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Diffusion Tensor Imaging in MDMA Users and Controls: Association with Decision Making

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Abstract: Diffusion Tensor Imaging (DTI) may provide information regarding effects of 3,4-methylenedioxymethamphetamine (MDMA) use on brain structure. Twelve MDMA users and 20 healthy controls underwent whole brain DTI data acquisition. Fractional anisotropy (FA), mean diffusivity (D_{av}), and longitudinal (λ_1) and transverse (λ_T) diffusivities were compared between MDMA users and controls in 6 regions of the corpus callosum. MDMA users also completed the Barratt Impulsiveness Scale (BIS), and a subset of subjects completed the Iowa Gambling Task (IGT). Results showed significantly smaller λ_1 in the rostral body of the corpus callosum in MDMA users, with no differences between groups on λ_T, FA, or D_{av}. MDMA users also had a significantly higher BIS nonplanning score and greater preference for disadvantageous choices on the IGT. There was a significant positive correlation between λ_1 in the rostral body of the corpus callosum and advantageous choices on the IGT. Further research on the etiology of these findings is warranted.

Keywords: Brain imaging, corpus callosum, diffusion tensor imaging, eigenvalues, MDMA

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INTRODUCTION

Because changes in serotonin neurons produced by 3,4-methylenedioxymethamphetamine (MDMA) administration are usually more subtle than gross neuronal death and axonal loss (1), there is controversy regarding whether these changes are evidence of "neurotoxicity" (reviewed in 2). However, it is well established that long term degeneration of serotonin (5-HT) axon terminals follows MDMA administration in animals (3).

Several brain imaging techniques have been used to ascertain whether changes in axon terminals seen in animal studies can be detected in human MDMA users. Studies using magnetic resonance spectroscopy (MRS) or voxel-based morphometry (VBM) to compare MDMA users and nonusers have shown mixed results. Chang et al. (4) used proton MRS (H^1 MRS) to investigate brain concentrations of N-acetylaspartate (NAA) and *myo*–inositol (MI), a neuronal/axonal marker and a glial marker respectively, in recreational MDMA users and normal controls. There were no significant differences in levels of the NAA between MDMA users and controls. However, the concentration of MI was greater in the MDMA users compared to the controls. In another study using H^1 MRS, Reneman et al. (5) compared NAA/Creatine, (Cr), NAA/Choline (Cho), and MI/Cr ratios between MDMA users and nonusers. Findings of that study were that the MDMA users had a significantly lower ratio of NAA/Cr and NAA/Cho in midfrontal gray matter. The ratio of MI/Cr in midfrontal gray matter was not significantly different between groups. Likewise, none of the ratios differed between groups for the midoccipital gray matter or parietal white matter.

Cowan et al. (6) used VBM to compare gray and white matter volumes between a group of MDMA users and controls. They discovered that the MDMA users had a significantly reduced volume of cortical grey matter overall, and specifically in bilateral Brodmann area (BA) 18, left BA 21 in the temporal lobe, and BA 45 in the frontal lobe. They also found reduced grey matter volumes along a midline region in the brain stem, and bilateral areas of the cerebellum. They did not find any significant differences in white matter volumes between the two groups.

Another brain imaging technique that could potentially shed light on the effects of MDMA use in humans is diffusion tensor imaging (DTI). DTI has the potential to provide information about brain microstructural white matter organization (reviewed in 7, 8), which could be altered by MDMA. DTI derived measures of fractional anisotropy (FA), mean diffusivity (D_{av}), and diffusivity values or eigenvalues of the diffusion tensor along the three principal directions in three-dimensional space could provide information about axonal morphology in MDMA users (9). While FA and D_{av} provide information about overall white matter

integrity (8), animal studies using DTI provide evidence that the individual eigenvalues may provide more specific information about the myelination and axonal morphology than FA or mean diffusivity (10, 11; reviewed in 9). Specifically, studies have suggested that damage to myelin increases diffusion perpendicular to the direction of fiber tracts (λ_T) with minimal effect on the eigenvalue that reflects diffusion along the fiber tract (λ_1), whereas axonal damage results in decreased λ_1 with relatively smaller effect on λ_T (11).

To our knowledge only one published study has examined DTI derived measures in MDMA users. De Win et al. (12) used DTI as part of an assessment of 131 subjects who were likely to use MDMA. Thirty subjects had a repeat scan after acknowledging on a questionnaire that they had used MDMA. On average, the subjects used $1.8 + 1.3$ MDMA tablets between the initial scan and follow-up. Results of that study were that there was an increase in FA of $\pm.9\%$ in the white matter of the centrum semiovale, and a decrease of 3.4% in apparent diffusion coefficient (ADC) in the thalamus after self-reported MDMA use. However, these findings were not significant after Bonferoni correction for multiple comparisons.

The purpose of this study was to compare MDMA users and non-MDMA using controls on measures of DTI, impulsivity, and decision making. Our hypothesis was that MDMA users would show increased impulsivity and impaired performance on the IGT, along with alterations of the corpus callosum on DTI.

METHODS

Subjects

Twelve subjects with a history of MDMA use and 20 non-drug using controls were studied. MDMA users were recruited based on a self-report of greater than 15 lifetime uses of MDMA. MDMA users did not meet DSM-IV criteria for any current Axis I disorder other than substance abuse as determined by the Structured Clinical Interview for DSM-IV (SCID) (13). Control subjects did not meet criteria for any current or past Axis I disorder. All subjects were also free from any clinically significant nonpsychiatric medical disorder by history and physical examination. Subjects were screened for any incidental pathology on structural MRI scans by a radiologist (LAK). Subjects also underwent the Addiction Severity Index (14) to document lifetime drug and alcohol use, as well as a urine toxicology screen and breathalyzer to document current alcohol and drug use.

Diffusion Tensor Imaging

Full brain DTI was acquired on all subjects using the methodology previously described in detail elsewhere (15). In brief, a diffusion sensitized dual spin echo prepared echoplanar imaging (SE-EPI) sequence was used on a 1.5 T General Electric echospeed CNV MRI scanner. The diffusion encoding scheme was based on the uniformly distributed and balanced rotationally invariant *Icosa21* encoding set (16). The focus of this analysis was the corpus callosum, divided into 6 segments (Genu, Rostral body, Anterior Midbody, Posterior Midbody, Isthmus, and Splenium) based on the previous work by Witelson (17) (see Figure 1). The rostrum was not included in the analysis because this region was not consistently visualized in all subjects. A region of interest was placed in each of the 6 segments for determination of Fractional Anisotropy (FA), mean diffusivity (D_{av}), and the longitudinal (λ_1) and transverse (λ_T) eigenvalues. The eigenvalue $\lambda_1$represents the diffusion along the direction of the fibers while λ_T represents diffusion perpendicular to the fiber tract axis.

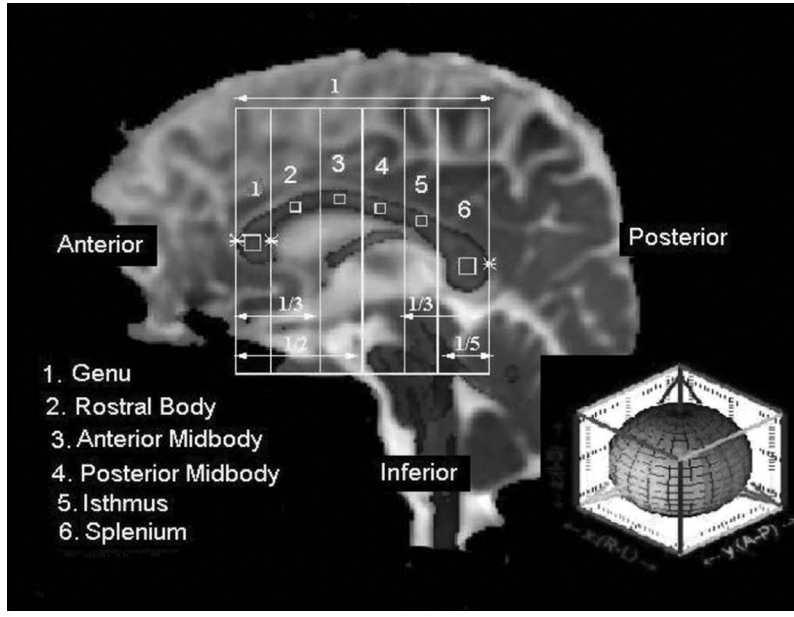

Figure 1. Regions of interest within corpus callosum.

Barratt Impulsiveness Scale (BIS-11)

All subjects completed the BIS-11 (18). This instrument is a 30-item questionnaire which has been used in several previous studies on impulsivity and aggression (19). We have previously shown increased impulsivity on the BIS in MDMA users (20).

Iowa Gambling Task

A subset of 11 MDMA users and 15 controls completed the Iowa Gambling Task (IGT) (21). The version of the IGT used was a computerized version of the original IGT in which subjects are asked to choose between four decks of cards that result in theoretical monetary rewards at different rates. Each deck (labeled A, B, C, and D) contains 60 cards. Subjects must make 100 choices over the testing session. Healthy controls are able to determine that two decks of cards lead to minimal short-term monetary rewards but over the long-term are more advantageous. This task has been able to differentiate between patients with frontal cortical lesions and controls (22, 23), and drug users and controls (24). The task takes about 15 minutes to complete. Scoring for the IGT was based on the total number of cards selected from the advantageous minus the disadvantageous decks across five blocks of 20 cards each.

Statistical Analyses

Group comparisons on DTI measures were made using a Student's t test, with Bonferroni correction for multiple tests over the 6 regions of the corpus callosum. BIS scores were compared between groups using a Student's t test. Quantity of lifetime alcohol consumption was compared between MDMA users and controls using a Mann-Whitney U test. A repeated measures ANOVA was used to compare groups on the pattern of responding across the 5 blocks of the IGT. Correlations between behavioral or drug use measures and DTI measures were made using a Spearman correlation coefficient.

RESULTS

Demographics and Substance Use

The mean age of the MDMA users was 27.3 ± 5.4 years, which was not statistically different from the controls (25.5 ± 4.5 years) ($t = 1.0$,

df = 30, p = .32). Within the MDMA users there were 2 females and 10 males. Within the controls there were 7 females and 13 males. Three MDMA users and 2 controls were left-handed, the remainder of the subjects were right-handed except for 3 controls in which handedness was not assessed. MDMA users reported using MDMA 181 ± 273 times for 6.2 ± 5.0 years, ranging from 1 year to 19 years. MDMA users also reported past use of marijuana (100%), cocaine (58%), benzodiazepines (58%), hallucinogens (50%), opiates (41.6%), and amyl nitrate (16.7%). Estimated total lifetime alcohol consumption in kilograms (kg) for MDMA users was 124.6 ± 92.1, which was significantly greater than for controls (12.7 ± 22.4) (Mann–Whitney U = 39.0, p = .002). All of the controls were negative for any drugs of abuse on urine toxicology at the time of scanning, and all subjects were negative for alcohol by breathalyzer at the time of scanning. The average duration since last MDMA use by self-report was 39.8 days at the time of scanning, ranging from 0 days to 101 days. Two MDMA using subjects were positive for MDMA at the time of scanning.

DTI Measures

After correction for multiple comparisons there was no significant difference between MDMA users and controls on FA, D_{av}, or the transverse eigenvalue λ_T (see Table 1). There was a significant difference between MDMA users and controls on the mean longitudinal eigenvalue λ_1 in the rostral body of the corpus callosum (t = 3.00, df = 30, Bonferroni corrected p = .03), with a significantly smaller mean longitudinal eigenvalue in MDMA users (mean ± S.D.) ($1216.0 + 70.8$) than controls (1323.0 ± 110.0) (units of $10^{-6}\,mm^2\,sec^{-1}$).

Behavioral Measures

One MDMA user was dropped from the BIS-11 analysis due to an incomplete BIS-11 form. For the 11 MDMA users and 20 controls who completed the form, the BIS-11 subscale nonplanning score was significantly higher in MDMA users (24.0 ± 5.0) compared to controls (19.7 ± 4.8) (t = −2.46, df = 29, p = .022). The BIS-11 total score was also higher in MDMA users than controls at a trend level of significance (t = −1.88, df = 29, p = .070). Results for the IGT showed a significant group (MDMA user vs. control) by block interaction (F = 4.26, df = 4,96, p = .003). As can be seen from Figure 2, controls shifted their choices from the disadvantageous decks of cards to the more

Table 1. Fractional anisotropy (FA), mean diffusivity (D_{av}), longitudinal (λ_1) and transverse (λ_T) eigenvalue means in 6 regions of the corpus callosum (units of $10^{-6}\,mm^2\,sec^{-1}$). Values are indicated as mean ± standard deviation; significant findings after Bonferroni correction are indicated by*

Region	1	2	3	4	5	6
			FA			
Controls N = 20	.601 ± .058	.422 ± .065	.392 ± .047	.414 ± .070	.413 ± .076	.578 ± .076
MDMA users N = 12	.612 ± .063	.403 ± .035	.367 ± .034	.413 ± .051	.371 ± .100	.606 ± .069
			D_{av}			
Controls N = 20	764.4 ± 69.9	871.2 ± 76.8	890.3 ± 108.5	874.3 ± 96.0	902.2 ± 94.5	761.6 ± 52.3
MDMA users N = 12	763.6 ± 85.3	814.8 ± 44.1	864.6 ± 123.7	819.5 ± 49.2	905.3 ± 115.2	758.2 ± 80.1
			λ_1			
Controls N = 20	1372.7 ± 116.5	1323.0* ± 109.9	1314.0 ± 148.1	1317.1 ± 136.1	1361.3 ± 157.9	1340.9 ± 100.8
MDMA users N = 12	1387.6 ± 151.0	1216.0* ± 70.8	1246.4 ± 161.8	1234.6 ± 83.1	1314.4 ± 197.2	1376.1 ± 192.9
			λ_T			
Controls N = 20	459.3 ± 68.8	645.3 ± 80.5	678.5 ± 98.4	652.9 ± 96.3	672.6 ± 91.4	471.9 ± 68.7
MDMA users N = 12	451.5 ± 75.5	614.2 ± 41.6	673.7 ± 107.5	612.0 ± 52.7	700.8 ± 109.2	449.3 ± 57.0

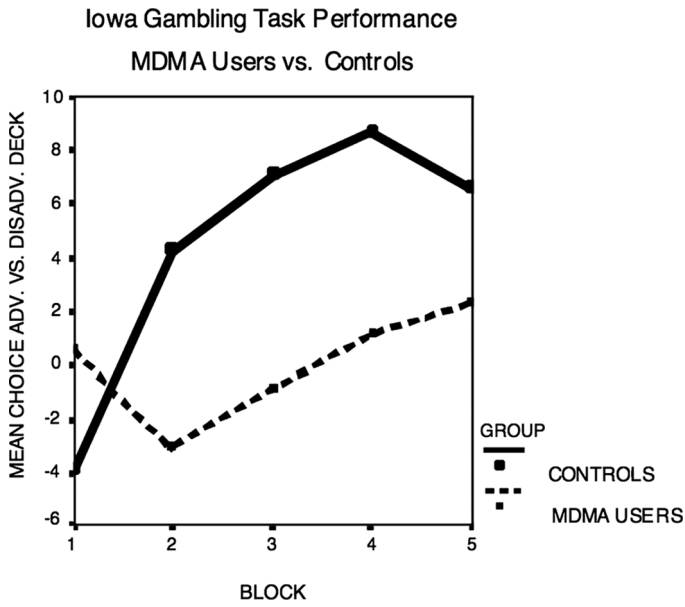

Figure 2. IGT performance in MDMA users and controls.

advantageous decks over the 5 blocks of the task; this shift in choice was less pronounced in the MDMA users.

Relationship Between Regional DTI and Substance Use History

Within MDMA users there was no significant correlation between the longitudinal eigenvalue in the rostral body and years of self-reported MDMA use (Spearman $r = .118$, $p = .716$). There was also no significant correlation between lifetime alcohol consumption and the longitudinal eigenvalue (Spearman $r = .245$, $p = .443$).

Relationship Between Regional DTI and Behavioral Measures

There was a significant correlation between the net score of choices of disadvantageous vs. advantageous decks of cards on the IGT and the longitudinal eigenvalue in the rostral body of the corpus callosum (Spearman $r = .593$, $p = .001$) (see Figure 3). Subjects who had a smaller longitudinal eigenvalue were more likely to choose from disadvantageous decks of cards on the gambling task.

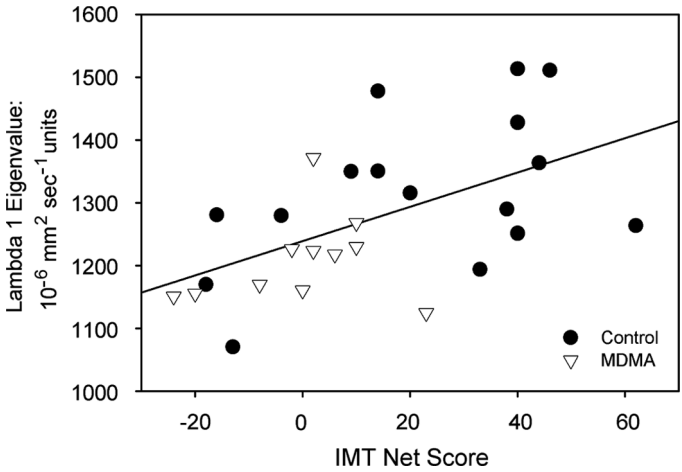

Figure 3. Correlation between IGT net score and longitudinal eigenvalues in rostral body of the corpus callosum.

DISCUSSION

MDMA users showed smaller longitudinal eigenvalues in the anterior corpus callosum compared to non-drug abusing controls. Prior research has shown that this pattern of reduction in the longitudinal eigenvalue with relatively less effect on the transverse eigenvalue is consistent with axonal damage (11). Thus the findings of this study are consistent with axonal damage in MDMA users compared to non-drug abusing controls. The finding that MDMA users showed a relative lack of ability to change preference for disadvantageous decks of cards to advantageous decks is consistent with impairment of the ventromedial prefrontal cortex based on previous studies by Bechara et al. (23). Other findings that are consistent with this include the fact that there was a significant correlation between performance on the IGT and the longitudinal eigenvalue in the anterior corpus callosum, as well as the fact that DTI fiber tracking has shown that fibers from this region of the corpus callosum extend into the medial prefrontal cortex (25, p. 92).

Two previous imaging studies found evidence that MDMA could affect medial prefrontal cortical brain function in humans. In a previous study by our group using fMRI (26), MDMA users had significantly greater blood oxygen level dependent (BOLD) activation in the medial frontal gyrus while performing a working memory task. Gamma et al. (27) found that a dose of MDMA produced a significant increase in regional cerebral blood flow on Positron Emission Tomography (PET)

in the left and right ventromedial prefrontal cortex in healthy subjects. Both of these studies support the premise that MDMA could have an effect on the medial prefrontal cortex in humans. Whether the effects of MDMA are "neurotoxic" remains controversial (reviewed in 2). Animal studies have shown that MDMA administration produces changes in nerve terminals rather than cell bodies (1), whereas axonal damage, such as axonal swelling and Wallerian degeneration has been shown to produce a relative reduction in the longitudinal eigenvalue in white matter in mice (11). Whether the changes in neuronal structure produced by MDMA administration in animals can be detected by DTI measures remains to be determined.

The finding of impaired decision making on the IGT in MDMA users is consistent with one previous study (28), but not another (29). One possible explanation for this is the fact that Ramaekers and Kuypers (29) were measuring acute effects of MDMA and therefore did not choose a sample of participants that represent heavy MDMA users. On the other hand, Quednow et al. (28) studied chronic MDMA users. This raises the possibility that deficits on the IGT may only become apparent after more substantial MDMA use.

The primary limitation of this study is that many of the MDMA users also used a number of other drugs besides MDMA, including marijuana, alcohol, and cocaine. Thus, it is possible that the DTI findings of a reduced longitudinal eigenvalue could be related to other drug use besides MDMA. However, previous DTI studies of cocaine users found a smaller transverse eigenvalue or FA rather than a smaller longitudinal eigenvalue in the anterior corpus callosum (15). Other studies in alcohol dependent subjects have shown differences in white matter on DTI compared to nonalcoholic controls (30). However, the total amount of alcohol consumed by the MDMA users in the present study was approximately 8 times less than the reported lifetime alcohol consumption in previous DTI studies in alcoholics (30), and there was no correlation between the quantity of alcohol consumed and the longitudinal eigenvalue in the present study.

In summary, the findings of this study of reduced longitudinal eigenvalue in the rostral body of the corpus callosum and poorer choices on the IGT in MDMA users compared to controls are consistent with impairment in the medial prefrontal cortex in MDMA users. Further research is warranted that controls for concomitant drug use in MDMA users.

DISCLOSURE/CONFLICTS OF INTEREST

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