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Research report

Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study

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Abstract

The popular recreational drug ecstasy (3,4-methylenedioxymethamphetamine=MDMA and related congeners) is neurotoxic upon central serotonergic systems in animal studies. So far, the most convincing evidence for neurotoxicity-related functional deficit in humans derives from neurocognitive studies demonstrating dose-related long-term learning and memory problems in ecstasy users. In our study we used functional magnetic resonance imaging (fMRI) and a working memory task to investigate cerebral activation in eleven heavy, but currently abstinent MDMA users and two equally sized groups of moderate users and non-users. There were no significan group differences in working memory performance and no differences in cortical activation patterns for a conservative level of significance However, for a more liberal statistical criterion, both user groups showed stronger activations than controls in right parietal cortex. Furthermore, heavy users had a weaker blood oxygenation level-dependent (BOLD) response than moderate users and controls in frontal and temporal areas. Our results may indicate subtle altered brain functioning associated with prior MDMA use, although alternative interpretations of these group differences must be considered.

Theme: Neural basis of behavior

Topic: Drugs of abuse: amphetamine and other stimulants

Keywords: MDMA; Ecstasy; Working memory; fMRI

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) has become a widely used recreational drug among young people. According to a recent German epidemiological study, 5.1% of the 14- to 15-year-olds and 7.1% of young adults have tried ecstasy at least once [38]. Several studies in other western European countries and the USA indicate similar frequencies and suggest that the popularity of ecstasy is still on the rise [1,14,29,40]. This is of great concern, since it is well known that laboratory animals develop widespread neurotoxic damage of central serotonergic axon terminals after repeated doses of MDMA [3,24,31–33,36]. There is growing evidence that toxic effects can be very long-lasting or even permanent in experimental animals [8,12] and may also occur in humans [17,19,20].

So far, the most convincing and consistent evidence for neurotoxicity-related functional deficit derives from neurocognitive studies demonstrating dose-related learning

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and memory problems in ecstasy users comprising episodic, semantic and working memory [4,11,16,21,23,25,26]. In addition, elevated impulsiveness [22], as well as impairments in selective attention [11] planning [35] and problem solving [18] were also demonstrated in abstinent ecstasy users, although these results have been less consistent. In many studies poorer cognitive performance was associated with heavier ecstasy use [4,11,15,18,21,30,37,41]. These finding strongly suggest that a dose-dependent neurotoxic effect may be responsible for a cognitive decline in ecstasy users. However, open trial studies with user populations are often concerned with confounding variables such as polydrug use patterns or premorbid neuropsychological performance.

If, however, some of the cognitive deficit observed in ecstasy users are indeed neurotoxicity-related, then the question arises whether specifi brain regions are particularly involved. In order to explore this issue, we investigated whether cognitive processing in abstinent ecstasy users is associated with altered cortical activation patterns as revealed by functional magnetic resonance imaging (fMRI). For several reasons we decided to use a working memory task for cognitive stimulation. First, a growing number of studies reported working memory deficit in ecstasy users [4,6,11,18,27,37,42]. Second, the cortical regions involved in working memory function have been widely explored in previous functional imaging studies [5]. The working memory network is known to include prefrontal and parietal and to a smaller extent cingulate, occipital, temporal and cerebellar regions. Given the fact that the MDMA-related neurotoxicity is widespread in animal studies it seemed reasonable to conduct our fMRI study using a cognitive task which activates several brain areas [3,12,24,31–33,36]. Finally, a working memory task with different levels of difficult (n-back task) was available. Such a task with graded difficult levels was required because the cognitive deficit in ecstasy users were shown to be mostly subtle [11]. A recent [$H_2^{15}O$]-PET study using a continuous performance test (CPT) reported no performance defici and no alteration in cerebral activation in ecstasy users compared to controls [9]. These latter finding are in line with the expectation that alterations in cognitive brain functions might manifest only when using demanding tasks. Based on these considerations, we hypothesized that low working memory performance in ecstasy users should be accompanied by alterations in the underlying cortical networks.

2. Materials and methods

21. Participants

Twenty-two ecstasy users were enrolled in this study. Using the median-split procedure we built a group of heavy and a group of moderate MDMA users ($n=11$ each, life-time dose at least 80, or less than 80 ecstasy tablets, respectively) and compared them to 11 healthy non-users. All subjects were right-handed and matched for age, sex and education (Table 1). Ecstasy users and controls were recruited directly in the dance scene, via word of mouth and via Internet. Users were included in the study if they had used MDMA regularly over at least 6 months with a minimum frequency of twice a month or if they had used MDMA on at least 20 occasions. Given the fact that the majority of ecstasy users experiment also with other typical club drugs, such as amphetamines and cannabis, users who reported experiences with those drugs were not excluded. However, subjects were excluded if they reported: (1) regular use of other legal or illegal psychotropic drugs such as opiates and benzodiazepines (regular use was define as use once per month or more frequently over 6 months or longer within the last 2 years); or (2) regular heavy use of alcohol (define as severe drunkenness occurring at a frequency of at least twice per month). The control group of non-users consisted of healthy persons who had never taken ecstasy and had no previous or current history of regular drug use or regular heavy alcohol use (definition according to the exclusion criteria of the ecstasy user groups). Exclusion criteria for all participants were: (1) a positive drug screen on the study day except for cannabis; (2) any current or previous axis I psychiatric diagnosis (except for drug abuse in the 2 user groups); (3) any organic brain disorder or any relevant general medical condition requiring pharmacological treatment; (4) metallic objects in the body; and (5) pregnancy. All ecstasy users agreed to abstain from drug use for at least 7 days prior to the study with the exception of cannabis from which some subjects agreed to abstain only on the study day. Given the fact that daily smoking of

Table 1
Demographic data of MDMA users and controls ($n=11$ in each group)

	Heavy users	Moderate users	Controls
Mean age (years)	27.00±3.92	23.27±2.49	25.64±2.34
Body weight (kg)	67.36±9.63	73.27±14.16	70.00±10.10
Men:women	8:3	8:3	8:3
Level of education			
Intermediate school (form 10)	3	1	3
At least preuniversity (form 13)	8	10	8

marijuana is part of the 'lifestyle' of most club drug users, it was implausible to insist on a longer period of abstinence. Subjects were screened by means of a preliminary telephone interview which was followed by a personal interview and medical history taking including the structured interview for the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and a detailed history of drug use. Drug screens were performed on the study day with urine samples for the following substance groups: amphetamines, methamphetamines, cocaine and its metabolite, marijuana, benzodiazepines, barbiturates and opiates. After detailed description of the study to the subjects, written informed consent was obtained and subjects were paid for their participation. The study was approved by the local ethics committee of the medical faculty at the RWTH Aachen.

22. Cognitive task

Subjects performed three n-back tasks consisting of the sequential visual presentation of single letters (B, C, D, G, P, T, F, N, L; duration of presentation 1500 ms; SOA 3000 ms). Subjects had to press a button, when a target stimulus appeared. Target definitio differed with respect to the experimental condition. In the 0-*back condition* the subjects had to respond when a stimulus within the sequence matched a target stimulus specifie at the beginning of the stimulus presentation (letter 'D'). In the 1-*back condition*, targets were define as stimuli within the sequence that were identical to the immediately preceding one. In the 2-*back condition* subjects had to respond if the presented letter matched the one that was presented two trials earlier. The 0-, 1-, and 2-back task differ in the amount of memory load and demands on executive control for the processing of information within working memory.

23. Experimental procedure

Before entering the scanner, all subjects were carefully instructed and trained in the n-back task by performing it once. Performance during this test was recorded and analyzed. In the fMRI study the PC-generated paradigms were presented to the subjects via a rear-projection screen and a mirror above the eyes, attached to the top of the head coil. For each task three OFF/ON cycles (90 s each) with rest as OFF condition (eyes open, 30 s) were employed (block-design). The tasks were presented in the sequence 0-back, 1-back, 2-back.

24. MR imaging procedure

Magnetic resonance imaging employing blood oxygenation level-dependent (BOLD) contrast was performed on a clinical 1.5 T Philips ACS NT Gyroscan (Philips, Eindhoven, The Netherlands) using a multishot T2* weighted gradient echo EPI sequence (imaging parameters: TR: 4000 ms, TE: 40 ms, FA: 40°, Matrix 64×64, FOV: 250×250 mm, 15 contiguous slices parallel to the AC–PC line covering the whole brain except for the cerebellum, voxel size 4×4×7 mm^3, no interslice gap). For anatomic reference and to exclude subjects with apparent brain pathologies, we additionally obtained a T1-weighted inversion recovery sequence (imaging parameters: TR: 2000 ms, TE: 22 ms, TI: 400 ms, Matrix 256×256, slice thickness: 7 mm). Head movements were minimized in all subjects using foam pads and Velcro straps. Images were acquired using a standard head coil. Every task was introduced by a verbal instruction presented via headphones.

25. Data analysis

Cognitive performance (reaction times [RT] and correct responses [CR]) was analyzed by means of analysis of variance with repeated measures for the task-factor (0-back, 1-back, 2-back) using SPSS 10.0 software (SPSS Inc., Chicago, IL). fMRI data were analyzed using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 5 (Mathworks Inc., Sherborn, MA). The scans obtained for each subject and each condition were initially realigned to the firs image of each scan. All mean images were subsequently transformed into the standard stereotaxic space corresponding to the atlas of Talairach and Tournoux [39]. Each normalized scan was smoothed with a Gaussian kernel (triple voxel size). Condition-specifi effects in every task were assessed by comparing the on-periods of each task with their respective control conditions (off-periods). Changes in regional blood flo were determined by applying the general linear model to each voxel. In order to explore differences between the three groups the computed contrasts (0-back, 1-back, 2-back) of each subject were entered into random-effects analyses. To account for both type 1 and type 2 error and to estimate the power of group differences, three ANOVAs with different height thresholds were computed (conservative level: $P<0.05$ (corrected); liberal levels: $P<0.01$ and $P<0.001$ (both uncorrected). Minimum cluster level was set to fiv voxels. MNI coordinates were converted into the stereotaxic space of Talairach and Tournoux [39] using a self-written automated Matlab-based script.

3. Results

31. Drug histories

The patterns of drug use in the two user samples are presented in Table 2. Concerning the use of ecstasy the two user groups differed significantl in terms of lifetime dose and duration of regular use. Other parameters of MDMA use patterns revealed no significan differences,

Table 2
Patterns of ecstasy, cannabis and amphetamine use in both user groups ($n=11$ in each group)

	Heavy users			Moderate users		
	Ecstasy	Amphetamine	Cannabis	Ecstasy	Amphetamine	Cannabis
Regular/sporadic/no use	11/0/0	6/1/4	6/0/5	10/1/0	5/0/6	7/0/4
Lifetime dose	258.18±220.25 tablets[a]	14.56±16.74 g	–	27.36±5.61 tablets[a]	7.91±15.20 g	–
Duration of regular use (months)	53.18±29.09[a]	19.91±28.09	52.36±54.27	16.20±13.28[a]	12.00±21.30	36.00±29.39
Average frequency of use (days per month)	2.78±3.59	4.33±3.67	9.00±11.65	1.80±1.38	1.64±2.63	13.23±13.93
Average daily or one night dose	1.91±0.94 tablets	190.91±188.17 mg	287.82±245.43 mg	1.57±0.76 tablets	122.73±180.78 mg	424.18±417.44 mg
Age at onset of use	21.27±3.77	21.13±2.90	15.17±1.60	20.18±2.79	17.80±2.28	16.50±2.20
Time since last dose (days)	89.27±210.48	204.25±313.45	3.17±2.99	330.09±520.65	67.40±97.00	4.25±3.24

[a] Significan group differences between heavy and moderate ecstasy users, $P=0.002$ (unpaired t-test, 2-tailed).

although heavy users tended to have a higher average frequency and a shorter period of abstinence than moderate users. In addition to the use of ecstasy, several subjects in both user groups reported concomitant amphetamine and cannabis use. The extent of amphetamine use tended to be higher in the heavy users; however, this difference failed to reach statistical significance Regular use of any other psychotropic drug was denied.

32. Behavioral results

Performance of subjects in the n-back tasks during the fMRI experiment is presented in Table 3. The effect of memory load was significan both on reaction times ($P=0.003$) and correct responses ($P=0.006$), but there was no significan difference between the three groups in reaction times ($P=0.509$) and no effect of correct responses ($P=0.334$). Heavy ecstasy users tended to perform slower in the 2-back condition, however, statistical analysis revealed no significan interaction of memory load and group ($P=0.152$). The data of the training session prior to the fMRI experiment were similar (data not shown).

33. fMRI results

All subjects had a normal structural MRI scan without focal brain lesions, as judged by an experienced neuroradiologist (A. Thron). In both groups of MDMA users as well as in the group of healthy controls functional MRI for all three tasks lead to significan and localized hemodynamic changes in prefrontal, parietal, occipital and cingulate brain regions, which are known to be involved in n-back tasks [5]. For the conservative level of significanc ($P<0.05$, corrected) the groups did not differ in terms of these brain regions (data not shown). Similarly, there were no activation differences in the 0-back task for the liberal criteria ($P<0.01$ and <0.001, uncorrected). However, using these liberal statistical criteria we found group differences in the mean level of activation in areas subserving the working memory both in the 1- and in the 2-back task.

34. 1-Back task

In the 1-back condition for the liberal criterion of $P<0.01$ (uncorrected) both user groups showed significantl larger activation than non-users in the right parietal cortex (Fig. 1A,B), with no significan differences between heavy and moderate MDMA users. These activation differences were lateralized to the right and localized in the supramarginal gyrus (Brodmann area (BA) 40). Compared to the control subjects this effect appeared to be more significan in the moderate user group (Maximum at Talairach coordinates [maxTC] 60, −28, 35; $Z=3.44$; cluster size [CS]=31) than in the heavy user group (maxTC 60, −32, 35; $Z=2.98$; CS=17). For the more conventional threshold of $P<0.001$ (uncorrected) only the difference between moderate users and controls achieved statistical significance

35. 2-Back task

For the liberal significanc level of $P<0.01$ (uncorrected) MDMA users showed increased activation of right parietal cortex compared to controls also in the 2-back task (Fig. 1C,D). In moderate users the maximum was located

Table 3
Cognitive performance in the n-back task: reaction time (RT) in ms and number of correct responses (CR) (group means and standard deviation, $n=11$ in each group)

	Heavy users		Moderate users		Controls	
	RT	CR	RT	CR	RT	CR
0-back	529.00±58.85	8.82±0.40	511.55±124.96	8.82±0.40	534.87±95.62	8.82±0.40
1-back	563.64±120.89	7.27±0.47	529.91±115.74	7.55±0.93	552.00±149.40	7.09±0.94
2-back	664.23±177.81	7.64±1.96	565.64±105.02	8.55±0.69	564.73±103.30	8.09±0.94

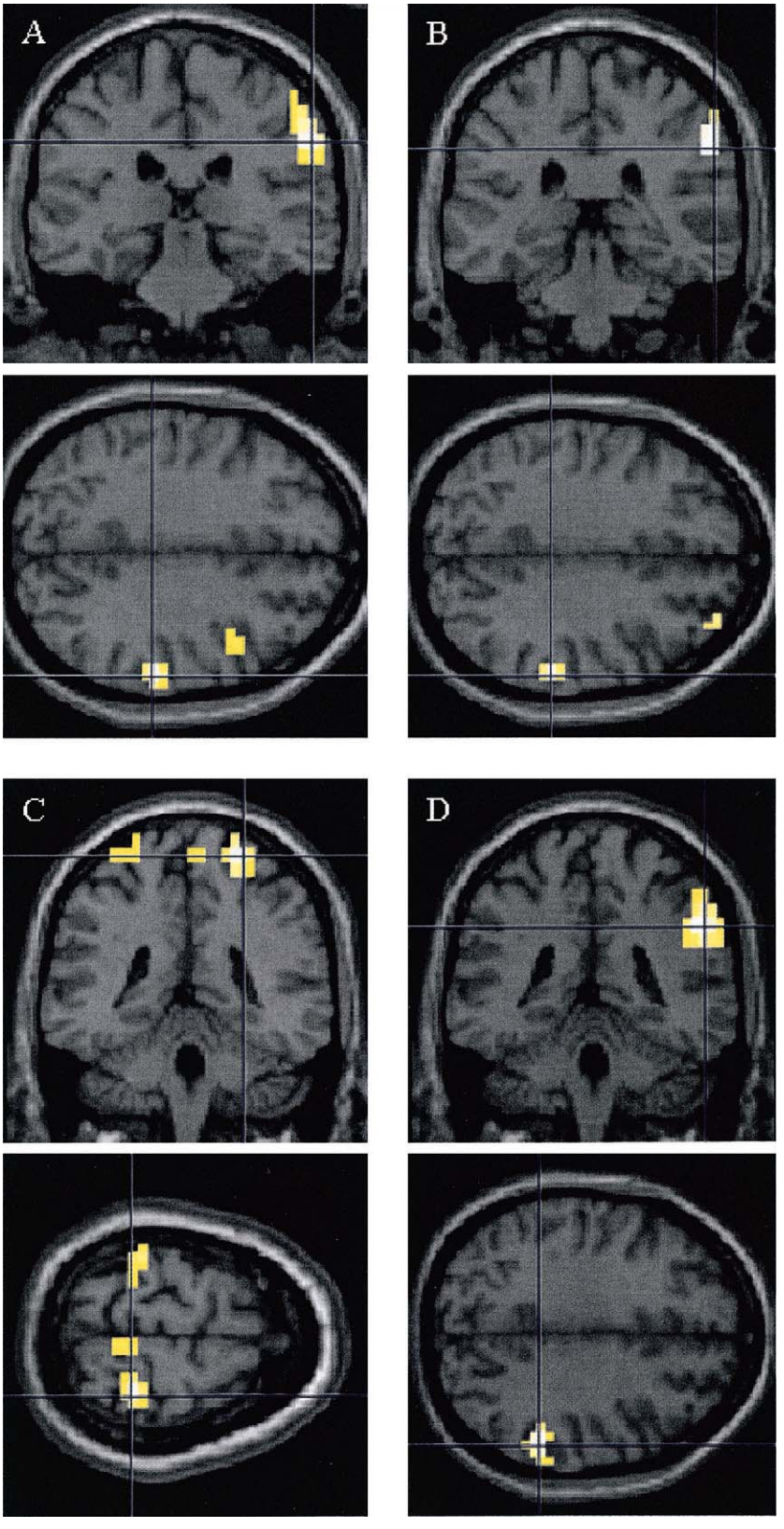

Fig. 1. Activation pattern differences in the 1-back task: moderate MDMA users>controls (A), heavy MDMA users>controls (B) and the 2-back task: moderate MDMA users>controls (C), heavy MDMA users>controls (D) ($P=0.01$, uncorrected).

more superior (BA 7) (maxTC 28, −40, 70; Z=3.47; CS=19). To a smaller extent this activation was found also in the left hemisphere (BA 40; maxTC −36, −36, 40; Z=2.84; CS=9). Compared to control subjects, heavy MDMA users showed a higher level of activation in right BA 40 (maxTC 56, −40, 35; Z=3.51; CS=34). Hence, the localization of the maximum signal change difference tended to be more inferior as compared to the moderate user group. A region in the left superior temporal lobe (BA 38: maxTC −44, 12, −14; Z=3.27; CS=75) showed less activation in heavy ecstasy users compared to control subjects (Fig. 2A,B). Further regions with a slightly lower degree of BOLD response in heavy MDMA users were located in the left superior frontal gyrus (BA 6: maxTC −4, 8, 56; Z=2.89; CS=19) and the anterior cingulate (maxTC 8, 32, 21; Z=2.88; CS=18). Compared to moderate MDMA users, heavy users showed lower signal changes in several left-lateralized frontal areas (Fig. 2C–E). These differences were most significan in the superior (BA 6 (maxTC −4, 8, 56; Z=4.13; CS=41) and BA9 (maxTC −28, 44, 28; Z=3.43; CS=27)) and inferior frontal gyrus (BA 47 (maxTC −48, 24, 0; Z=3.36; CS=34)). Using the more conventional threshold of $P<0.001$ (uncorrected) we could only verify the lower activation in the left superior temporal lobe in heavy ecstasy users compared to control subjects.

Adding task performance as a covariate in these analyses did not interfere with the presented results. Finally, in order to investigate associations between the extent of previous ecstasy use and BOLD signal changes in MDMA users we conducted additional correlation analyses. However, we found no significan relations between cluster sizes and patterns of drug use.

4. Discussion

Eleven heavy recreational ecstasy users and two equally sized matched groups of moderate ecstasy users and healthy non-users were examined with fMRI and a n-back task with increasing memory load. A growing number of studies have demonstrated working memory impairments in abstinent ecstasy users as well as deficit in episodic memory and learning [11,18,41,42]. To our surprise, in our study, performance in the n-back task revealed no statistically significan group differences, although heavy users tended to perform more slowly in the 2-back task. However, two recent studies also failed to demonstrate working memory deficit [7,15]. Thus, working memory impairment in ecstasy users might be less robust than deficit in episodic memory and learning.

Subjects of all three groups showed typical cortical activation patterns with no group differences for a conservative significanc level in the n-back task. However, for a more liberal criterion heavy users had relatively weaker BOLD responses in left frontal and temporal regions in the most demanding 2-back condition. Furthermore, heavy and moderate users showed elevated activation in the right parietal cortex with the 1- and 2-back task. However, given the relatively unimpaired cognitive performance in both user groups, the subtle difference in terms of cortical activation patterns are difficul to interpret. It is possible that the relatively weaker signals in frontal and temporal regions of heavy users during the 2-back task are associated with prior MDMA use, although we found no associations of activation patterns with the extent of previous drug use. However, it is also possible that other factors such as motivational aspects or different cognitive strategies might account for the observed activation differences. For example, in a study with normal subjects longer reaction times in a verbal n-back task were associated with higher cortical activations in bilateral parietal regions [13]. The authors suggest that this association may reflec a more powerful involvement of phonological storage function with longer response latencies [2,13]. In our study parietal activation was enhanced in both user samples and both the 1-back and 2-back condition, whereas only heavy users showed prolonged reaction times and only in the 2-back task. It is conceivable, however, that a different cognitive style does not inevitably lead to different performance, but may still account for differences in terms of cortical activation.

Ecstasy users in this study had also used amphetamines and cannabis. This poses a major problem for a non-ambiguous interpretation of the data, since the impact of these drugs on cognitive performance is well known. For example, in a recent study cannabis users reported short-term memory problems [34]. In another study, cognitive deficit including working memory problems were detectable at least 7 days after heavy cannabis use [28]. However, it has to be taken into account that this study dealt with the cognitive effects of *heavy* cannabis use. In contrast, participants in our study reported only *moderate* marijuana smoking. For example, none of our subjects would have suited the inclusion criteria of at least 5000 episodes of marijuana smoking, as it was define in the study by Pope and colleagues [28]. Furthermore, in a former study we found that moderate cannabis users performed equally well as healthy controls in a working memory task [11]. Nevertheless, the amount of amphetamine and cannabis use differed in both user groups, although these differences failed to achieve statistical significance Hence, we cannot eliminate the eventuality that these drugs are in part responsible for the accomplishment of our results.

In addition, both user groups tended to have a different length of abstinence from MDMA. Thus, to further clarify the impact of abstinence from MDMA, we computed an additional analysis (2-sample t-test) between abstinent and current ecstasy users, who reported a similar cumulative dose. This analysis revealed no differences in terms of

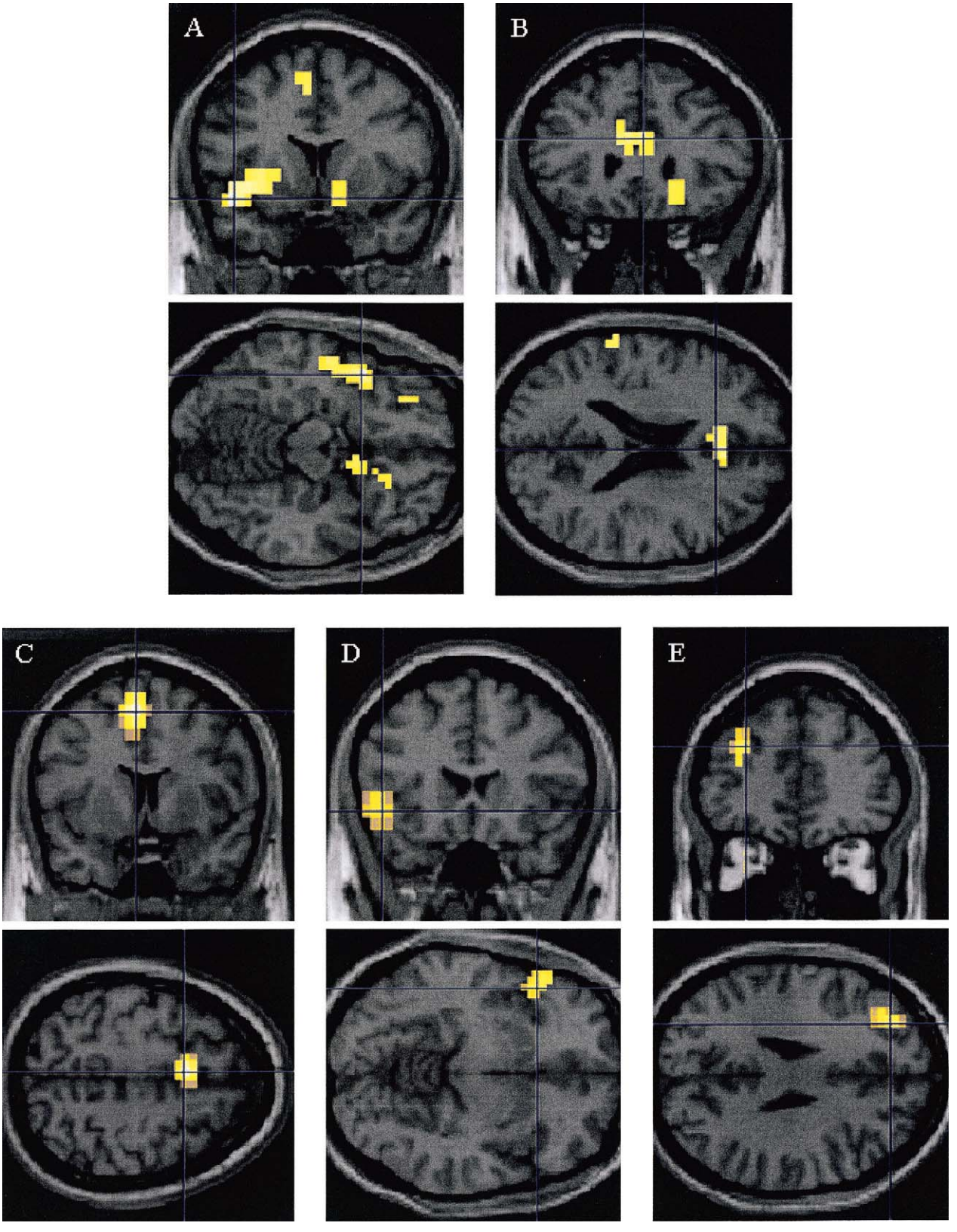

Fig. 2. Activation pattern differences in the 2-back task: controls>heavy MDMA users (A, B) and moderate MDMA users>heavy MDMA users (C, D, E) ($P=0.01$, uncorrected).

cortical activation in any task even for the liberal level of significance

It is impossible to perfectly control for all of the methodological shortcomings in this fiel of research. However, 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 fiel studies with ecstasy users. So far, only two studies dealing with alterations of neuroendocrine regulation and memory performance have chosen this approach [10,43]. Longitudinal studies combining cognitive tests with functional neuroimaging are needed in order to clarify the impact of ecstasy use on cognitive brain function.

In summary, moderate and heavy ecstasy users were not impaired in a working memory task, and for a conservative level of significanc they did not differ from healthy non-users in terms of cortical activation patterns in the fMRI working memory study. However, for a liberal level of significanc both user groups showed stronger activations in right parietal cortex, whereas heavy users showed weaker BOLD responses in frontal and temporal regions. These differences may indicate altered brain function associated with prior MDMA use. However, group differences may also be related to other factors such as motivation and varying cognitive strategies. This question cannot be answered in cross-sectional studies and should be addressed in future longitudinal investigations.

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