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A preliminary longitudinal study of white matter alteration in cocaine use disorder subjects

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ABSTRACT

Background: Previous diffusion tensor imaging (DTI) studies have consistently shown that subjects with cocaine use disorder (CocUD) had altered white matter microstructure in the corpus callosum. It is believed that these alterations are due to preexisting factors, chronic cocaine use, or both. However, there is no published longitudinal DTI study on human cocaine users yet which could shed light on the relationship between cocaine use and DTI findings.
Methods: This study used a longitudinal design and DTI to test if the white matter microstructure shows quicker alteration in CocUD subjects than controls. DTI data were acquired from eleven CocUD subjects who participated a treatment study and eleven non-drug-using controls at baseline (Scan 1) and after ten weeks (Scan 2). The baseline fractional anisotropy (FA), a general measure of white matter microstucture, and the change in FA (ΔFA, equals Scan 1 FA minus Scan 2 FA) were both compared between groups.
Results: The two groups did not show a difference in FA at baseline. The CocUD subjects had significantly greater ΔFA than the controls in the left splenium of the corpus callosum. In CocUD subjects, greater ΔFA in this region was associated with shorter lifetime cocaine use and greater number of positive cocaine urine samples collected during the treatment.
Conclusion: The finding in the left splenium is consistent with previous animal studies and provide indirect evidence about the effects of chronic cocaine use on white matter alterations. The subject sample size is small, therefore the results should be treated as preliminary.

1. Introduction

Diffusion tensor imaging (DTI), which exploits the directionality of diffusion of water molecules in tissues, is a reliable technique for non-invasively investigating the microstructure of white matter (Taber et al., 2002; Pfefferbaum et al., 2003). Though there exist exceptions (e.g., Kelly et al., 2011), the majority of previous DTI studies (Moeller et al., 2005, 2007; Lim et al., 2002, 2008; Ma et al., 2009, 2015a; Lane et al., 2010; Romero et al., 2010; Xu et al., 2010; Bell et al., 2011; Nakamura-Palacios et al., 2016; Yip et al., 2016) have reproducibly shown that cocaine use disorder (CocUD) is associated with white matter alterations, with consistent findings in the corpus callosum (Moeller et al., 2005, 2007; Ma et al., 2009, 2015a; Lane et al., 2010; Xu et al., 2010; Bell et al., 2011). The white matter alterations found in CocUD may be related to impulsivity (Moeller et al., 2005), decision-making (Lane et al., 2010), treatment outcomes (Xu et al., 2010), or abstinence duration (Bell et al., 2011).

It is believed that the white matter alterations found in human CocUD subjects are preexisting before the onset of drug use, due to chronic drug use, or both (Narayana et al., 2009). However, our literature search did not find any published human longitudinal

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DTI studies showing the effects over time of cocaine use on white matter microstructure. The human studies reviewed above all used cross-sectional design (i.e., comparing patients with controls at one time point), and therefore cannot determine if the white matter alterations found in these studies were caused by chronic cocaine use or not. Animal studies (Narayana et al., 2009; Narayana et al., 2014) have been conducted in order to answer this question indirectly. These animal studies (Narayana et al., 2009; Narayana et al., 2014) found that the rats receiving cocaine daily for four weeks had white matter differences in corpus callosum (especially splenium of corpus callosum) compared to saline treated rats.

In light of previous animal studies and human cross-sectional studies, this preliminary study used a longitudinal design and DTI to test if the white matter microstructure is relatively more altered over time in CocUD subjects than non-drug-using controls. Eleven CocUD subjects who participated a treatment study and eleven non-drug-using controls were scanned at baseline and after ten weeks. We hypothesized that within this ten-week time frame, changes in white matter would be related to drug use in cocaine users.

2. Methods

2.1. Subjects

This study was approved by the local university Committee for the Protection of Human Subjects (CPHS) and was performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from each subject before being included in this study.

Treatment-seeking CocUD subjects and healthy controls were recruited via newspaper advertisements and were initially screened by a brief telephone interview. Following the phone screen, eligible subjects attended an in-person intake assessment session, in which they were screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID-IV-TR) (First et al., 2002), and completed a medical history and physical examination. Information about each participant's demographic and drug use history was also collected at the intake interview. For all subjects, the Addiction Severity Index (McLellan et al., 1992) was obtained to document lifetime drug and alcohol use. Immediately prior to MRI scanning, a urine sample was obtained from each subject to screen for tetrahydrocannabinol, opiates, cocaine, amphetamines, benzodiazepines, and pregnancy (for females only). Each subject was also screened for recent alcohol use by measuring breath alcohol concentration.

Subject inclusion criteria were: (1) 18–55 years old; (2) free of alcohol at the time of magnetic resonance imaging (MRI) scanning; (3) CocUD subjects met criteria for current cocaine dependence as determined by Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996); and (4) non-drug using controls had no current or lifetime history of any DSM-IV substance use or psychiatric disorder. Exclusion criteria were: (1) met current or past DSM-IV Axis I disorder other than substance abuse or dependence; (2) taking medication or having disorders that could affect the central nervous system; (3) claustrophobia during MRI simulator sessions; (4) having any definite or suspected clinically-significant brain abnormalities on the Fluid-Attenuated Inversion Recovery (FLAIR) MRI scans; (5) positive urine drug screen (for controls only); and (6) positive pregnancy test result (for females only).

Based on the inclusion and exclusion criteria, 11 CocUD subjects (CocUD group) and 11 non-drug-using controls (control group) were included for final analysis. Please see Table 1 for the age, sex, handedness, education, lifetime duration of cocaine use (years), lifetime alcohol use (kg), and severity of cocaine dependence as measured by KMSK (Kellogg et al., 2003). The two groups did not differ significantly in age ($t = 1.34$, degree of freedom [df] = 20, $p = 0.20$), and years of education ($t = 0.73$, $df = 20$, $p = 0.48$). Fisher's exact tests revealed that the two groups did not differ significantly in sex (2-tail $p = 1.00$) and handedness (2-tail $p = 1.00$). The between-group difference in lifetime alcohol use was trend toward significance ($t = 2.00$, $df = 20$, $p = 0.06$). All CocUD subjects had DSM-IV diagnoses of current cocaine dependence and past cocaine dependence. Please see Table 1 for additional DSM-IV diagnoses of the subjects in the two groups.

2.2. Treatment

All the CocUD subjects also participated a treatment study (Schmitz et al., 2014), which spanned 16 weeks. During the treatment study, each CocUD subject could have received placebo, modafinil, naltrexone, l-dopa, or d-amphetamine. There were three subject visits (Monday, Wednesday, and Friday) per week. Urine samples were collected during each visit. The total number of positive cocaine urine samples per subject during the treatment period (mean ± standard deviation) was 26.0 ± 9.2 (range 15–43) and the total number of negative urine samples per subject during the treatment period was 6.3 ± 7.8 (0–25). The negative urine samples occupied 17.9% ± 19.9% of total urine samples, and three CocUD subjects provided 0 negative urine samples.

2.3. Longitudinal study design

For each subject, there were two MRI scanning sessions. The second scanning session (Scan 2) occurred approximately 10 weeks after the first scanning session (Scan 1). There was no significant difference ($t = 0.64$, $df = 20$, $p = 0.53$) in the time interval (ΔT) between Scan 1 and Scan 2 between the CanUD group (72.0 ± 13.1 days) and the control group (67.5 ± 19.3 days). For the CocUD subjects, Scan 1 occurred 10.2 ± 8.4 days before the initialization of the treatment. Therefore there was a mismatch between the timing of the treatment-related urine drug testing and the time between the two MRI scanning sessions.

2.4. MRI data acquisition

For each scanning session (Scan 1 or Scan 2), MRI data were acquired on a Philips 3.0 T Intera system with a six channel receive head coil (Philips Medical Systems, Best, Netherlands). Whole brain diffusion-weighted images (DWI) were acquired in the transverse plane using a single shot diffusion sensitized spin echo echo-planar imaging (EPI) sequence, with the following parameters: b-factor = 1000 s/mm^2, repetition time = 6100 ms, echo time = 84 ms, 44 contiguous axial slices, field-of-view = 240 mm × 240 mm, 112 × 112 acquisition matrix, 256 × 256 reconstructed matrix, 0.9375 mm × 0.9375 mm reconstructed in-plane resolution, slice thickness = 3 mm, and zero interslice gap. The diffusion tensor encoding scheme was based on the uniformly distributed and balanced rotationally invariant Icosa21 (21 gradient directions) tensor-encoding set (Hasan and Narayana, 2003). A SENSE acceleration factor of 2 was used for the DWI acquistion. The diffusion-encoded volumes were acquired with fat suppression. The DTI acquisition time was approximately 7 min. FLAIR scans and T2-weighted spin-echo scans were acquired in Scan 1 and were read by a board-certified radiologist in order to rule-out any incidental brain pathology.

2.5. DTI data processing

The DTI images in each scanning session were processed using the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl, ver-