Pharmacological MRI in the assessment of monoaminergic function

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CHAPTER 9

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)) (Gardner et al., 2009). 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 (Gardner et al., 2009), 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 mm³ 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 (van de Pol et al., 2007). 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 analyzed using the Student t test. Categorical variables were analyzed using the χ² 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 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%±2.4%, p=0.022), analysed using voxel-based morphometry (VBM).

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.
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 (Gardner et al., 2009). 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 (Hatzidimitriou et al., 1999). 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 (Ricaurte and McCann 2001). 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 phonton emission CT with a radioligand that
binds to the 5-HT transporter (SERT) (Reneman et al., 2001; de Win et al., 2008). 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 (Reneman et al., 2001).
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 (McCann et al.
2005). 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 (Cowan et al., 2003), 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 analyzed 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 (Jack et
al. 1992). 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 (e.g., 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 neurocognitive 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 (Gardner et al., 2009); (2) documented memory impairments in ecstasy users (Parrott 2000); (3) a decline in memory performance in prospective studies even following low exposure (Schilt et al., 2007); (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 (Thompson et al., 2004).

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 (Parrott 2000). All but one study failed to find any relationship between a decrease in SERT densities and memory impairment in ecstasy users (McCann et al., 2008). 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.