Investigating the potential neurotoxicity of ecstasy (MDMA). An imaging approach

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Chapter 4

Reduced N-acetylaspartate levels in the frontal cortex of 3,4-Methylenedioxymethamphetamine ("Ecstasy") users - Preliminary Results

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Abstract

Background and purpose - The perceived safety of the popular recreational drug of abuse methylenedioxy-methamphetamine (MDMA, or "Ecstasy") is at odds with animal evidence indicating that MDMA damages brain cortical serotonin (5-HT) neurons at doses that closely approach those used by humans. Few data are available on the potential neurotoxic effects of MDMA on the human brain. Methods - Fifteen abstinent male MDMA users (mean cumulative lifetime exposure: 723 tablets; mean time since last tablet: 12.0 weeks) and 12 age matched male controls who claimed never to have used MDMA were enrolled in the study. The effects of MDMA use on cortical neurons was studied using single voxel proton magnetic resonance spectroscopy ($^1$H MRS). Measurements of N-acetylaspartate/creatine (NAA/Cr), NAA/Choline (Cho) and myoinositol (MI)/Cr were obtained from mid-frontal gray matter, mid-occipital gray matter, and right parietal white matter. Data were analyzed using general linear model-based MANOVA. Results - The ratios of NAA/Cr and NAA/Cho, markers associated with neuronal loss or dysfunction, were significantly reduced in the frontal cortex of MDMA users ($p = 0.04$ and $p = 0.03$, respectively) compared to controls. NAA/Cr nor NAA/Cho ratios were significantly different between both groups in occipital gray ($p = 0.72$ and $p = 0.12$, respectively) matter and parietal white matter ($p = 0.18$). Furthermore, a significant association was observed between extent of previous MDMA use and NAA/Cr or NAA/Cho ratios in the frontal cortex ($p = 0.50$, $p = 0.01$ and $p = -0.55$, $p < 0.01$, respectively).

Conclusion - Reduced NAA/Cr and NAA/Cho ratios on $^1$H MRS provide evidence for neuronal pathology in the frontal cortex of MDMA users, which correlates with the degree of MDMA exposure. These data suggest that MDMA may be a neurotoxin in humans, as it is in animals.

Introduction

It has become increasingly apparent that the popular recreational drug 3,4-methylenedioxy-methamphetamine MDMA ("Ecstasy") can lead to toxic effects on brain serotonin (5-HT) neurons in animals and possibly human beings. In animals, damage to 5-HT neurons has been demonstrated by reductions in various markers unique to 5-HT axons, including brain 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), and the density of 5-HT transporters (Battaglia et al., 1987; Ricaurte et al., 1988; 1992; Schmidt 1987; Stone et al., 1986). Anatomical studies in MDMA-treated animals indicate that these neurochemical changes are secondary to a distal axonotomy of 5-HT neurons (O'Hearn et al., 1988; Wilson et al., 1989).

Although there is good evidence for a neurotoxic potential of MDMA in animals, there is a lack of studies investigating the potential neurotoxic effects of MDMA in humans. A few studies have evaluated the cerebrospinal fluid 5-HIAA concentrations in MDMA and found either normal (Peroutka 1987) or decreased levels (McCann et al., 1994; Ricaurte et al., 1990). Neuroendocrine challenge tests have been employed, but, to our knowledge, have not been validated for detecting neuronal injury (Scheffel et al., 1998). Recent brain-imaging studies have investigated the effect of MDMA on human 5-HT neurons using either positron emission tomography (PET) or single photon emission computed tomography (SPECT) (McCann et al., 1998; Semple et al., 1999; Reneman et al., 2001a; 2001b). Studies reported alterations in the density of pre-synaptic 5-HT transporters in MDMA users, similar to those observed in MDMA-treated rodents and non-human primates (Scheffel et al., 1998), affecting 5-HT rich brain regions such as the hypothalamus and cortical gray matter, while leaving cortical white matter relatively unaffected.

These observations, suggestive of neurotoxicity in human MDMA users, press for a need to further investigate the possible neurotoxic effects of MDMA in the human brain. Particularly since the perceived safety of MDMA is at odds with animal evidence of MDMA neurotoxicity, and increasing prevalence of hazardous patterns of use among recreational MDMA users (Boot et al., 2000). For instance, a recent report suggests that the intake of multiple tablets in a single-use episode is increasing (Topp et al., 1999).

Furthermore, MDMA is often used in environments that are hot and crowded with limited access to drinking water, increasing the risk of hyperthermia, which exacerbates MDMA neurotoxicity in rats (Malberg et al., 1998).

Proton magnetic resonance spectroscopy ($^1$H MRS) of the brain is a noninvasive study for certain aspects of cerebral biochemistry. Peaks of N-acetyl (NA) groups (primarily N-acetylaspartate, NAA), choline-containing compounds (Cho) and creatine plus phosphocreatine (Cr) are present in the spectrum. Determination of the myoinositol (MI) peak is also possible using short echo times. NAA is contained almost exclusively within neuronal cell bodies and axons (Howe et al., 1999), and considered a marker for neuronal loss or dysfunction (Higuchi et al., 1997; Urenjak et al., 1993). Determining NAA/Cr and NAA/Cho ratios is commonly employed and seems
valid since NAA/Cr and NAA/Cho ratios are reduced in a variety of brain diseases associated with neuronal loss.

The present study was designed to evaluate whether MDMA use leads to alterations in metabolite ratios, in particular NAA/Cr and NAA/Cho, using single voxel 1H MRS. MDMA is known to induce 5-HT neurotoxicity in cortical gray matter of animals, leaving cortical white matter relatively unaffected. Therefore, we hypothesized that NAA/Cr and/or NAA/Cho ratios in gray, but not white matter brain regions studied are lower in MDMA users compared to controls.

Methods

Subjects

MDMA users were compared with ecstasy-naïve but drug using controls. Subjects were recruited with flyers distributed at venues associated with the “rave scene” with the help of an agency that provides harm reduction information and advice. We reduced limiting factors associated with potential pre-existing differences and use of other drugs by recruitment of controls from the same population as the ecstasy users. This differs conspicuously from most previous studies, where controls came from a university or general population. Subjects selected were group-matched for gender and age, between 18 and 45 years, otherwise healthy.

The eligibility criterion for the MDMA group was previously use of minimum 50 tablets of ecstasy. The controls were healthy subjects with no self-reported prior use of ecstasy. A detailed drug-history questionnaire was obtained from all subjects. Participants agreed to abstain from use of psychoactive drugs for at least 1 week prior to the study, and were asked to undergo urine drug screening (with an enzyme-multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine and metabolite, opiates, and marijuana) before enrolment. Exclusion criteria were: a positive drug screen, pregnancy, and a severe medical or neuropsychiatric illness that precluded informed consent. Subjects were interviewed with a structured automated diagnostic psychiatric interview (Composite International Diagnostic Interview: CIDI, version 2.1) to screen for current axis I psychiatric diagnoses.

The institutional Medical Ethics Committee approved the study. After complete description of the study to the subjects, written informed consent was obtained from all participants.

Magnetic resonance spectroscopy

Brain 1H MRS was performed on a 1.5 T Signa Echo Speed (General Electric Medical Systems, Milwaukee, WI) using the standard quadrature head coil. The MR protocol consisted of multislice sagittal and coronal fast spin-echo PD/T2-weighted images (echo time /relaxation time [TR/TE], 4000/22-97 msec; slice thickness, 5 mm; field-of-view, 23 cm; matrix, 256 x 256).

The 1H spectra were collected from three different brain regions: mid-frontal gray matter, mid-occipital gray matter and right parietal white matter (Figure 1).

Figure 1. PD-weighted MR image (TR/TE 4000/22 msec) shows the three voxel locations for the localized 1H MRS studies: mid-frontal gray matter (left), mid-occipital gray matter (middle), and right parietal white matter (right).

Voxel size was 4.5 cc (15 x 15 x 20 mm) and chosen carefully to ensure that each voxel contained primarily gray or white matter. Data were acquired using a fully automated execution of PROB E (Proton Brain Examination) provided by the manufacturer of the MR scanner. The PRESS sequence was chosen for its known robustness (Bottomley 1987) and was optimized for the chosen echotimes and locations (TR/TE, 3000/35 msec; 128 averages and 2.5 kHz bandwidth). The spectroscopic data acquisition provides a water suppressed proton spectrum over a range from 4.3 - 0.5 ppm. The pure metabolic signal was apodized, zerofilled and Fourier transformed to produce the spectrum. The numerical analysis was based on peak amplitude by normalizing the linewidths of the peaks. This analysis effectively measures areas and ratio of areas (Webb et al., 1994). All peaks in the designated spectral area were curve-fitted using a Marquardt fitting routine. Because absolute measures of 1H MRS metabolites are influenced by various technical parameters including transmit gain and receiver settings, MRS signals are commonly measured as ratios of one metabolite of another. Presently, NAA/Cr, NAA/Cho and MI/Cr ratios were calculated.

Statistics

Comparisons between MDMA users and controls for
descriptive variables such as age, verbal intelligence and other recreational drug exposure than MDMA, were performed using two-tailed unpaired Student's t tests.

The main effect of MDMA use on metabolite ratios (NAA/Cr, NAA/Cho, and MI/Cr) was studied by general linear model-based multivariate ANOVA (MANOVA), taking possible correlations between brain regions studied and multiple comparisons into account. Gray matter (frontal cortex and occipital cortex) and white matter (white parietal matter) were analyzed separately, with age, extent of previous cannabis and amphetamine use as covariates. If MANOVA revealed a significant effect, we investigated differences in metabolite ratios between groups by one-way ANOVA.

Since the use of methamphetamine has been associated with reductions in NAA in the basal ganglia and frontal white matter of MDMA users (Ernst et al., 2000), the data were also analyzed excluding those subjects who indicated having used amphetamine in addition to MDMA the past 3 months (the use of methamphetamine is very uncommon in the Netherlands, unlike in, for instance, the United States).

The a priori postulated correlation between NAA levels, extent of previous MDMA use, and duration of abstinence were assessed using Spearman's correlation coefficient. The chance of a type I error (α) was set at 0.05. All data was analyzed using SPSS (SPSS Software Inc, Chicago, IL, USA version 9.0).

Results
The two groups were similar for age. Recreational drug use of alcohol and tobacco was comparable between MDMA users and control subjects. MDMA-users indicated to have used more cannabis and amphetamine the past 3 months prior to this investigation than controls. This difference was significant for the extent of previous cannabis use (p = 0.006), but not for amphetamine (p = 0.18) (Table 1). 4 out of 15 MDMA users indicated having used amphetamine the past 3 months.

In the MDMA group, participants had generally used more than 700 tablets over a period of 2-3 years. Most of the MDMA users had not used MDMA for weeks, and some indicated not to have used MDMA for several months (Table 1).

**MRI**
Visually, no significant brain atrophy or white matter lesions could be detected on the images in either MDMA users or control subjects.

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<tr>
<td><strong>Table 1.</strong> Demographics, characteristics of MDMA use and other recreational drug exposure*</td>
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<tr>
<td></td>
<td>Controls</td>
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<tr>
<td></td>
<td>n = 12</td>
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<tr>
<td><strong>Age</strong></td>
<td>27.0 (4.1)</td>
</tr>
<tr>
<td><strong>MDMA</strong></td>
<td></td>
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<tr>
<td>Duration of use (y)</td>
<td>–</td>
</tr>
<tr>
<td>Usual dose (tablets)</td>
<td>–</td>
</tr>
<tr>
<td>Lifetime dose (tablets)</td>
<td>–</td>
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<tr>
<td>Time since last tablet (weeks)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Alcohol</strong> (units/week)</td>
<td>13.4 (11.9)</td>
</tr>
<tr>
<td><strong>Tobacco</strong> (cig./day)</td>
<td>10.8 (3.7)</td>
</tr>
<tr>
<td><strong>Cannabis</strong> (no. joints last 3 months)</td>
<td>2.3 [0.5]</td>
</tr>
<tr>
<td><strong>Amphetamine</strong> (no. times used last 3 months)</td>
<td>–</td>
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* Data are expressed in mean ± SD values

**1H MRS**
A significant mean group effect was observed in the two gray matter brain regions studied (F = 2.82, df = 6.0, p = 0.045), but not white matter (F = 1.79, df = 3.0, p = 0.180). The covariance effects of age, extent of previous cannabis and amphetamine use were not significant (p = 0.73, p = 0.77 and p = 0.14, respectively) on the significant mean group effect observed in gray matter. An ANOVA analysis demonstrated that NAA/Cr and NAA/Cho ratios in the frontal gray matter of MDMA users were significantly lower compared to controls (p = 0.04 and p = 0.03, respectively), but not in occipital gray matter (p = 0.72 and p = 0.12, respectively). Results are summarized in Table 2 and Figure 2.

No lactate or excess lipids were observed in any of the spectra. When amphetamine users were excluded from the analysis, NAA/Cr and NAA/Cho ratios in the frontal cortex were still significantly lower in MDMA users when compared to controls (p = 0.004 and p = 0.046, respectively).

No significant correlations were observed between metabolite ratios and duration of abstinence from MDMA. However, a significant association was observed in the frontal cortex between extent of previous MDMA use (log transformed) and NAA/Cr (p = -0.50, p = 0.012) and NAA/Cho (p = -0.550, p = 0.003; Figure 3). The higher the MDMA exposure, the lower NAA/Cr and NAA/Cho ratios.
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Discussion
In the present study we observed reductions in NAA/Cr and NAA/Cho in the frontal gray matter of MDMA users, and found that decreases in NAA/Cr and NAA/Cho ratios are usage-related.

NAA is a correlate marker for healthy mature neurons (Urenjak et al., 1993) therefore, a reduction in NAA indicates reduced neuronal density. NAA levels are reduced in a number of pathological processes affecting the integrity of neurons (Arnold et al., 1994; Brownell et al., 1998). For instance neurotoxic damage to dopaminergic neurons induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in persistent decreases in NAA levels in monkey brain (Brownell et al., 1998). Reductions in NAA may be reversed by treatment in some instances (Cendes et al., 1997; De Stefano et al., 1995; Vion-Dury et al., 1995).

Taken in conjunction with the results of previous studies showing selective decreases in concentrations of cerebrospinal fluid 5-HIAA (McCann et al., 1994, Ricaurte et al., 1990) and 5-HT transporter densities in MDMA users (McCann et al., 1998; Semple et al., 1999; Reneman et al., 2001a; 2001b), and similar findings in MDMA-treated animals with documented neurotoxic lesions (Battaglia et al., 1987; Hatzidimitriou et al., 1999; O'Hearn et al., 1988; Scheffel et al., 1998; Schmidt 1987), these data provide further evidence that human MDMA users may be susceptible to MDMA-induced neuronal pathology. In support of this are the presently observed dose-dependent decreases in reductions of NAA/Cr and NAA/Cho in MDMA users. However, in view of the small brain mass occupied by 5-HT nerve terminals (e.g., much less than 1%), it is not likely that the presently observed reductions of around 13% in NAA levels are the result of MDMA-induced gross loss of 5-HT neurons in the prefrontal cortex. Rather, they reflect non-specific neuronal loss or dysfunction of neurons in the prefrontal cortex of MDMA users.

We observed reductions in NAA/Cr and NAA/Cho in frontal gray matter but not occipital gray matter or right parietal white matter. This finding was in agreement with our hypothesis, with the exception that no significant reductions in NAA levels were observed in occipital gray matter. Regional differences in the neurotoxic effects of MDMA within gray matter of the cortex have been shown, but seem to vary with the technique used. For instance, when looking at reductions in regional brain levels of 5-HT or 5-HIAA (as measured with HPLC-EC) in an MDMA-treated baboon, the occipital cortex was the brain region most affected (Scheffel et al., 1998). However, in that same

<table>
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<th>(^7^H) MRS findings in gray and white matter regions in MDMA users and control subjects</th>
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<tr>
<td></td>
<td>Controls (n=12)</td>
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<tr>
<td><strong>Gray matter</strong></td>
<td></td>
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<tr>
<td>Mid-frontal gray matter</td>
<td></td>
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<tr>
<td>NAA/Cr</td>
<td>1.62 ± 0.20</td>
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<tr>
<td>NAA/Cho</td>
<td>2.06 ± 0.23</td>
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<tr>
<td>Ml/Cr</td>
<td>0.65 ± 0.08</td>
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<tr>
<td>Mid-occipital gray matter</td>
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<tr>
<td>NAA/Cr</td>
<td>1.56 ± 0.19</td>
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<tr>
<td>NAA/Cho</td>
<td>3.04 ± 0.52</td>
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<tr>
<td>Ml/Cr</td>
<td>0.60 ± 0.07</td>
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<tr>
<td><strong>White matter</strong></td>
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<tr>
<td>Right parietal white matter</td>
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<tr>
<td>NAA/Cr</td>
<td>1.90 ± 0.10</td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>1.84 ± 0.16</td>
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<tr>
<td>Ml/Cr</td>
<td>0.64 ± 0.06</td>
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Data are expressed in mean ± SD values
\(^7^H\) MRS: F=1.79, df=1,0, p=0.18
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Figure 2. Proton MRS spectra from the mid-frontal gray matter region of a control subject (23 y of age) and an MDMA using subject (cumulative lifetime exposure: 200 tablets; age: 26 y of age). The spectrum in the MDMA user is representative for the whole group and shows a reduction in NAA with similar Cr levels in the MDMA user. Note that MI levels are elevated in this specific MDMA using subject, even though (for the group as a whole) mean MI measures in MDMA users did not statistically differ from control subjects.

In line with the present study, reductions in NAA concentrations have recently been reported for methamphetamine users, a compound with similar actions to MDMA (Ernst et al., 2000). In this study, NAA concentrations in the frontal white matter and basal ganglia of methamphetamine users were significantly reduced compared to controls. Methamphetamine has shown to be neurotoxic to both dopaminergic as serotoninic neurons in rodents. Recent PET studies in abstinent methamphetamine users have shown reductions in dopaminergic terminals similar to those reported in methamphetamine-treated non-human primates (McCann et al., 1998b; Vilemagne et al., 1998).

One other study has used $^1$H MRS to investigate the effects of MDMA on brain neurochemistry (Chang et al., 1999). In this study, no difference between MDMA users and control subjects in NAA/Cr was observed. Discrepancies between the present study and the study by Chang may be attributed in part to the fact that the subjects in our study had on average used nearly 6 times as much MDMA: the cumulative lifetime exposure to MDMA was on average 131 tablets in the study by Chang (based on 100 mg MDMA/tablet or capsule), whereas the MDMA users in our study had exposed themselves on average to 723 tablets.

Apart from the observed reductions in NAA/Cr and NAA/Cho ratios in the frontal cortex of MDMA users, no metabolite abnormalities were observed in

Figure 3. Correlation between NAA/Cho in the frontal cortex and extent of previous MDMA use. Open circles: controls, closed circles: MDMA using subjects.
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the present study. In particular, we did not observe significant alterations in MI/Cr ratios in MDMA users, even though in some subjects elevated MI/Cr measures were observed (Figure 3). In contrast, Chang and co-workers reported previously a significant increase in MI and MI/Cr in the parietal white matter of MDMA users (Chang et al., 1999). MI is believed to be located primarily in glial cells and absent from neurons. Elevations may be attributed to gliosis and reactive astrogliosis. However, normal aging has been shown to increase MI (Chang et al., 1996; Fowler et al., 1997). Discrepancies between the study by Chang and the present, may be attributed in part to age-associated differences between both studies. In the present study, subjects (both MDMA users and controls) were on average younger with a much smaller age range: median age of MDMA users in the Chang study was 43.0 ± 14.6, with an age range of 19-75 years, whereas in the present study median age of MDMA users was 26.0 ± 5.3, ranging from 20 to 38 years. However, precise quantification of ‘near-water’ resonance peaks, such as MI at 3.56 ppm, is difficult in water suppressed 1H MRS, and may therefore also account for the discrepancy between the studies.

Although NAA is found almost exclusively within neurons (Urenjak et al., 1993), the exact functional implications of reduced NAA levels remain unclear. In addition to serving as a storage form of aspartate, NAA is in the metabolic pathway for glutamate and, although not thought to be a neurotransmitter per se (Tsai et al., 1995), is capable of inducing calcium influx by means of N-methyl-D-aspartate receptor agonists in vitro (Rubin et al., 1993). Interestingly, a recent study has shown increased NAA measures in rats during experimental status epilepticus, suggesting that NAA correlates with the functional status of neurons. In line with this, NAA levels in the prefrontal cortex of patients with schizophrenia have been shown to be strongly correlated with activation during a working memory task (Bertolino et al., 2000). Furthermore, we recently reported a strong association between delayed memory function and NAA/Cr ratios in the prefrontal cortex of ecstasy users (Reneman et al., 2001c).

Several potential limitations of the current study should be mentioned. First, as with all retrospective studies, there is a possibility that pre-existing differences between MDMA users and controls underlie differences in NAA concentrations. For instance, critics have argued that low 5-HT function may be a cause rather than an effect of MDMA use, because low concentrations of 5-HT have been linked to impulsivity and sensation seeking in humans (Reed et al., 1999).

However, since NAA, to our knowledge, has not been linked to impulsivity and sensation seeking, the present study makes it less probable that observed decreases in NAA/Cr and NAA/Cho are a cause rather than an effect of MDMA use. Second, because most of the MDMA users had experimented with other recreational drugs, mainly cannabis and amphetamine, we can not completely rule out the possibility that the present findings are unrelated to cannabis or amphetamine use. However, urine drug tests indicated that no participant had used cannabis in the week prior to the study. While the effects of cannabis use on NAA levels are (to our knowledge) still unknown, methamphetamine has been shown to reduce NAA levels (Ernst et al., 2000). In the present study, NAA/Cr and NAA/Cho ratios in the frontal cortex were still significantly lower in MDMA users when compared to controls, when MDMA users who also had used amphetamine in the past 3 months were excluded from the analysis. Also, no significant effect of cannabis or amphetamine use on NAA/Cr and NAA/Cho ratios in the frontal cortex was observed in the statistical analysis, making it less probable that the findings of the present study should be attributed to either of these drugs. In addition, observed decreases in NAA/Cr and NAA/Cho ratios are unlikely to be due to direct pharmacological effects of MDMA, since MDMA using participants reported that they had abstained from use of MDMA or other psychoactive drugs for at least 1 week before the study. Furthermore, we had to rely upon retrospective accounts of drug history using a drug-history questionnaire. A recent survey investigated the validity of the drug-history questionnaire that was used in this study. It was found that in 93% of the cases the reported use of ecstasy was in agreement with the drug urine test (Van de Wijngaart et al., 1997). However, drug usage and abstinence period were also verified by urine drug screening. Blood and urine samples can detect drugs like cannabis 2-3 weeks after use, but MDMA and other amphetamine derivatives can be detected only 24-48 h after the last dose. Therefore, we were only able to objectively confirm abstinence from cannabis, but not MDMA, in the 2-3 weeks before the study. In future studies, hair-sample analysis would be a useful way to assess more appropriately what drug was taken at what time and to ascertain previous use of MDMA. Finally, single voxel proton spectra were acquired and processed automatically in this study. It has been shown that the standard variations of NAA/Cr ratios are much lower using this method compared to studies relying on manual adjustment of the instrument and/or manual
processing. Of the remaining variability, how much is controllable, and how much is biological variation in the normal population? One potential source of error is the partial volume effect. Contamination of the volume of interest with different tissue types will lead to variation in the results. In future studies this may be corrected via tissue segmentation to identify grey/white matter fractions. NAA/Cr ratios are known to be higher in white than in gray matter. Therefore, contamination of a gray voxel with white matter will increase NAA/Cr ratios, and consequently an underestimation of MDMA's neurotoxic effects on 5-HT neurons, because MDMA is known to induce 5-HT neurotoxicity in cortical gray matter, leaving cortical white matter relatively unaffected (Scheffel et al., 1998).

Conclusion
Our results suggest that MDMA use may lead to changes in NAA levels of the frontal cortex of MDMA users as measured with \(^1\)H MRS, and that these changes are dose-related. These findings confirm and extend previous observations suggesting that human MDMA users may be at risk of developing neuronal injury. The present findings will provide a cogent argument for consumers to make informed decisions about recreational MDMA use. Additional studies are needed to determine whether changes in NAA concentrations in MDMA users are reversible with longer periods of abstinence, and whether reduced NAA levels are associated with functional impairments.

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