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ORIGINAL INVESTIGATION

Memory-related hippocampal functioning in ecstasy and amphetamine users

A prospective fMRI study

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Abstract
Rationale Recreational use of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) has been associated with memory impairments. Functional neuroimaging studies with cross-sectional designs reported altered memory-related hippocampal functioning in ecstasy-polydrug users. However, differences might be pre-existing or related to the concomitant use of amphetamine.
Objective To prospectively investigate the specific effects of ecstasy on memory-related hippocampal functioning.
Methods We used an associative memory task and functional magnetic resonance imaging (fMRI) in 40 ecstasy and/or amphetamine users at baseline (t1) and after 12 months (t2). At t1, all subjects had very limited amphetamine and/or ecstasy experience (less than 5 units lifetime dose). Based on the reported drug use at t2, subjects with continued ecstasy and/or amphetamine use ($n=17$) were compared to subjects who stopped use after t1 ($n=12$).
Results Analysis of repeated measures revealed that encoding-related activity in the left parahippocampal gyrus changed differentially between the groups. Activity in this region increased in abstinent subjects from t1 to t2, however, decreased in subjects with continued use. Decreases within the left parahippocampal gyrus were associated with the use of ecstasy, but not amphetamine, during the follow-up period. However, there were no significant differences in memory performance.
Conclusions The current findings suggest specific effects of ecstasy use on memory-related hippocampal functioning. However, alternative explanations such as (sub-)acute cannabis effects are conceivable.

Keywords Amphetamine · Cognition · Ecstasy · fMRI · Hippocampus · Longitudinal design

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Introduction

The popular recreational drug "ecstasy" (3,4-methylenedioxymethamphetamine [MDMA]) causes selective and persistent lesions to central serotonergic nerve terminals in laboratory animals (Fischer et al. 1995; Green et al. 2003; Hatzidimitriou et al. 1999). Although these data cannot be extrapolated directly to human recreational users, a growing number of studies suggest that MDMA might be harmful to the serotonergic system in humans. Several studies reported subtle abnormalities in psychological and neurocognitive functioning in MDMA users that might reflect functional sequelae of long-lasting alterations in serotonergic systems (Gouzoulis-Mayfrank and Daumann 2006a; Green et al. 2003; Parrott 2000; Reneman et al. 2006; Schilt et al. 2007). Recent reviews and well-controlled studies suggest ecstasy-specific impairments in learning and memory (Fox et al. 2002; Gouzoulis-Mayfrank and Daumann 2009;

Gouzoulis-Mayfrank et al. 2003; Kalechstein et al. 2007; Schilt et al. 2007, 2008; Zakzanis et al. 2007; but see Halpern et al. 2011). Given this selective pattern of mnemonic impairments, the authors consistently suggested that dysfunctions in the hippocampal formation might represent the neuroanatomical basis of memory deficits in ecstasy users. However, in some studies ecstasy users demonstrated impairments in memory functions primarily associated with the frontal cortex (Brown et al. 2010; Quednow et al. 2006). These findings might suggest that memory deficits in ecstasy users are not only the result of hippocampal dysfunction, but also of dysfunction of frontal regions.

In recent years, functional magnetic resonance imaging (fMRI) has increasingly been used to investigate the neural correlates of ecstasy-associated memory impairments. Ecstasy users displayed abnormal neural activity in the associative memory-related network, including (para-)hippocampal regions (Daumann et al. 2005; Roberts et al. 2009). However, findings from a recent study addressing the specific effects of ecstasy and other drugs of abuse on cognitive brain function could not confirm specific effects of ecstasy on hippocampal functioning (Jager et al. 2008). In this study memory impairments and hippocampal dysfunctions were associated with the use of amphetamine, a drug commonly co-used by ecstasy users.

Moreover, methodological problems hamper the interpretation of previous fMRI studies. In particular the lack of pre-use data, poorly matched controls and the widespread co-use of cannabis and amphetamine in ecstasy users represent important confounding factors (Gouzoulis-Mayfrank and Daumann 2006b; Lyvers 2006; Pedersen and Skrondal 1999). In addition, the generalizability of findings remains limited because most studies focused on heavy users. Summarizing, results regarding the effects of ecstasy use on functional brain activity and the neuroanatomical basis of ecstasy-associated memory impairments remain inconclusive.

The aim of the present study therefore was to investigate the specific effects of moderate ecstasy use on memory-related brain function. Based on previous studies in this field of research, effects in hippocampal regions were of particular interest. To control for known confounders in this field of research, a prospective longitudinal design with moderate users of ecstasy and amphetamine was incorporated. Specific effects of ecstasy and commonly co-used amphetamine were disentangled estimating dose–response relationship.

Materials and methods

Participants

Subjects in the present study were part of a larger prospective study on the effects of recreational drug use. A subsample of 50 participants was examined at baseline (t1) and after an interval of 12 months (t2) using fMRI. Main inclusion criterion at baseline was a high probability of future ecstasy and/or amphetamine use, operationalized as having "first but very limited experience with ecstasy and/or amphetamine." Exclusion criteria at baseline were: (1) having used more than five ecstasy tablets and/or 5 g amphetamine, (2) use of all other illicit substances except for cannabis, (3) childhood diagnosis of attention-deficit hyperactivity disorder (ADHD) and (4) any current or previous axis I psychiatric diagnosis (exceptions: nicotine dependence, cannabis abuse and dependence). Further exclusion criteria on both study days were: (1) history of alcohol abuse and/or dependence (according to DSM IV, APA 1994), (2) regular intake of any medication (regular use was defined as using the medication at least once a week), (3) intake of any psychotropic substances except for cannabis 7 days prior to testing, (4) use of cannabis on the day of the examination. Additional exclusion criteria for the fMRI investigation were (1) left-handedness, (2) pregnancy and (3) other known contraindications for MRI scanning.

Procedure

Following a detailed study description, written informed consent was obtained from all participants. All subjects subsequently underwent a structured interview according to the DSM IV. To exclude participants with childhood ADHD, all participants completed the German version of the Wender Utah Rating Scale (WURS) (Ward et al. 1993) and were excluded if they exceeded the recommended cut-off score (Ward et al. 1993). On both study days, subjects underwent a detailed structured interview assessing the use of amphetamine and ecstasy, including the following parameters of use: (1) age of first use, (2) time since the last use in days, (3) average frequency of use measured by average days of use per month, (4) maximum days of use per month ever, (5) estimated cumulative lifetime dose, as well as (6) average and (7) highest daily or one night dose ever used. Studies validating self-reported voluntary substance use found a high reliability of the reported drug quantity (Martin et al. 1988; Rothe et al. 1997). Randomly taken hair samples from approximately 50 % of study participants were analyzed for amphetamines (amphetamine, methamphetamine, MDMA, 3,4-methylenedioxyamphetamine [MDA], 3,4-methylenedioxy-*N*-ethylamphetamine [MDEA]) and cannabinoids (tetrahydrocannabinol [THC], cannabidiol [CBD], cannabinol [CBN]) by the Institute of Legal Medicine of the University of Cologne (detailed information on the analysis protocols are given in the Supplementary information). Results from this quantitative analysis confirmed the self-reported substance use patterns. Qualitative drug screens were performed on the day of the

examination with urine samples for amphetamines, benzodiazepines, cocaine, methadone, MDMA and cannabis (enzyme-multiplied immunoassay; von Minden GmbH). In order to control for confounding variables, concomitant substance use and health behaviour were assessed on both study days. Current intellectual functioning was assessed by the Raven Standard Progressive Matrices (Raven 2000). Cannabis use was assessed by a cannabis-specific version of the drug interview. Additionally, the following aspects were assessed: (1) use of alcohol and tobacco (frequency of alcoholic drinks per week, cigarettes per week, years of tobacco use), (2) use of medication (number of uses: hypnotic, analgesic, stimulating and sedative medications per week) and (3) sleep (hours of sleep per night, frequency of sleep problems).

The study was in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee of the Medical Faculty of the University of Cologne.

Associative memory task

On both study days, participants performed an associative memory task. In a previous study, this task was used to assess differences in hippocampal functioning between ecstasy users and controls (for details, see Daumann et al. 2005). Briefly, the associative memory fMRI-paradigm consisted of two encoding and one retrieval fMRI time-series. A blocked periodic design was used with alternating active and control conditions. Participants learned 16 visually presented face–profession combinations in the active condition of the encoding runs. During the active condition of the retrieval run the 16 faces were displayed without the profession. Participants then had to indicate to which of two given categories (academic or artistic) they belonged. In the control condition, facial contours were displayed. During the retrieval condition, participants had to indicate whether the left or right ear of the contour was larger. Total scanning time was 8:15 min.

Imaging parameters

fMRI data was acquired on a clinical 1.5-T Philips ACS NT Gyroscan (Philips, The Netherlands) using a single-shot multislice T2* weighted gradient echo EPI sequence (imaging parameters: TR, 3,000 ms; TE, 50 ms; flip angle, 90°; matrix, 64×64; field of view, 192×192 mm, 30 contiguous slices parallel to the AC–PC line covering the whole brain; voxel size, 4×4×7 mm, no interslice gap). A total of 56 dynamic scans for each of the two encoding runs and the retrieval run were recorded. Each time-series was preceded by five dummy scans to allow for equilibration of the MRI signal. For anatomic reference and to exclude subjects with apparent brain pathologies, a T1-weighted Fast Field Echo sequence (imaging parameters: TR, 25 ms; TE, 4.6 ms; TI, 400 ms; flip angle, 30°; matrix, 256×256; slice thickness, 2 mm) was obtained. Images were acquired using a standard head coil.

Data analysis

To obtain information about the impact of continued ecstasy and amphetamine use on cognitive performance and associated neural activity, the sample was divided into two groups: (1) users who completely stopped ecstasy and/or amphetamine use after t1 (controls), and (2) users who continued use after t1 (at least five ecstasy tablets and/or 5 g amphetamine in the 12-month follow-up period) (users). In line with previous research strategies in ecstasy users (Bedi and Redman 2008; Parrott et al. 1998; Daumann et al. 2004), subjects with only sporadic use after t1 were excluded from further analysis. Between-group differences for age, education, substance use, potential confounders (use of alcohol (frequency of alcoholic drinks per week), nicotine (years of tobacco use, cigarettes per week), and medication (frequency of hypnotic, analgesic, stimulating and sedative medications per week), as well as the quality of sleep (hours of sleep per night, frequency of sleep problems) and performance were analyzed by means of unpaired Student *t*-tests; in case the normality assumption was violated by means of Mann–Whitney *U*-test. Gender distribution was analyzed by means of Pearson χ^2 test. Differences in performance between both study days were analyzed by means of repeated measures analyses of variance (ANOVA) with the between-subject factor GROUP (controls vs. users) and the within-subject factor TIME (t1 vs. t2). In addition, change scores between t1 and t2 were computed. Analyses were computed using SPSS Statistics 18.0 (SPSS Inc., Chicago, IL).

Functional magnetic resonance imaging data were preprocessed and analyzed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). Images were initially realigned to the first image of each scan. Mean images were subsequently normalized with the SPM5 MNI template (resampled to $2\times2\times2$ mm^3 voxels), and smoothed with a Gaussian kernel (triple voxel size). Raw time-series were detrended by the application of a high-pass filter (cutoff period: 128 s). The preprocessed data were analyzed using a two stage procedure for repeated measures ANOVA (Henson and Penny 2003). Separate analyses of the two identical encoding runs revealed similar activation patterns. Consequently, the encoding runs were summarized on the first level analysis. In an initial step, subject-specific changes in BOLD response were assessed using linear contrasts of the GLM parameters. To explore between-group differences at baseline, contrasts of task were entered into separate two-sample *t*-tests. Separate contrasts for the main

effects of task and time (t1, t2) were computed for each subject. Main effects of the factors GROUP and TIME and interaction effects of the factors GROUP × TIME were computed entering the appropriate first level contrasts in two-sample *t*-tests.

Because of our a priori hypothesis, analyses were restricted to anatomically defined task-specific regions of interest (ROI) (WFU pickatlas (Maldjian et al. 2003, 2004; Tzourio-Mazoyer et al. 2002). Based on findings from previous studies analyses were restricted to the hippocampus and parahippocampus. All analyses were computed with the standard threshold of $p<0.05$ and corrected for multiple comparisons (family-wise error [FWE]). For the ROI analyses the FWE correction was implemented in a small volume correction, based on the size of the ROIs. Minimum cluster size was set to ten voxels.

Results

Participants and group-assignment

Of the 50 users who participated in the fMRI investigation at baseline, 40 users (30 males, ten females; age range at baseline: 18–30 years, mean: 22.30 years, SD: 3.48) could be re-examined at follow-up (86 %). Ten participants dropped out because they either moved without giving notice of their new address ($n=7$), simply lost interest in the study ($n=2$), or developed a manifest psychiatric disorder ($n=1$). From the 40 users who could be re-examined, 12 had stopped to use ecstasy and amphetamine after t1 and served as a control group (CG). Seventeen participants fulfilled the criteria for continued use of ecstasy and/or amphetamine during the follow-up period (at least five ecstasy tablets and/or 5 g amphetamine between baseline and follow-up) (UG). Eleven participants reported only sporadic use of ecstasy and/or amphetamine during the follow-up period and therefore, were excluded from the analyses (for completeness demographic data and drug use patterns of the sporadic user group [SG] are presented in Tables 1, 2 and 3).

Demographics, drug use and confounders at baseline

The experimental groups were of comparable age ($t(27)=0.54$, $p=0.60$), education ($t(27)=0.34$, $p=0.74$) and gender distribution (Pearson $\chi^2(1, n=29)=0.513$, $p=0.474$) and reported similar patterns of previous ecstasy and amphetamine use at baseline. At baseline UG had used more amphetamine ($t(27)=-2.19$, $p=0.04$) and reported a shorter time since the last use of ecstasy ($t(27)=2.81$, $p=0.01$) and amphetamine ($t(24)=2.16$, $p=0.04$). Analysis of potential confounding variables at baseline yielded no significant between-group differences in current intellectual functioning ($t(27)=0.17$, $p=0.86$), quality of sleep (average hours of sleep: $t(27)=-0.14$, $p=0.89$, frequency of sleep problems: $t(27)=0.23$, $p=0.82$). Moreover, the groups reported comparable use of cannabis (all $p>0.13$), alcohol ($t(27)=0.82$, $p=0.42$), nicotine (cigarettes per week: $t(27)=-0.57$, $p=0.57$; years of use: $t(27)=0.20$, $p=0.84$) and medication (mean number of uses per week: hypnotic medication — UG, 0.20, SD 0.07; CG, 0.00, SD 0.00, $t(27)=1.16$, $p=0.26$; analgesic medication — UG, 0.13, SD 0.38; CG, 0.08, SD 0.03, $t(27)=0.90$, $p=0.38$; stimulating medication — UG, 0.02, SD 0.07; CG, 0.47, SD 0.10, $t(27)=-0.76$, $p=0.45$; sedative medication — UG, 0.05, SD 0.11; CG, 0.03, SD 0.02, $t(27)=0.40$, $p=0.69$) (for details on demographics and drug use patterns at baseline, see Tables 1 and 3).

Patterns of interim drug use

Interim abstinent users reported complete abstinence from ecstasy and amphetamine at follow-up, but continued to use cannabis. Although, a direct between-group comparison revealed no significant differences in any parameter of interim cannabis use (all $p>0.192$), the UG reported a higher interim cumulative cannabis dose (mean interim dose in grams: UG, 146.65, SD 194.06; CG, 71.56, SD 100.98). In addition, the CG reported a substantial shorter time since last cannabis use (mean time since last use in days: UG, 25.40, SD 76.44; CG, 13, SD 100.98). Analysis of further potential confounding variables at follow-up yielded no significant between-group differences regarding the use of alcohol ($t(27)=-0.11$, $p=0.92$), nicotine ($t(27)=0.27$, $p=0.79$), and medication (mean number of uses per week: hypnotic medication: UG, 0.10, SD 0.17; CG, 0.06, SD 0.14, $t(27)=0.77$, $p=0.45$; analgesic medication: UG, 0.20, SD 0.19; CG, 0.16, SD 0.18, $t(27)=0.56$, $p=0.58$; stimulating medication: UG, 0.04, SD 0.09; CG, 0.47, SD 0.10, $t(27)=-0.14$, $p=0.89$; sedative medication: UG, 0.06, SD 0.09; CG, 0.03, SD 0.08, $t(27)=0.68$, $p=0.50$) (for details on interim drug use patterns, see Tables 2 and 3).

Performance

Repeated-measures ANOVA with group (users vs. controls) as between-subject factor and time point (t1 vs. t2) revealed neither a significant main effect of group and time point and no significant interaction on associative memory performance (all $p>0.102$) (Fig. 1). Additional analysis of change scores (t2−t1) revealed that both groups showed improved performance at t2 and that improvements were larger in the controls (UG, mean, 1.12, SD, 3.67; CG, mean, 2.00, SD, 2.95; estimated effect size using Cohen's $d=0.27$, $r=0.13$). However, within- and between-group differences failed to reach statistical significance (all $p>0.48$).

Table 1 Baseline demographic features and drug use patterns of interim abstinent users (controls, $n=12$), users who continued using ecstasy and/or amphetamine (user, $n=17$) and sporadic users (sporadic, $n=11$)

	Controls ($n=12$)	User ($n=17$)	Sporadic ($n=11$)
Demographics			
Age	23.42±3.97	22.71±3.18	21.91±3.17
	(18–30)	(18–28)	(18–27)
Gender m:f[a]	11:1	14:3	6:5
Education (years)	15.17±3.03	14.80±2.65	14.81±2.36
	(11–20)	(10–19)	(12–18)
Cannabis use patterns			
Age of first use	15.58±1.83	15.59±2.37	14.64±1.50
	(13–19)	(12–21)	(12–17)
Lifetime dose (g)	814.33±891.34	762.74±893.32	476.81±4898.55
	(2.5–2,880)	(0–3,640)	(3–1,250)
Duration of regular use (months)	53.90±32.16	56.40±39.79	42.90±31.11
	(0–96)	(0–122)	(3–108)
Days of use per month (average)	11.95±11.65	13.09±11.61	14.68±11.56
	(0–30)	(0–30)	(0–30)
Days of use per month (maximum) [2]	19.92±12.59	22.10±11.39	21.91±9.79
	(0–30)	(0–30)	(3–30)
Average daily dose (joints)	2.70±1.29	2.53±2.04	2.11±1.86
	(0.5–4.5)	(0.5–6.0)	(0.5–6.0)
Highest daily dose ever used (joints)	9.25±8.99	10.35±6.67	7.36±6.35
	(1–30)	(0.5–20)	(0.5–20)
Time since last use (days)[b]	175±281.20	111.62±214.49	126.55±383.25
	(1–730)	(1–545)	(1–1,280)
Number of positive THC screenings at baseline t1	4	9	6
Ecstasy use patterns			
Age of first use	19.78±2.53	20.56±3.15	19.60±3.71
	(15–22)	(16–26)	(15–27)
Lifetime dose (pills)	2.66±1.77	3.26±1.59	3.15±1.75
	(0–5)	(0–5)	(0–5)
Average one night dose (pills)	1.01±0.30	1.40±0.93	1.37±1.31
	(0.5–1.5)	(0.5–3)	(0.5–3)
Highest one night dose (pills)	1.61±0.65	2.07±1.19	1.67±1.26
	(1–3)	(1–4)	(0.5–4)
Time since last use (days)**	828.33±769.06	194.40±331.87	350.35±314.20
	(180–2,373)	(9–1,277)	(24–1,095)
Amphetamine use patterns			
Age of first use	19.67±2.45	19.88±3.16	18.90±3.34
	(15–22)	(16–25)	(15–27)
Lifetime dose (g)*	2.29±1.63	3.52±1.38	2.41±1.71
	(0–5)	(0–5)	(0–5)
Average one night dose (g)	0.39±0.23	0.53±0.33	0.47±0.32
	(0.20–0.90)	(0.15–1.10)	(0.15–1.00)
Highest one night dose (g)	0.85±0.68	1.23±0.80	615.00±272.89
	(0.30–2.50)	(0.20–3.00)	(0.25–1.00)
Time since last use (days)[2]*	470.67±759.15	208.31±481.90	123.30±216.25
	(14–2,373)	(14–570)	(7–720)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The t-values were calculated using unpaired t-test; two-tailed ($df=27$)

[a]Comparison tested with Pearson χ^2 test ($df=1$); exact significance (two-sided) are reported

[b]Comparison tested with Mann–Whitney U-test; asymptotic significance (two-sided) reported

*Significant difference, $p<0.05$

**Significant difference, $p<0.01$

Table 2 Patterns of interim drug use of interim abstinent users (controls, $n=12$), users who began using ecstasy and/or amphetamine on a regular basis (user, $n=17$) and sporadic users (sporadic, $n=11$)

	Controls ($n=12$)	User ($n=17$)	Sporadic ($n=11$)
Interim cannabis use patterns			
Interim cumulative dose (g)	71.56±100.98 (0–285)	146.65±194.06 (0–650)	40.27±79.26 (0–260)
Duration of regular use (months)[a]	5.92±1.79 (0–12.5)	8.64±5.39 (0–72.0)	5.90±5.82 (0–13.0)
Days of use per month (average)	11.83±10.85 (0–30)	18.67±9.62 (0–30)	15.16±13.87 (0–30)
Days of use per month (maximum)	19.29±10.99 (0–30)	23.62±8.29 (0–30)	20.70±11.14 (0–30)
Average daily dose (joints)	2.00±1.04 (1.00–4.20)	2.26±2.06 (0.30–6.90)	1.92±0.88 (1.00–3.00)
Highest interim daily dose (joints)	5.87±6.42 (1.00–20)	5.58±4.37 (1.00–16)	7.07±5.34 (1.00–15)
Time since last use (days)[a]	13.57±24.46 (1–68)	25.40±76.44 (1–300)	44.57±99.76 (1–270)
Number of positive THC screenings at follow-up t2	3	10	5
Interim ecstasy use patterns		$n=15$	$n=7$
Interim cumulative dose (pills)	×	9.50 ±7.89 (0–30)	2.95±4.22 (0–12)
Days of use per month (average)	×	0.96±1.48 (0.5–4.5)	0.02±0.32 (0.2–1.5)
Days of use per month (maximum)	×	2.71±2.36 (1.0–10.0)	2.00±3.10 (0.2–2.0)
Average 1-night dose (pills)	×	1.36±0.66 (0.5–2.5)	1.17±0.96 (0.25–2.00)
Highest interim 1-night dose (pills)	×	2.02±1.06 (0.75–4.0)	2.64±3.45 (0.25–3.00)
Time since last use (days)	×	86.33±80.12 (14–27)	75.43±55.32 (20–180)
Interim amphetamine use patterns		$n=16$	$n=6$
Interim cumulative dose (g)	×	10.61±7.52 (0.20–30.00)	0.75±0.89 (0.10–2.50)
Days of use per month (average)	×	2.11±2.18 (0.8–6.5)	0.30±0.63 (0.1–0.5)
Days of use per month (maximum)	×	4.21±4.88 (2.0–15.0)	2.00±1.86 (0.1–2.0)
Average 1-night dose (g)	×	0.77±0.65 (0.25–2.50)	0.45±0.24 (0.10–0.75)
Highest interim 1-night dose (g)	×	1.14±0.67 (0.25–3.00)	0.59±0.32 (0.10–1.00)
Time since last use (days)	×	47.44±73.03 (10–300)	89.00±62.72 (14–180)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The *t*-values were calculated using unpaired *t*-test; two-tailed ($df=27$)

[1]Comparison tested with Mann–Whitney *U*-test; asymptotic significance (two-sided) reported

*Significant difference, $p<0.05$

**Significant difference, $p<0.01$

Functional MRI

All subjects had a normal structural MRI scan without focal brain lesions or anatomical abnormalities.

Associative memory

Separate analyses for effect of the factor TASK at baseline revealed no significant between group differences. Whole-

Table 3 Patterns of alcohol and tobacco use at baseline (t1) and during the 12-months follow-up period (t1–t2) for interim abstinent users (controls, $n=12$), users who began using ecstasy and/or amphetamine on a regular basis (user, $n=17$) and sporadic users (sporadic, $n=11$)

	Controls ($n=12$)	User ($n=17$)	Sporadic ($n=11$)
Alcohol and tobacco use at baseline (t1)			
Alcoholic drinks per week**	6.37±0.59 (2.0–7.5)	6.08±1.08 (3.0–8.5)	4.00±2.04 (2.0–8.0)
Cigarettes per week	26.48±11.46 (7.1–47.8)	28.74±10.79 (11.9–50.3)	24.36±23.37 (4.2–60.0)
Years of tobacco use	5.25±4.03 (1.5–12.0)	4.95±3.70 (0.5–12.0)	3.90±3.64 (3.0–12.0)
Interim alcohol and tobacco use (t1–t2)			
Alcoholic drinks per week	6.20±1.17 (4.5–9.0)	6.26±1.63 (3.0–9.0)	4.72±2.53 (1.5–8.0)
Cigarettes per week	25.50±18.6 (15.5–54.0)	23.29±23.87 (9.0–60.0)	29.81±25.63 (8.0–72)

Mean ± standard deviation (range). Only significant differences between controls and users are reported

The t-values were calculated using unpaired t-test; two-tailed ($df=27$)

*Significant difference, $p<0.05$

**Significant difference, $p<0.01$

brain analysis of the encoding tasks revealed a significant BOLD effect for the main effect of the factor TASK (encoding > control) in the associative memory network. ROI analysis indicated bilateral activity within the hippocampal formation, most pronounced in the right parahippocampal gyrus (Fig. 2; maximum t-value located at Talairach space, $x=31$, $y=-9$, $z=-13$; $t=9.66$). Whole-brain and ROI analysis revealed no significant main effect of the factor TIME. Whole-brain analysis of the interaction effects of the factors GROUP × TIME revealed no significant results; however, ROI analysis of the hippocampal formation indicated a significant interaction effect of the factors GROUP × TIME in the left parahippocampal gyrus (Fig. 3; maximum at $x=-19$, $y=-40$, $z=-4$; cluster size 14 voxels; $t=6.33$, $p<0.05$, FWE corrected). Analysis of the individual BOLD response differences between baseline and follow-up (t2> t1) at the maximum of the parahippocampal cluster indicated increased activity in the CGs between t1 and t2; but decreased activity in the UGs. Because the groups showed a large variation in the amount of cannabis used between t1 and t2 (see Table 2) an additional ANCOVA with the estimated cumulative interim dose of cannabis as covariate was performed. After controlling for the amount of cannabis used between t1 and t2 the interaction effect of the factors GROUP × TIME in the left parahippocampal cluster remained significant (maximum at $x=-19$, $y=-40$, $z=-4$; cluster size 21 voxels; $t=7.04$; FWE corrected).

Analyses of the retrieval task revealed a significant main effect of the factor TASK in the associative memory network (for detailed description, see Becker et al. 2010). However, ROI analysis revealed that during retrieval no significant activity passed the threshold for significance within the hippocampal formation (minimum voxel size: 10, $p<0.05$, FWE and small volume corrected). Whole-brain and ROI analyses revealed no significant main or interaction effect. Analysis of between-group differences for the effect of the factor TASK (retrieval > control) at both time points revealed no significant results.

To further explore the group × time interaction effect during encoding, individual parameter estimates for the pooled encoding conditions were extracted from a spherical ROI (radius=6 mm) centered at the maximum t-value of the parahippocampal cluster. Repeated-measures ANOVAs for the encoding condition with group (controls vs. users) as between-subject factor and time point (t1 vs. t2) as within subject factor revealed a significant interaction ($F(1,26)=20.27$, $p<0.001$) in the absence of a main effect of group ($F(1,26)=0.49$, $p=0.49$) or time point ($F(1,26)=0.83$, $p=0.37$). Post hoc multiple comparisons using Bonferroni-corrected paired t-tests revealed increased encoding-related

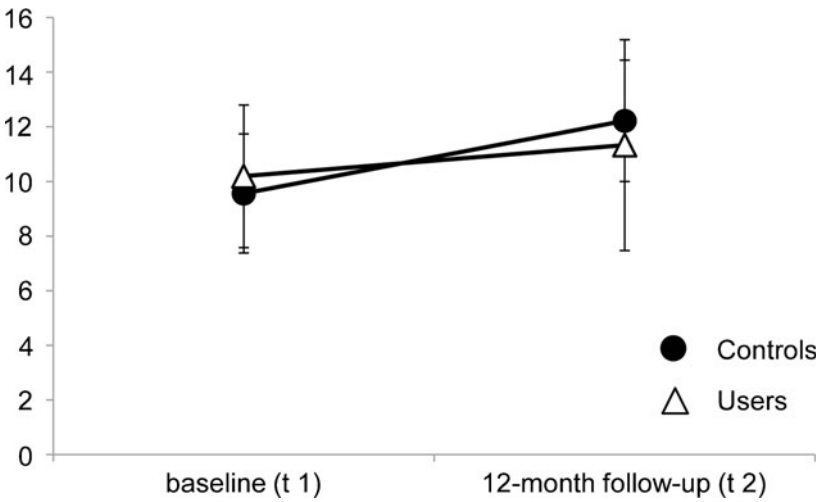

Fig. 1 Mean (±standard deviation) correct retrieved profession categories during the retrieval run of the associative memory task (maximum correct responses=16) of interim abstinent users (controls, $n=12$) and users who began using ecstasy and/or amphetamine on a regular basis (user, $n=17$) at baseline (t 1) and 12-month follow-up (t 2)

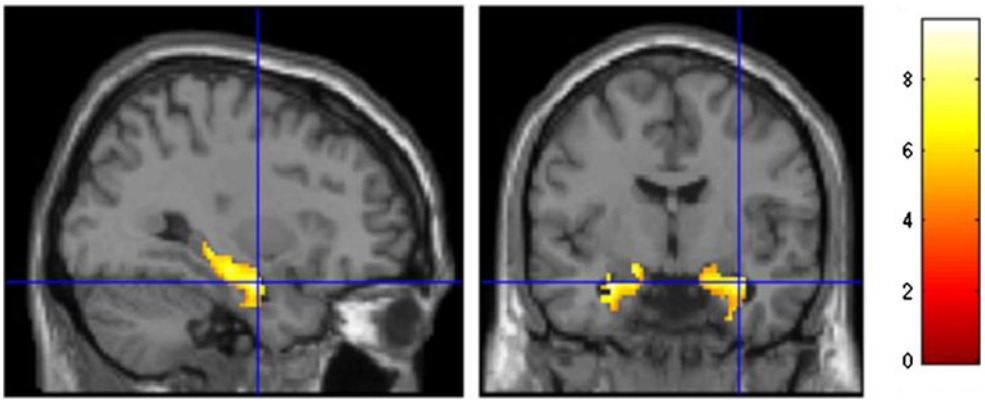

Fig. 2 Main effect of task for the pooled encoding conditions of the associative memory task (active>control; $p<0.05$, FWE and small volume corrected) in the ROI comprising the hippocampus and parahippocampal gyrus (bilateral). Maximum t-value located at $x=31$, $y=-9$, $z=-13$ (Talairach space)

activity from t1 to t2 in the control group ($t(11)=-2.95$, $p=0.013$), whereas users displayed a significant decrease from t1 to t2 ($t(16)=3.38$, $p=0.004$) (Fig. 4). In addition post hoc test using Bonferroni-corrected unpaired t-tests were used to test for between-group differences at both time points. Compared to controls, users displayed significantly higher encoding-related activity at t1 ($t(27)=-3.57$, $p=0.001$), but not at t2 ($t(27)=1.65$, $p=0.11$).

Correlation analyses

To disentangle specific contributions of ecstasy and amphetamine use to interim changes in left parahippocampal BOLD response in the UGs, individual contrast images for the main effect of the factor TIME and different parameters of interim amphetamine ecstasy use (interim cumulative dose, highest reported interim 1-night dose, time since last use at t2) were entered in an SPM simple regression. Statistical power of this exploratory analysis was increased restricting the analysis to the left parahippocampus (structurally defined using WFU pickatlas; Maldjian et al. 2003, 2004; Tzourio-Mazoyer et al. 2002). A higher cumulative interim ecstasy dosage was related to lower activity at t2 relative to t1 (maximum at $x=-28$, $y=-42$, $z=0$; cluster size 12 voxels; $t=5.76$, $p<0.001$, uncorrected). An additional analysis of correlations between interim changes and parameters of cannabis use revealed no significant results.

Discussion

The present prospective study investigated the effects of moderate recreational ecstasy use on hippocampal functioning. fMRI was used to examine memory-related hippocampal functioning in 40 subjects with very low amphetamine and/or ecstasy experience (less than five units lifetime dose). After a 12-month follow-up subjects were re-examined. At the 12-month follow-up subjects were classified according to their interim ecstasy and/or amphetamine use: (1) subjects with continued use during follow-up (>5 ecstasy tablets and/or > grams of amphetamine) ($n=17$) and (2) subjects with complete abstinence after the initial examination. To clearly separate the groups 11 subjects with only sporadic use during the follow-up period were excluded from further analysis. Analysis of behavioral data revealed no significant differences between abstinent and continuing users in associative memory performance as measured by retrieval accuracy. However, encoding-related activity in the left parahippocampal gyrus changed differentially between the groups. Repeated-measures analysis revealed a significant GROUP × TIME interaction effect in this region such that encoding-related activity decreased in continuing ecstasy and/or amphetamine user but increased in abstinent subjects from baseline to follow-up. In subjects with continued use, decreases within the parahippocampal gyrus showed a dose–response relationship with the extent of interim

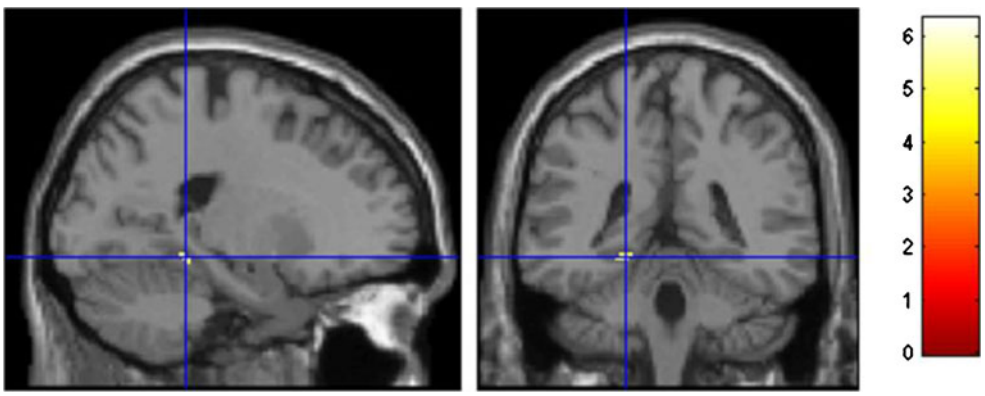

Fig. 3 Group × time interaction effect in left parahippocampal gyrus during encoding. Crosshairs at maximum t-value ($t=6.33$; $p<0.05$, FWE and small volume corrected) located in Talairach space at $x=-19$, $y=-40$, $z=-4$

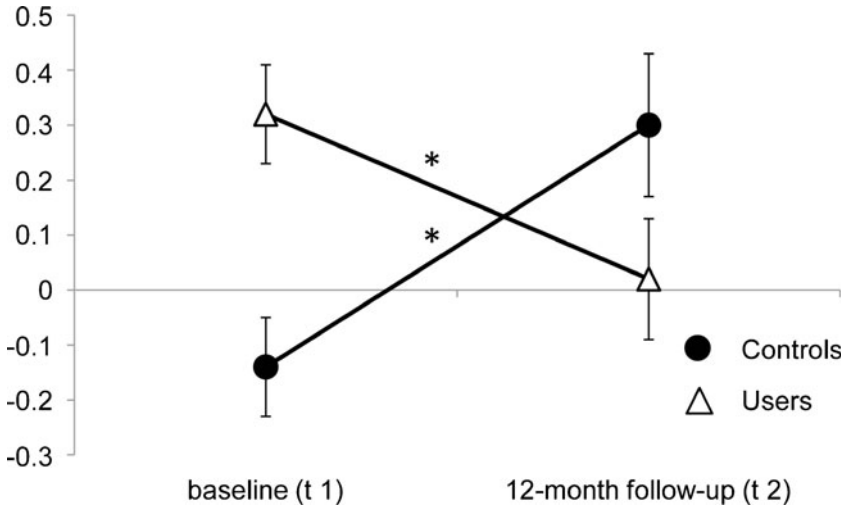

Fig. 4 Extracted parameter values for the encoding condition at baseline (t1) and 12-month follow-up (t2). Post hoc Bonferroni-corrected paired *t*-tests revealed increased encoding-related activity from t1 to t2 in the control group ($t(11)=-2.95$, $p=0.013$), whereas users displayed a significant decrease from t1 to t2 ($t(16)=3.38$, $p=0.004$)

ecstasy use, but not interim amphetamine or cannabis use, suggesting ecstasy-specific effects.

Besides the effects of ecstasy alternative explanations of the observed effects are conceivable. First, regular use of cannabis has been associated with altered hippocampal functioning up to 7 days after last use (Eldreth et al. 2004; Jager et al. 2007; Nestor et al. 2008; Becker et al. 2010). Continuing users in the present study had more THC-positive urine samples at follow-up and had used more cannabis during the follow-up period; therefore, confounding (sub-acute) effects of cannabis on hippocampal functioning cannot be excluded. However, between-group effects remained stable after controlling for interim cannabis use and decreases within the continuing users did not show significant associations with the time since last cannabis use. Second, already at the initial examination future abstinent and future regular users demonstrated differences in hippocampal activity. Differences in the abstinence periods at baseline might have confounded the initial data acquisition. However, interim regular users reported similar abstinence periods prior to both examinations suggesting that the lengths of abstinence might not fully account for the observed hippocampal decreases in this group. Moreover, baseline differences might represent pre-existing differences in hippocampal functioning that might lead to continued ecstasy and/or amphetamine use.

In line with previous cross-sectional studies in moderate users of ecstasy (Halpern et al. 2004; Gouzoulis-Mayfrank et al. 2003; Reneman et al. 2006), the present study did not detect significant deficits in memory performance. However, a prospective study found that a low cumulative dose of ecstasy (mean cumulative dose, 3.2 tablets) was associated with a subtle decline in verbal memory (Schilt et al. 2007). In this study neuropsychological performance in incident ecstasy users before and after a period of first ecstasy use was compared to baseline and follow-up performance of matched controls, who did not start to use ecstasy. Using change scores (follow-up minus baseline) the authors found that verbal memory performance changed differentially between the groups. Ecstasy naïve controls showed improved performance at follow-up, whereas incident users failed to improve. Notably, analysis of change scores in the present study revealed a similar, yet non-significant pattern of attenuated re-test effects in the continuing users. Given that estimated effect sizes in both studies were rather small the sample size in the present study was not sufficient to detect possible effects on the behavioral level.

Despite this lack of effects on the behavioral level we found significantly decreased parahippocampal activity after continued use. This is in line with previous cross-sectional reports on decreased parahippocampal activity in heavy poly-drug ecstasy users (Daumann et al. 2005) and adolescents with moderate ecstasy use (Jacobsen et al. 2004). Decreases within the left parahippocampal gyrus showed a dose–response relationship with the extent of interim ecstasy use, but not with parameters of interim amphetamine or cannabis use, suggesting ecstasy-specific effects. Previous findings on specific effects of amphetamine on hippocampal functioning in the context of ecstasy use (Jager et al. 2008) could not be confirmed in the present sample. Diverging results might be explained in terms of differences in study design and sample characteristics. Whereas the previous study used a multiple regression approach to disentangle ecstasy- and amphetamine-specific effects, the present study used a prospective longitudinal design. Moreover, heavy ecstasy users participating in the previous study had used substantially larger cumulative doses of ecstasy and amphetamine, than the moderate users in the present study. It is conceivable that ecstasy-specific effect might become apparent even with low cumulative ecstasy doses, whereas amphetamine-specific effects become only apparent with higher cumulative doses. Admittedly, associations between interim ecstasy use and changes in neural activity were rather weak in the present sample. Due to the relatively low doses

of interim ecstasy use and the short follow-up period, parameters of ecstasy use showed very limited variation in the present sample. Furthermore, confounders such as variations in the amount of MDMA within the ecstasy tablets used, or inaccuracies in self-reported drug use are likely to have a stronger biasing effect on dose–response relationships in samples with moderate use, compared to samples with heavier use patterns. Findings from the correlational analysis therefore represent preliminary findings that need to be confirmed in future studies.

In contrast to previous investigations from our own research team and other groups (Daumann et al. 2003, 2004; Moeller et al. 2004; Quednow et al. 2006), the present study failed to find evidence of ecstasy-associated dysfunctions in fronto-parietal regions. Again, the comparably low cumulative doses of ecstasy and amphetamine used in the present sample might explain the diverging results. Deficits in fronto-parietal regions might only become apparent after heavy and prolonged use.

The hippocampus and parahippocampus display relatively high rates of serotonergic denervation after MDMA exposure and relatively low recovery after abstinence in animal studies (Fischer et al. 1995; Hatzidimitriou et al. 1999). Human ecstasy users show long-term alterations in biochemical markers of the serotonergic system (Ricaurte et al. 1990; McCann et al. 2008; Kish et al. 2010; Reneman et al. 2001). Serotonin mediates vasoconstriction and in laboratory animals and MDMA has been shown to induce persisting effects on cerebral blood flow (Ferrington et al. 2006; Rosa-Neto et al. 2004) Findings from a recent prospective study in low dose ecstasy users suggest sustained effects of ecstasy on brain microvasculature (de Win et al. 2008). As it has been proposed that changes in vasculature directly affect the BOLD signal underlying functional MRI (Carusone et al. 2002), findings from the present study might suggest ecstasy-related changes in brain microvasculature, possibly mediated by lower serotonergic tone in the continuing users.

However, further analysis of the interaction effect in the parahippocampal region revealed that the interaction was also driven by relatively increased activity in the interim abstinent users. Given that some studies suggest normalization of the serotonergic system after prolonged abstinence (Buchert et al. 2004), we cannot exclude the possibility that recovery processes in the abstinent users might underlie the present findings. To recruit participants with a high probability of future ecstasy use and to avoid large oversampling, we decided to recruit participants who had first but very limited experience with ecstasy and/or amphetamine at baseline. However, recent findings from prospective studies with novice ecstasy users suggest that even first low cumulative doses of ecstasy might lead to measureable alterations in serotonergic functioning (de Win et al. 2007, 2008; Schilt et al. 2007). Given that adolescent ecstasy users with moderate use have shown reduced hippocampal activity (Jacobsen et al. 2004) and serotonergic alterations in ecstasy users might be reversible (Buchert et al. 2004), interaction effects in the present sample might reflect long-term recovery processes in the abstinent users. However, in other studies the moderate use of ecstasy was not associated with measurable alterations (Gouzoulis-Mayfrank et al. 2003; Halpern et al. 2004) and findings from a follow-up study suggest that altered cerebral activation patterns, at least in former heavy ecstasy users, do not reverse after several months of abstinence (Daumann et al. 2004).

Although the prospective design of this investigation might help to overcome some methodological shortcomings of previous studies, we are well aware of its methodological limitations, inherent to virtually every open-field study. First, although this study incorporated a prospective design, most known confounders were controlled for and a broad range of methods was used to recruit participants (advertisement in magazines and newspapers, notifications posted on campus, radio interviews), we cannot exclude that unknown factors or selective sampling might have contributed to the present findings. Only experimental designs with randomly selected samples could offer evidence of causality; however, direct experimental approaches in humans remain controversial. Second, most participants used amphetamine and ecstasy. During the last years this pattern of poly drug use has become established in recreational ecstasy users (Gouzoulis-Mayfrank and Daumann 2006a; Smart and Ogborne 2000). Even though alterations in the present sample were only related to the extent of interim ecstasy use, and interim doses of amphetamine and ecstasy were not associated (Pearson correlation; $p=0.649$), we cannot completely rule out that complex interaction effects among the drugs might have led to the present findings. Third, drug histories were assessed by self-report. Before participants were included in the baseline examination they were interviewed about their drug histories (without being told of the precise inclusion and exclusion criteria). Furthermore, analysis of randomly taken hair samples was used to confirm self-reported drug use at baseline and follow-up. However, due to short hairstyles and the fact that the adherence of drugs onto hair varies strongly depending on the physical characteristics of the hair and the kind of care applied to it, we cannot completely rule out that inaccuracies in the reported drug histories might have biased our results. Fourth, there was no control on purity or amount of MDMA in the ecstasy tablets used. However, recent data suggest that in the years 2006 and 2007 nearly 99 % of the tablets sold as ecstasy were monopreparations, with approximately 98 % containing MDMA (EMCDDA Annual report: the state of the drugs problem in Europe 2007). Fifth, in the present study we did not control for acute alcohol intoxication. The use of breath analyzers in future studies

might help to overcome this shortcoming. Finally, although detailed information about the pattern of drug use was assessed within the drug use interview, the environment in which the drug was actually used was not assessed. Findings from previous studies suggest that the neurotoxic effects of MDMA may be enhanced under certain conditions, such as hot, overcrowded surroundings and long periods of dancing; possibly mediated by an increase in body temperature (Colado et al. 1998; Green et al. 2003; Parrott 2004). However, there does not seem to be an easy solution for this issue.

In conclusion, findings from the present prospective study suggests that moderate use of ecstasy is associated with altered hippocampal functioning. However, confounding effects of cannabis on hippocampal functioning could not be ruled out. Further research should address the specific effects of cannabis in the context of ecstasy use and incorporate longer follow-up periods to address progression, persistency and reversibility of the alterations.

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Conflicts of interest None of the authors has declared any conflict of interest.

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