problems	−0.40**	−0.19	0.34*
Recognition memory % correct	Words	0.19	−0.10	−0.31*

HADS Hospital Anxiety and Depression Scale, *UHSCMQ* Uplifts, Hassles, Stressors, Cognitive Failures, and Memory Problems Questionnaire, *PRMQ* Prospective and Retrospective Memory Questionnaire

*p<0.05, **p<0.01

Table 4 Correlations between word recognition memory, event-related potential components, and drug consumption

	n	Latent variable	Recollection component	Familiarity component
Alcohol	40	−0.39**	−0.26	0.23
Cannabis	35	−0.16	−0.13	0.06
Ecstasy	21	−0.13	−0.19	−0.15
Poppers	20	−0.45*	−0.50*	0.15
Magic mushrooms	19	−0.38	−0.39	0.19
Cocaine	17	0.21	0.27	−0.09
Amphetamines	16	−0.07	0.22	0.15
Ketamine	13	−0.52	−0.40	0.40
LSD	12	0.65*	0.26	−0.59*
Tobacco	12	0.07	0.08	0.03
Barbiturates/benzodiazepines	11	−0.27	−0.59*	0.14

All values are self-estimated lifetime uses except alcohol (units per week) and tobacco (cigarettes per day)

LSD lysergic acid diethylamide

*$p<0.05$, **$p<0.01$

Face recognition memory

The grand average ERPs for face recognition memory were analyzed using PLS which identified a latent variable that discriminated between the ERPs to 'true new' and 'true old' words. That is, there was a significant repetition effect (permutation test, $p<0.001$) that was strongest in the parietal region from 400–700 ms but was also present from 200–400 ms, particularly at frontal sites. However, as there was no significant difference in latent variable scores between groups ($F_{2,\ 39}=1.021$, $p<.370$), these data will not be reported further here.

Discussion

The primary finding of this study is that abstinent Ecstasy/polydrug users showed lower amplitude ERPs in a word recognition memory task than either cannabis users or illicit-drug-naive controls whereas face recognition memory ERPs were unaffected. Furthermore, the attenuation of the ERP was restricted to the late positive component that has previously been linked with recollection while the earlier component that has been shown to index familiarity was unaffected. In short, the Ecstasy/polydrug users showed an attenuation of a neural response that is associated with the relatively 'pure' cognitive process of verbal recollection. However, although there is considerable evidence to suggest that the late positive component of the ERP indexes verbal recollection, without direct behavioural confirmation (e.g., recollection/familiarity judgements) of a cognitive deficit, this interpretation should be treated with some caution. Although the focus of this study was on the effects of MDMA, because Ecstasy/polydrug users invariably use other drugs teasing out the specific effects of Ecstasy from those of other substances is problematic (Gouzoulis-Mayfrank and Daumann 2006). This is particularly the case when, as in the present study, the estimates of lifetime consumption of various illicit drugs was measured using self-report. Such estimates are inevitably crude and rely on accurate memory of behaviours extending over many years that might be affected by the intoxicating effects of the substances concerned, any long-term effects on memory that illicit drug use might have, as well as by social pressures that might encourage either the denial or exaggeration of the true level of use. More accurate information is rarely available, and was not in this study. The data are summarised in Table 2. Therefore, it should be considered as broadly indicative of the level of illicit drug use rather than as an accurate record of the true level of drug use.

The poor quality of the lifetime consumption measures might also account for the lack of correlation between the ERP components and lifetime consumption of most of the illicit drugs listed in Table 4. Significant correlations were found between the ERP components and alcohol, poppers, LSD, and barbiturates/benzodiazepines suggesting that these substances too might have durable effects on memory. No such associations were found with either Ecstasy or cannabis which could mean that even though Ecstasy use affects the recollection component of the ERP, the size of this effect is not closely related to cumulative lifetime consumption. However, it is at least as likely that the estimate of lifetime consumption is too inaccurate to ensure detection of such an association even if it were there.

Similar concerns about self-reported illicit drug use apply to the period of abstinence prior to testing which was also based on self-report. None of the participants

showed any evidence of intoxication at the time of testing but a more objective measure of recent drug use (e.g., hair, blood, or urine testing) would have been better for excluding recent use.

Ecstasy/polydrug users almost invariably smoke cannabis (Parrott et al. 2002), but as the cannabis group's ERPs did not differ significantly from those of the illicit drug-naive controls, cannabis use cannot explain these results. Alcohol and tobacco use can also be discounted as the Ecstasy/polydrug group was not distinguished by its use of either. The role of SSRIs is of particular interest because of their serotonergic effects but excluding users from the analysis made little difference to the pattern of results suggesting that they did not play an important role in the findings reported here. Some substances (e.g., opiates) were used too infrequently in the sample to be likely causes of the memory effects reported here but others (e.g., cocaine, amphetamines, poppers, and ketamine) were used to a significant extent and their relevance cannot be dismissed. There is evidence, for example, that amphetamine (Gouzoulis-Mayfrank and Daumann 2009), ketamine (Morgan et al. 2010), and cocaine (O'Malley and Gawin 1990) each have long-term effects on cognitive functioning, including episodic memory. The problem of polydrug use is compounded by the fact that although most Ecstasy tablets contain MDMA (Parrott and Kaye 1999), the dosage varies significantly and other substances such as caffeine and amphetamine are sometimes included (Tanner-Smith 2006; Vogels et al. 2009).

An estimate of the importance of the confounding role of other recreational drugs can be gleaned from quantitative reviews on the long-term effects of Ecstasy on cognitive functioning. (Rogers et al. 2009) in their meta-analysis attempted to estimate the effects of multiple confounding factors, including other recreational drugs, using meta-regression techniques. They concluded that although amphetamine, cocaine, and cannabis use all significantly modulated the effects of Ecstasy on cognition, the directions of these effects were inconsistent. This suggests that even if MDMA consumption is a likely causal factor for the results we report here, other recreational drugs may are likely to be important too. The Ecstasy/polydrug users in this study did not show any functional deficits in recognition memory which is unsurprising because recognition memory is robust and any impairment seen is usually preceded by other memory problems (e.g., recall) (Aggleton and Brown 2006). Indeed, the lack of a performance difference between groups was advantageous as it allowed us to deconvolve the behavioural and neural responses. Demonstrating that two or more groups differ simultaneously in their neural response and functional performance is trivial and simply shows that different behaviours have different neural correlates. In this case, the groups were functionally indistinguishable and yet still showed a different neural response.

The simplest way in which a smaller neural response might be generated would be if fewer neurons were synchronously active when the memory stimuli were presented. However, as ERPs are generated by averaging the EEG response to many trials, the same effect would be seen by an increased variability in the latency of the responses, even if the number of neurons synchronously active on each trial remained the same. Alternatively, given that ERPs may be generated by a phase-reorganization of the background EEG (Sayers et al. 1974), then the difference seen might be due to more pervasive changes in the oscillatory dynamics of the cortex. Which of these mechanisms, or which combination of these mechanisms, is relevant here is unclear but a neurotoxin could potentially interfere with each of them.

Similar changes in memory ERPs are seen as part of the normal ageing process (Swick and Knight 1997; Joyce et al. 1998). Not only do older adults show lower amplitude memory ERPs but recollection is affected most even though recognition memory performance is unchanged (Joyce et al. 1998). In short, the pattern of changes seen in the Ecstasy/polydrug group is similar to that seen in older adults. Research into the effects of Ecstasy has focused on the young and relatively little is known about the effects in middle-aged and older adults. What evidence there is suggests that middle-aged Ecstasy/polydrug users show the same type of deficits on cognitive testing as younger adults (Schilt et al. 2010) but the question as to whether the effects of Ecstasy and ageing interact has not yet been adequately addressed.

The ERP components identified here provide a link between the underlying neural processes involved in recognition memory and the subjective experience of the participants (Table 3). The ERP repetition effect was significantly correlated with several measures of self-reported memory problems, in each case, poorer subjective memory was associated with lower amplitude ERPs. Interestingly, the components of the ERP were differentially associated with subjective experience with recollection being significantly correlated with prospective memory and familiarity with retrospective memory. The association between recollection and prospective memory might seem surprising, but neuropsychological investigations have shown that recollection is crucial for prospective memory and (Burgess and Shallice 1997) state that "PR [Prospective Remembering] often involves a special application of the processes used in RM [Retrospective Memory], especially recollection". Objective memory performance was significantly correlated with familiarity but not recollection. The lack of correlation with recollection is unsurprising as recollection is not necessary for successful performance of

the task as most individuals will have a recollective experience on only a proportion of the trials whereas familiarity will occur on all correctly remembered trials. This also accounts for why the familiarity was significantly correlated with subjective ratings of retrospective memory.

Although ERPs are well suited to use on experimentally induced neural activity to fractionate complex cognitive processes, they are much less useful for identifying where this neural activity occurs. Consequently, the neural correlates of recollection and familiarity are unknown and, even though these processes have been studied using fMRI, little consensus about their functional anatomy has emerged (Kafkas and Migo 2009). However, evidence from neuropsychological case studies has shown that verbal recognition memory depends upon the left hemisphere and face recognition memory on the right (Morris et al. 1995). Our results showed that verbal memory was affected, but not non-verbal memory, suggesting that Ecstasy/polydrug use affects the left hemisphere more than the right. Quantitative reviews of the neuropsychological effects of Ecstasy have consistently reported greater impairments of verbal memory than non-verbal memory (Rogers et al. 2009) and this too suggests that the left hemisphere is more seriously affected than the right. More direct evidence has come from recent evidence using structural MR imaging, which reported a left-sided bias in cortical thinning due to Ecstasy use (Kish et al. 2010). One likely explanation for this left hemisphere effect is that neurotransmitter systems, including serotonin, are asymmetrically distributed. (Arato et al. 1991) reported significantly higher levels of the serotonin metabolite 5H1AA in the right medial frontal region of the human brain at post-mortem. More recent work using PET radio-ligand mapping of the main inhibitory serotonin receptor (serotonin-1A) in vivo has confirmed that asymmetries exist but that the pattern also shows regional variation that reflect functional asymmetries in language processing (Fink et al. 2009).

MDMA affects several neurotransmitters systems, including dopamine, but there is evidence from the cognitive effects of acute tryptophan depletion (ATD), a method of experimentally and reversibly decreasing central serotonergic activity, to suggest that the role of serotonin is critical (Young et al. 1985). A recent review, (Mendelsohn et al. 2009) concluded that ATD impaired verbal episodic memory but had little if any effect on non-verbal (pattern recognition and spatial) memory. Of particular note is that although performance on verbal recognition memory itself was unaffected, source memory, the behavioural measure of recollection, was significantly impaired by ATD (McAllister-Williams et al. 2002) although they found no significant difference in the recollection component of the ERPs. Nevertheless, the parallels between the long-term effects of Ecstasy and acute tryptophan depletion on cognition are strong.

Overall, there is evidence for a specific abnormality in the ERPs of Ecstasy/polydrug users that is not seen in non-Ecstasy using cannabis users or illicit-drug-naive controls. This abnormality is specific in both its modality (i.e., words, not faces) and in the putative cognitive function that is affected (i.e., recollection but not familiarity). Although both these features might be explained as a consequence of damage to the serotonergic system and are consistent with the known serotonergic neurotoxicity of MDMA, the polydrug use of the participants means that it would be premature to attribute this effect to Ecstasy use alone.

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