



## SHORT REPORT

# Preliminary evidence of hippocampal damage in chronic users of ecstasy

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### ABSTRACT

Various studies have shown that ecstasy (3,4-methylenedioxymethamphetamine) users display significant memory impairments, whereas their performance on other cognitive tests is generally normal. The hippocampus plays an essential role in short-term memory. There are, however, no structural human data on the effects of ecstasy on the hippocampus. The objective of this study was to investigate whether the hippocampal volume of chronic ecstasy users is reduced when compared with healthy polydrug-using controls, as an indicator of hippocampal damage. The hippocampus was manually outlined in volumetric MRI scans in 10 male ecstasy users (mean age 25.4 years) and seven healthy age- and gender-matched control subjects (21.3 years). Other than the use of ecstasy, there were no statistically significant differences between both groups in exposure to other drugs of abuse and alcohol. The ecstasy users were on average drug-free for more than 2 months and had used on average 281 tablets over the past six and a half years. The hippocampal volume in the ecstasy using group was on average 10.5% smaller than the hippocampal volume in the control group ( $p=0.032$ ). These data provide preliminary evidence that ecstasy users may be prone to incurring hippocampal damage, in line with previous reports of acute hippocampal sclerosis and subsequent atrophy in chronic users of this drug.

Recently, two cases of acute hippocampal toxicity were reported following chronic use of the popular recreational drug ecstasy (3,4-methylenedioxymethamphetamine (MDMA)).<sup>1</sup> Where initial scans on admission following brief tonic-clonic seizures showed swelling and high signal in the hippocampus, 3 months later, right hippocampal atrophy was evident. Although an infectious encephalitic cause could not be ruled out, the authors postulated that ecstasy ingestion caused an acute toxic insult to the hippocampus, leading to the atrophy observed on the MRI images. Although various studies, including longitudinal studies, have reported memory impairments, even in moderate users of this drug, there are no structural human data (such as volume measurements) on the effects of ecstasy on the hippocampus. The objective of this study was to investigate whether the hippocampal volume of chronic ecstasy users was reduced when compared with healthy polydrug-using controls, as an indicator of hippocampal damage.

We used previously acquired volumetric MRI scans to compare hippocampal volume in 10 male ecstasy users (mean age 25.4 years, SD 2.1) with seven healthy age- and gender-matched control subjects (21.3 years, SD 3.9). The eligibility criterion for the ecstasy group was previous use of at least 50 tablets of ecstasy lifetime. The seven controls were healthy male subjects with no self-reported prior use of ecstasy. Because, in the acute phase, hippocampal swelling has been noted following ecstasy ingestion,<sup>1</sup> participants agreed to abstain from use of all psychoactive drugs for at least 2 weeks before the study and were asked to undergo urine drug screening (with an enzyme multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolite, opiates and marijuana) before enrolment. Beyond urine drug screening, exclusion criteria included a severe medical or neuropsychiatric illness that precluded informed consent and use of serotonin (5-HT) acting medications. MRI scans were acquired at 3 T (Philips Intera; Philips Medical Systems, Best, The Netherlands) with a phased array six-channel receiver head coil with parallel imaging. A sagittal 3D spoiled gradient echo T1W, TR/TE=9/53 ms, FOV 232×256 mm, 170 slices voxel size 0.9×1.0×1.0 mm<sup>3</sup> was acquired. The measurement of hippocampal atrophy was done using a region-of-interest (ROI) analysis technique, with excellent interobserver agreement (COV <5%), as previously described.<sup>2</sup> An experienced operator, blinded to the clinical status, manually outlined the hippocampus in a series of contiguous sections. Left and right hippocampal volumes were averaged.

Differences in age and continuous variables of other drug exposure (log-transformed if necessary) were analysed using the Student *t* test. Categorical variables were analysed using the  $\chi^2$  test. Differences in hippocampal volume were analysed using the univariate analysis of variance (ANOVA) with one between-group factor (group) and one covariate (age).

The ecstasy users were somewhat, but statistically significantly, older ( $p=0.016$ ) compared with control subjects. Although the ecstasy users had used more amphetamine and cocaine, there were no significant differences between both groups in recreational drug exposure, other than ecstasy. The ecstasy users were on average drug-free for more than 2 months and had used on average 281 tablets over the past years (table 1). The hippocampal volume in the ecstasy-using group was on

**Table 1** Characteristics of drug of abuse and alcohol exposure

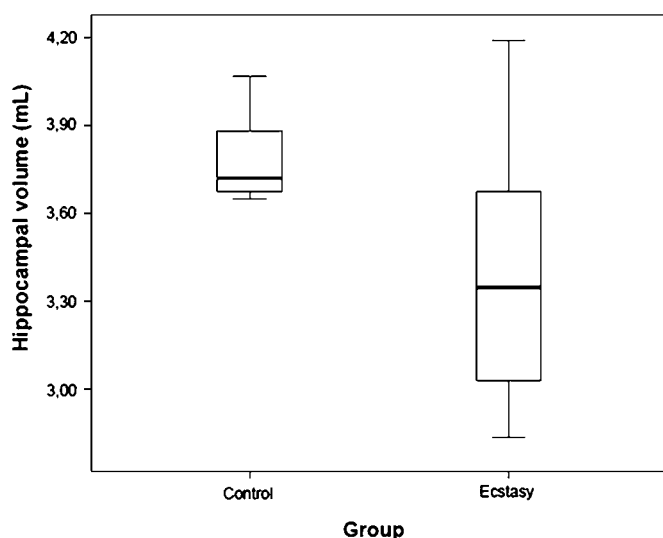
	Ecstasy, n=10*	Controls, n=7	p Value
Last 3 month use of alcohol, no of times used			0.13†
None	0	1	
10–19	0	2	
20–39	4	3	
>40	5	1	
Tobacco, no of cigarettes/day			0.13†
None	2	6	
1–5	6	7	
6–20	2	0	
>20	1	0	
Cannabis, no of times used			0.60†
None	3	5	
1–5	3	1	
10–39	2	1	
>40	1	0	
Amphetamine (g)	0.3±0.7	0±0	0.16‡
Cocaine no of lines	0.8±1.6	0±0	0.21‡
Characteristics of ecstasy use			
Duration of use (years)	6.5±3.1		
Lifetime exposure (total no of tablets)	281±250.97 (range 50–900)		
Usual dose (no of tablets/occasion)	3.65±3.08 (1–9)		
Time since last tablet (months)	2.14±2.34 (range 0.5–7)		

\*Drug-history questionnaire missing for one control subject.

† $\chi^2$  test.

‡Log-transformed.

average 10.5% smaller than the hippocampal volume in the control group (3.8 ml±1.6 vs 3.4 ml±4.4,  $p=0.032$ , figure 1). There were no significant differences between left or right hippocampal volume, or between total brain volumes within each group. After correcting for total brain volume, there were no differences in the proportion of total white-matter volume, but the proportion of overall grey-matter volume was on average 4.6% lower in the ecstasy-using group (51.5%±1% vs 49.1%±



**Figure 1** Hippocampal volume in ecstasy users and control subjects. Lower hippocampal volume in ecstasy users compared with control subjects (3.8 ml±1.6 vs 3.4 ml±4.4,  $p=0.032$ ) as derived by manual delineation. Box plot: median (dark line), 25th percentile (bottom of the box), 75th percentile (top of the box), minimum and maximum (T-bars). There were no outliers.

2.4%,  $p=0.022$ ), analysed using voxel-based morphometry (VBM).

Taken together, these data provide preliminary evidence suggesting that ecstasy users may be prone to incurring hippocampal damage, following chronic use of this drug. This finding is in line with previous reports of acute hippocampal sclerosis and subsequent atrophy in chronic users of this drug.<sup>1</sup> Furthermore, studies in non-human primates treated with MDMA have shown reductions in 5-HT immunoreactive axons by 20–66% in the hippocampus up to 7 years after treatment.<sup>3</sup> In fact, MDMA is a 5-HT neurotoxin in rodents, as demonstrated by reductions in various markers unique to 5-HT axons, including 5-HT, 5-hydroxyindolacetic acid and the density of serotonin-reuptake inhibitor (SERT)s.<sup>4</sup> In line with this, we and others observed reductions in SERT densities in 5-HT-rich brain regions in animals, but also recreational users of this drug using single photon emission CT with a radioligand that binds to the 5-HT transporter (SERT).<sup>5,6</sup> We also observed memory deficits in these ecstasy users but unfortunately could not visualise SERT in the hippocampus owing to the low spatial resolution of SPECT.<sup>5</sup> However, positron emission tomography (PET) studies with the SERT ligand [11C]McN5652 have found reductions in SERT density in the order of 39% in ecstasy users.<sup>7</sup> There is thus accumulating evidence suggesting that MDMA is toxic towards brain 5-HT axons and axon terminals in animals and humans, including the hippocampus.

The fact that we observed reductions in overall grey-matter volume, albeit less extensive than in the hippocampus, suggests that the effects of ecstasy on grey-matter volume may not be specific for the hippocampus. The current observations are probably applicable to other 5-HT-rich brain regions as well. Indeed, a previous study reported multiple regions of grey-matter reduction in ecstasy users,<sup>8</sup> including the occipital cortex, temporal cortex and frontal cortex. However, the grey matter in the hippocampus was not affected in that study in which regional grey- and white-matter volumes were analysed using VBM. This is probably explained by different analysis techniques in both studies. Up to now, however, ROI analysis constitutes the gold standard in brain-atrophy measurements.<sup>9</sup> The statistical power is higher in ROI-based analyses than a voxel-based analysis technique such as VBM, in which one has to correct for multiple comparisons. Furthermore, the linear (typically AFFINE) transformation used in most VBM studies is less accurate in outlining medial-temporal-lobe structures, thus masquerading hippocampal changes even further.

In view of the small brain mass occupied by the 5-HT axon terminals in the hippocampus (eg, much less than 1%), it is not likely that the present observation of reduced hippocampal volume can be fully ascribed to MDMA-induced loss of 5-HT axons and terminals in the hippocampus. Additional explanations are: indirect changes induced by ecstasy, such as changed neuronal and glial structures owing to a decrease in growth factors (serotonin mediates trophic effects), vasospastic ischaemia, pre-existing differences in hippocampal volume that leads to ecstasy use and toxic effects of drugs other than ecstasy. Although none of the control subjects had used amphetamine or speed, the effect of this difference was not statistically significant. An additional ANOVA analysis also found no significant effect of amphetamine ( $p=0.52$ ) or cocaine ( $p=0.10$ ) on hippocampal volume. To rule out pre-existing differences in hippocampal volume, or effects of other drugs of abuse and alcohol, a prospective study in which the effects of ecstasy on hippocampal volume are studied and compared with neuro-cognitive performance is needed. However, the following

observations most likely point towards the direction of direct and/or indirect toxic effects of ecstasy on the hippocampus: (1) hippocampal swelling and subsequently atrophy in two patients following ecstasy ingestion<sup>1</sup>; (2) documented memory impairments in ecstasy users<sup>10</sup>; (3) a decline in memory performance in prospective studies even following low exposure<sup>11</sup>; (4) animal and human studies demonstrating 5-HT neurotoxic effects of MDMA in the hippocampus; and (5) correlations between memory impairment and hippocampal volume in users of the related amphetamine derivative methamphetamine.<sup>12</sup>

In conclusion, chronic users of ecstasy may be prone to incurring hippocampal damage. Since the hippocampus plays an essential role in long-term memory, the present findings are of particular interest in view of the various studies showing that ecstasy users display significant memory impairments, whereas their performance on other cognitive tests is generally normal.<sup>10</sup> All but one study failed to find any relationship between a decrease in SERT densities and memory impairment in ecstasy users.<sup>13</sup> In that study, the strength of the relationship between verbal memory function and SERT was also greater in controls than in ecstasy users. Hippocampal atrophy is a hallmark for diseases of progressive cognitive impairment in older patients, such as Alzheimer's disease. The current findings of hippocampal damage may better explain the memory deficits observed in ecstasy users than previous PET and SPECT studies on SERT densities, and call for further investigations in prospective studies.

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## REFERENCES

1. **Gardner H**, Lawn N, Fatovich DM, *et al*. Acute hippocampal sclerosis following ecstasy ingestion. *Neurology* 2009;**73**:567–9.
2. **van de Pol LA**, Barnes J, Scahill RI, *et al*. Improved reliability of hippocampal atrophy rate measurement in mild cognitive impairment using fluid registration. *Neuroimage* 2007;**34**:1036–41.
3. **Hatzidimitriou G**, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/–)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 1999;**19**:5096–107.
4. **Ricaurte GA**, McCann UD. Experimental studies on 3,4-methylenedioxymethamphetamine (MDA, 'ecstasy') and its potential to damage brain serotonin neurons. *Neurotox Res* 2001;**3**:85–99.
5. **Reneman L**, Booij J, de Bruin K, *et al*. Effects of dose, sex, and long-term abstinence from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001;**358**:1864–9.
6. **de Win MM**, Jager G, Booij J, *et al*. Neurotoxic effects of ecstasy on the thalamus. *Br J Psychiatry* 2008;**193**:289–96.
7. **McCann UD**, Szabo Z, Seckin E, *et al*. Quantitative PET studies of the serotonin transporter in MDMA users and controls using [<sup>11</sup>C]McN5652 and [<sup>11</sup>C]DASB. *Neuropsychopharmacology* 2005;**30**:1741–50.
8. **Cowan RL**, Lyoo IK, Sung SM, *et al*. Reduced cortical grey matter density in human MDMA (Ecstasy) users: a voxel-based morphometry study. *Drug Alcohol Depend* 2003;**72**:225–35.
9. **Jack CR Jr**, Petersen RC, O'Brien PC, *et al*. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. *Neurology* 1992;**42**:183–8.
10. **Parrott AC**. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology* 2000;**42**:17–24.
11. **Schilt T**, de Win MM, Koeter M, *et al*. Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. *Arch Gen Psychiatry* 2007;**64**:728–36.
12. **Thompson PM**, Hayashi KM, Simon SL, *et al*. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci* 2004;**24**:6028–36.
13. **McCann UD**, Szabo Z, Vranesic M, *et al*. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/–)3,4-methylenedioxymethamphetamine ('ecstasy') users: relationship to cognitive performance. *Psychopharmacology (Berl)* 2008;**200**:439–50.



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