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ORIGINAL INVESTIGATION

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Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) is neurotoxic in animal studies and its use has been associated with cognitive impairments in humans. *Objective:* To study hippocampal activation during the retrieval from episodic memory in polyvalent users of ecstasy. *Methods:* Twelve polyvalent ecstasy users and twelve matched controls were examined by means of functional magnetic resonance imaging (fMRI) while they retrieved face-profession associations from episodic memory. *Results:* Ecstasy users had a normal structural MRI scan without focal brain lesions or anatomical abnormalities. They exhibited equal retrieval accuracy during memory retrieval to that of the matched controls. Yet, their retrieval-related activity was lower and more spatially restricted in the left anterior hippocampus than that of the controls. *Conclusions:* These results provide evidence for abnormal hippocampal functioning in MDMA users even at the presence of normal memory performance. This finding may be linked to MDMA-induced neurotoxicity and suggests that diminished hippocampal activation during memory retrieval might be a more sensitive or earlier index of MDMA-related neurotoxicity than neuropsychological performance.

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Introduction

The synthetic drug 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) has been shown to be neurotoxic upon central serotonergic systems in animal studies when administered at high or repeated doses (Ricaurte et al. 1992, 2000). Growing evidence suggests that these toxic effects can be long-lasting or permanent (Fischer et al. 1995; Hatzidimitriou et al. 1999) and may also occur in human recreational ecstasy users (McCann et al. 1998, 2000; Reneman et al. 2001). Serotonin (5-HT) is thought to be involved in the modulation of numerous functions including cognition, particularly memory processes (Riedel et al. 1999; Buhot et al. 2000). To date, studies of ecstasy users have accumulated evidence in favor of dose-related impairments in some, but not all, cognitive functions. The most pronounced deficits in MDMA users seem to affect learning and memory abilities (Bolla et al. 1998; Parrott and Lasky 1998; Morgan 1999; Gouzoulis-Mayfrank et al. 2000, 2003; Rodgers 2001; Bhattachary and Powell 2001; Zakzanis and Young 2001a; McCardle et al. 2004). In addition, deficits of central executive control, working memory and selective attention as well as elevated impulsivity and poor problem solving have also been found, although these results have been less consistent (Curran and Travill 1997; Morgan 1998; McCann et al. 1999; Dafters et al. 1999; Wareing et al. 2000; Gouzoulis-Mayfrank et al. 2000; Verkes et al. 2001; Zakzanis and Young 2001b; Zakzanis et al. 2002; Wareing et al. 2004).

This pattern of cognitive performance with predominant memory dysfunction in ecstasy users suggests that the function of the hippocampus, a region which is linked especially to memory processes, might be more profoundly affected by the neurotoxic effects of MDMA use than the function of neocortical regions (Fox et al. 2002; Gouzoulis-Mayfrank et al. 2003). Indeed, the hippocampus and para-

hippocampal gyrus display relatively high rates of serotonergic denervation after MDMA exposure and relatively low rates of recovery after abstinence from MDMA in animal studies (Ricaurte et al. 1992; Fischer et al. 1995; Hatzidimitriou et al. 1999). Of all the brain regions examined in a recent study with non-human primates, the subiculum, a part of the hippocampal formation with important connections to the mamillar bodies and the anterior nucleus of the thalamus, showed the largest reduction in the density of 5-HT immunoreactive axons 7 years after treatment with MDMA (Hatzidimitriou et al. 1999). This finding concurs with the known vulnerability of the hippocampal area to various toxic events (Guo et al. 1999). Because the hippocampal area plays a prominent role in episodic memory (memory for episodes and their temporo-spatial context) (Henke et al. 1997), we expected to find memory-related hippocampal dysfunction in ecstasy users versus controls by use of functional magnetic resonance imaging (fMRI).

Methods

Subjects

Seven male and five female subjects (mean age: 26.27± 3.66 years, years of education: 12.75±0.87) who had been taking MDMA on a regular basis were recruited. A control group of seven male and five female subjects (mean age: 26.25±2.56 years, years of education: 12.90±0.30) was matched for age, level of education and cannabis use with the MDMA group. Inclusion and exclusion criteria were the same as in a previous study by our group (Daumann et al. 2003). MDMA users agreed to abstain from drug use for at least 7 days prior to the study with the exception of cannabis. Both MDMA users and controls agreed to abstain from cannabis for at least 1 day prior to testing. Drug screens for stimulant amphetamines, MDMA, cocaine and its metabolite, cannabis, benzodiazepines, barbiturates and opiates were performed on urine samples on the study day. Subjects were excluded if they had a positive drug screen on the day of the study (except for cannabis).

Procedure

All subjects underwent two encoding runs separated into two fMRI time series and one retrieval fMRI time series. The encoding time series consisted of two conditions, an experimental condition including the associative learning of 16 face-profession (written professions) pairs, and a control condition including the repeated encoding of a single facial contour. The encoding instruction simply required subjects to learn the face-profession combinations. The retrieval fMRI time series consisted also of one experimental and one control condition. The previously presented 16 faces were presented again in the experimental condition with the instruction to retrieve the associated professions and to indicate their category (academic or artist) by button press. Facial contours were presented in the control condition with the instruction to indicate by button press whether the area of the left or the right ear was larger. This control condition was used to match for motor output and eye-scanning patterns. All stimuli were presented for 5 s (for details of the stimuli see Henke et al. 2003). In a previous pilot study with eight normal subjects on the same scanner, the face-profession retrieval task had yielded reliable bilateral hippocampal activity (left maximum: −16, −24, −15; cluster size: 34 voxels; z=3.92; df=7; P<0.001; right maximum: 24, −20, −15; cluster size: 24 voxels; z=4.04; df=7; P<0.001, n=8), while the face-profession encoding task had failed to yield consistent hippocampal activation (unpublished data, not shown). Therefore, in the present study, we focused on the retrieval results.

Imaging parameters

Functional (BOLD) data were acquired with blocks of four trials on a 1.5 T Philips Gyroscan scanner with a standard headcoil. Functional data were acquired with a single-shot gradient-refocused echo-planar sequence (TR: 4.0 s, TE: 50 ms, flip angle: 90°, slice thickness: 4 mm, 25 slices). For anatomic reference and to exclude subjects with apparent brain pathologies, we additionally obtained a T1-weighted inversion recovery sequence (imaging parameters: TR: 2,000 ms, TE: 22 ms, TI: 400 ms, Matrix 256×256, slice thickness: 3 mm). The study was in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee at the RWTH Aachen.

Statistics

Group differences for age, drug use and memory performance were analyzed by means of Student t-tests, and differences in the level of education by means of the Mann–Whitney U-test using SPSS 11.0 software (SPSS, Inc., Chicago, IL, USA). fMRI data were analyzed with SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Scans were realigned and spatially normalised into standard stereotactic space (MNI template). Reconstructed voxel size was 3×3×3 mm^3. Data were smoothed with a Gaussian kernel of 9 mm. Individual voxel-by-voxel parameter estimation was carried out using the general linear model. The resulting individual beta-maps were compared by means of linear contrasts of the experimental conditions and the control conditions. Group contrasts were computed by use of a random-effects model. Data were corrected for multiple comparisons within boxes of 10×10×10 mm^3 around medial temporal voxels that had exhibited significant activation differences between conditions in a previous pilot study with eight subjects [P=0.05, small volume corrected (svcorr.)]. The resulting SPM(t)-maps were transformed into Talairach space (Talairach and Tournoux 1988).

Results

Drug histories and task performance

Patterns of use of ecstasy, amphetamine and cannabis are presented in Table 1. MDMA users and controls exhibited a comparable use of cannabis with a similar age of first use (t=1.02, df=22, P=0.31), duration of regular use (t=0.21, df=22, P=0.88), time passed since last use (t=1.08, df=22, P=0.30) and average number of cannabis sessions per month (t=0.52, df=22, P=0.60). However, the daily cannabis dose was significantly higher in the MDMA users than the controls (t=−3.19, df=22, P<0.01). Of the 12 MDMA users (but no control subject) 6 reported concomitant use of stimulant amphetamines. All subjects denied regular heavy use of alcohol (defined as severe drunkenness occurring at a frequency of at least twice per month) or regular use of any other psychotropic drug (defined as use once per month or more frequently over 6 months or longer within the last 2 years). Retrieval performance in terms of accuracy did not differ significantly between MDMA users and controls (users: 11.1±2.2 correct responses; controls: 11.6±2.6 correct responses; t=0.68, P=0.50, df=22).

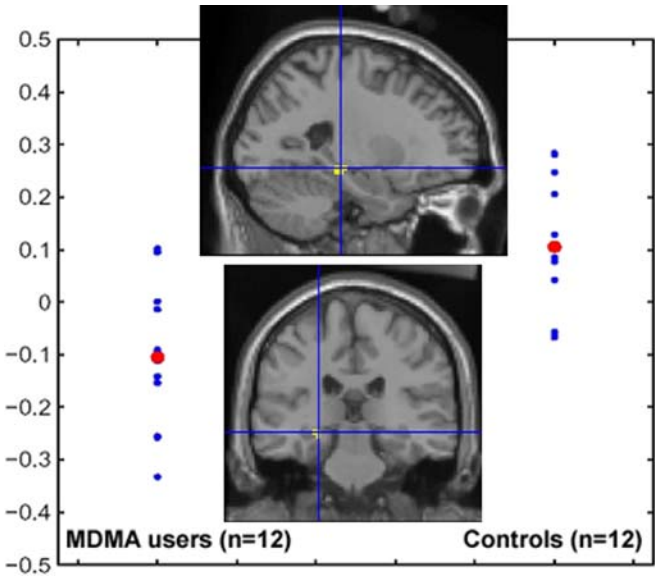

Fig. 1 Lower and more spatially restricted retrieval-related activity in the left anterior hippocampus of MDMA users compared with matched controls (n=12 in each group; z=3.20; df=22; P<0.05, small volume correction). The scatter plot illustrates the individual distribution of relative signal differences at maximum (−24, −27, −9)

Functional MRI results

All subjects had a normal structural MRI scan without focal brain lesions or anatomical abnormalities. As in the pilot study (see "Procedure") the retrieval-control contrast resulted in bilateral hippocampal activity in the control group (left maximum: −24, −15, −12; cluster size: 38 voxels; z=4.08; df=11; P<0.001, n=12; right maximum: 18, −15, −18; cluster size: 37 voxels; z=3.87; df=11; P<0.001, n=12). The comparison of the retrieval-control contrast between MDMA users and controls yielded significantly lower activity levels in the left hippocampus (maximum: −24, −27, −9; cluster size: 10 voxels; z=3.20; df=22; P<0.05, svcorr.) in the ecstasy-using sample (Fig. 1). We found no other significant fMRI signal differences between MDMA users and controls, and no significant correlation between hippocampal BOLD-response and task performance or drug use patterns in ecstasy users. Finally, we compared amphetamine users with non-amphetamine users within the ecstasy sample. However, this analysis did not give any additional significant results.

Conclusions

Our results provide evidence for the hypothesis that ecstasy users show neural dysfunction in the hippocampus. This result is in line with the well-known long-lasting toxic effects of MDMA on brain 5-HT neurons (Hatzidimitriou et al. 1999) and supports a large number of studies reporting (subclinical) memory deficits (Gouzoulis-Mayfrank et al. 2003; Fox et al. 2002) and hippocampal dysfunction (Jacobson et al. 2004) in ecstasy users. Indeed, it has been shown that the serotonin-containing neurons of the median raphe nucleus targeting the hippocampus are critically

Table 1 Patterns of ecstasy, amphetamine and cannabis use in ecstasy users and cannabis use in controls (n=12 in each group)

	MDMA users			Controls
	Ecstasy	Amphetamine	Cannabis	Cannabis
Regular/sporadic/no use	12/0/0	6/0/0	6/0/0	5/1/0
Lifetime dose	201.73±224.18 tablets	165.07±185.92 g	x	x
Duration of regular use (months)	31.64±26.73	42.00±31.06	96.33±44.91	76.80±30.12
Average frequency of use (days per month)	2.15±1.37	2.83±1.65	14.27±13.65	22.00±10.93
Average daily or one night dose	2.69±1.85 tablets	212.06±251.32 mg	725.00±301.19 mg	330.82±171.76 mg
Age at onset of use	20.38±3.77	19.82±3.74	15.38±1.60	16.00±2.24
Time since last dose (days)	51.64±56.37	367.38±870.53	29.29±66.61	36.80±80.05
THC-screen in urine sample on study day	–	–	6 positive/6 negative	4 positive/8 negative

x: subjects felt that they were unable to give a reliable estimate

involved in memory functions (Vertes and Kocsis 1997) and that activation of serotonin 5-HT_{1A} receptors stimulates neurogenesis in the dentate gyrus (Gould 1999).

Surprisingly, MDMA users in our sample exhibited similar retrieval accuracy during memory retrieval as the matched controls. One possible explanation for this negative finding may be that the fMRI-memory task has been a less sensitive marker for cognitive decline in ecstasy users than other memory tasks that we and others used in previous neuropsychological studies (Bolla et al. 1998; Parrott and Lasky 1998; Morgan 1999; Gouzoulis-Mayfrank et al. 2000, 2003; Rodgers 2001; Bhattachary and Powell 2001; Zakzanis and Young 2001a; McCardle et al. 2004).

Alternatively, the absence of significant differences in performance between ecstasy users and controls could be simply due to lack of statistical power because of the relatively small sample sizes in the present functional imaging study relative to the mostly larger sample sizes in studies on cognition.

It is conceivable, however, that a reduced BOLD response reflects neural malfunction already at a time when memory performance is still within normal range. Interestingly, in clinical populations, fMRI signal alterations in the left hippocampus were shown to predict incipient cognitive decline years before the manifestation of a measurable cognitive failure (Bookheimer et al. 2000). However, in the same study, better memory performance was associated with smaller and more focal BOLD signal. This challenges our own results, since the territory of neural tissue recruited during memory retrieval was smaller in ecstasy users than in controls. Hence, one might conclude that ecstasy users in our study exhibited a relatively higher neural efficiency. However, for signal intensity to be increased in response to cognitive demands there has to be enough intact neural tissue. For example, Bäckman et al. (1999) found decreased hippocampal activity during episodic retrieval in patients in an early phase of Alzheimer's disease. Based on our findings, it remains unclear whether MDMA has the potential to induce substantial neural loss in recreational ecstasy users. To account for this issue, future studies should combine functional imaging, morphometric and/or spectroscopic approaches to further investigate the relationship between potential anatomical and functional alterations in recreational ecstasy users. First structural evidence comes from a voxel-based morphometry study in ecstasy users (Cowan et al. 2003). The authors reported decreased gray matter concentration in MDMA polydrug users in several neocortical regions, the bilateral cerebellum and the midline brainstem. Furthermore, in a most recent proton magnetic resonance spectroscopy study of our own research group, we found no differences between *N*-acetylaspartate/creatine ratios of users and controls in neocortical regions, yet a tendency towards lower ratios in the left hippocampus of MDMA users (Daumann et al. 2004). However, in both studies, data were not correlated with functional imaging measures (Cowan et al. 2003; Daumann et al. 2004).

The present study has methodological limitations which are inherent to open-trial studies with user populations. Most importantly, the tendency towards polyvalent drug use has strongly increased over the past years, thus making it almost impossible to recruit pure ecstasy users. In the present study, half of the MDMA users reported regular concomitant use of stimulant amphetamines, which were also shown to be neurotoxic in animals (Villemagne et al. 1998) and possibly in humans (Volkow and Fowler 2002). Although we found no statistical differences between amphetamine users and non-amphetamine users, this lack of significance could be due to the small size of the samples. Therefore, given the cross-sectional nature of our study, we cannot rule out the possibility that amphetamine use may have contributed to the lower hippocampal activation in our users. Longitudinal studies, in which subjects are examined at regular intervals, should help to overcome a large number of common methodological limitations to be encountered in open-field studies with ecstasy users.

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