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Diffusion Tensor Imaging in Bipolar Disorder with Cocaine Dependence vs. a Healthy Control: Preliminary Findings

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Abstract

Diffusion Tensor Imaging (DTI) has been a useful technology to examine brain anomalies in relation to white matter atrophy in neurologically impaired patient populations. Of particular interest is using DTI to better characterize brain structure in patients with mental illness or addiction. To that end, the available data show white matter atrophy in brain areas that underlie executive functioning, emotion, and memory in those with bipolar disorder. In those with substance use disorders, the current data illustrate white matter atrophy in the corpus callosi. However, studies examining white matter connectivity and atrophy in those with co-occurring bipolar and cocaine use disorders are lacking. Here, an exploratory case series illustrating differences in white matter connectivity among two subjects with co-occurring bipolar and cocaine use disorders in comparison to a healthy control are shown.

Keywords: Diffusion tensor imaging; Bipolar; Cocaine

Introduction

Over 8.9 million Americans have co-occurring mood and substance abuse disorders [1]. The lifetime rate of substance abuse in those with bipolar disorder is about 60% with half of this subset addicted to cocaine [2]. In the past decade, diffusion tensor imaging (DTI) techniques have provided mounting evidence showing that atrophied white matter tracks primarily in the corpus callosi and frontocortical areas are common in bipolar disorder without cocaine abuse [3-5]. Others find corpus callous and orbitofrontal areas with white matter atrophy in those with cocaine abuse without bipolar illness [6,7]. However, imaging data demonstrating brain structure is different in those with co-occurring bipolar disorder and cocaine dependence in comparison to healthy controls is lacking. To our knowledge, there are no DTI data illustrating white matter fiber tract differences between patients with bipolar disorder + cocaine dependence compared to age-matched healthy controls. This exploratory case series provides preliminary evidence that shows white matter atrophy and reduced tractographic fibers in subjects with co-occurring bipolar disorder with cocaine dependence versus a healthy control.

Methods

Study design and participants

An exploratory case series using MRI and DTI methods was conducted to examine whole brain architecture and white fiber tracts in a healthy control and four subjects with co-occurring bipolar disorder with cocaine dependence. Co-occurring disorder subjects who volunteered to participate in this case series were enrolled after completing a 20-week, double-blind randomized antipsychotic trial described in detail elsewhere (Nejtek et al.)[8]. In accordance to the Declaration of Helsinki, university institutional review board approval and written informed consent was obtained from all subjects prior to enrollment. The imaging protocol lasted about 60-minutes and after completion of the imaging, subjects received $70 compensation.

Exclusion criteria were subjects younger than 20 years old and older than 48 years old who had any kind of non-removal metal resting on or inside any internal or external body parts including but not limited to devices such as a pacemaker, heart valves, internal clips, shunts, stents, pins, screws, wires, plates, piercings, neurostimulator, intrauterine device, cochlear implant, insulin pump, venous umbrella, injuries resulting in embedded metal shards, fragments, metallic tattoos, or any type of prosthetic device. Other exclusion criteria included any kind of neurological disease or disorder, brain injury, pregnancy, claustrophobia, panic disorder, polydrug dependence (other than cocaine) and any substance use within the past 14-days. As subjects completing the parent study had been followed for 20-weeks, verification of drug use relied on clinical study records and weekly urine drug screen analyses.

Imaging protocol

Fractional anisotropy (FA) indicates the preferential diffusion of water along axons in the regions of interest reflecting white matter tract integrity. DTI 3D colorations presented here were based on image mapping of FA defined as the point where λavg is the average over the 3 eigenvalues used to display the direction of the 1st eigenvector consisting of tract families as follows: Red=Left/Right association tracts, Green=Anterior/Posterior projection tracts, Blue=Feet/Head callosal tracts. Various combined colorations indicate tracts that may merge, connect, or overlap. Example: Corticocortical connections through corpus callosum are Magenta (red association +blue callosal) while projections to the temporal lobe are Pink. Yellow=green projection + red association tracts; Cyan = green projection + blue callosal tracts (see Wakana et al for further detail) [9].

Landmark parameters were determined with a straight line boundary manually drawn laterally left to right through the frontal

horn of the lateral ventricle to include the rostral corpus collosum, cingulate gyrus, orbitofrontal, and inferior frontal gyrus. Talairach coordinate transformations were applied for anatomical accuracy. Head placement was secured with a quadrature head coil. A 1.5T Philips MR instrument was used for all imaging (Philips Medical Systems, Best, Netherlands). Analysis software available for use as needed, were Statistical Parametric Mapping (SPM), Analyses of Functional NeuroImages (AFNI), and BrainVoyager.

Exploratory MRI and DTI protocols included: (a) High resolution T1 weighted structural acquisition in 3D mode with Fast Spoiled Gradient Recalled sequences (SPGR) to produce near-isotropic voxels on sagittal slices (thickness = 1.25 mm), matrix = 256x192, flip angle = 35, Field of View (FOV)=220 mm, Number of Excitations (NEX) = 2; (b) T2 weighted in 2D mode and Turbo Spin Echo (TSE), Fluid Attenuation Inversion Recovery (FLAIR) acquisitions to acquire axial slices and identify white matter hyperintensities and to differentiate between neurological damage and other potential abnormalities using same parameters as above except with slice thickness=2.5 mm, dual Echo Time (TE)=20 ms and 80 ms. Other parameters of TSE FLAIR included scans performed in 25 directions (b=1000 mm/sec2), TR=7000, Inversion Time (TI)=2200, TE=100 and 120, Echo Train Length=16-20, FOV=220 mm, matrix=256x256 and 128x128 (as appropriate), flip angle = 90 degrees, slice thickness=5.00 mm, repetition time TR /TE = 7000/100 ms, NEX = 3; foldover direction = anterior-posterior for DTI with 3D high resolution scans using SPGR sequencing.

Results

We were unable to retrieve the high quality image data from two out of the four study patients to visually compare to the healthy control. Figure 1 shows multiple slice colored fiber tractography of a 30-year old healthy control. The control was imaged first to test the imaging parameters, determine the ease and feasibility of employing the imaging protocol, and to help pinpoint the minimum and maximum length of time a subject with co-occurring disorders would be comfortable in the scanner.

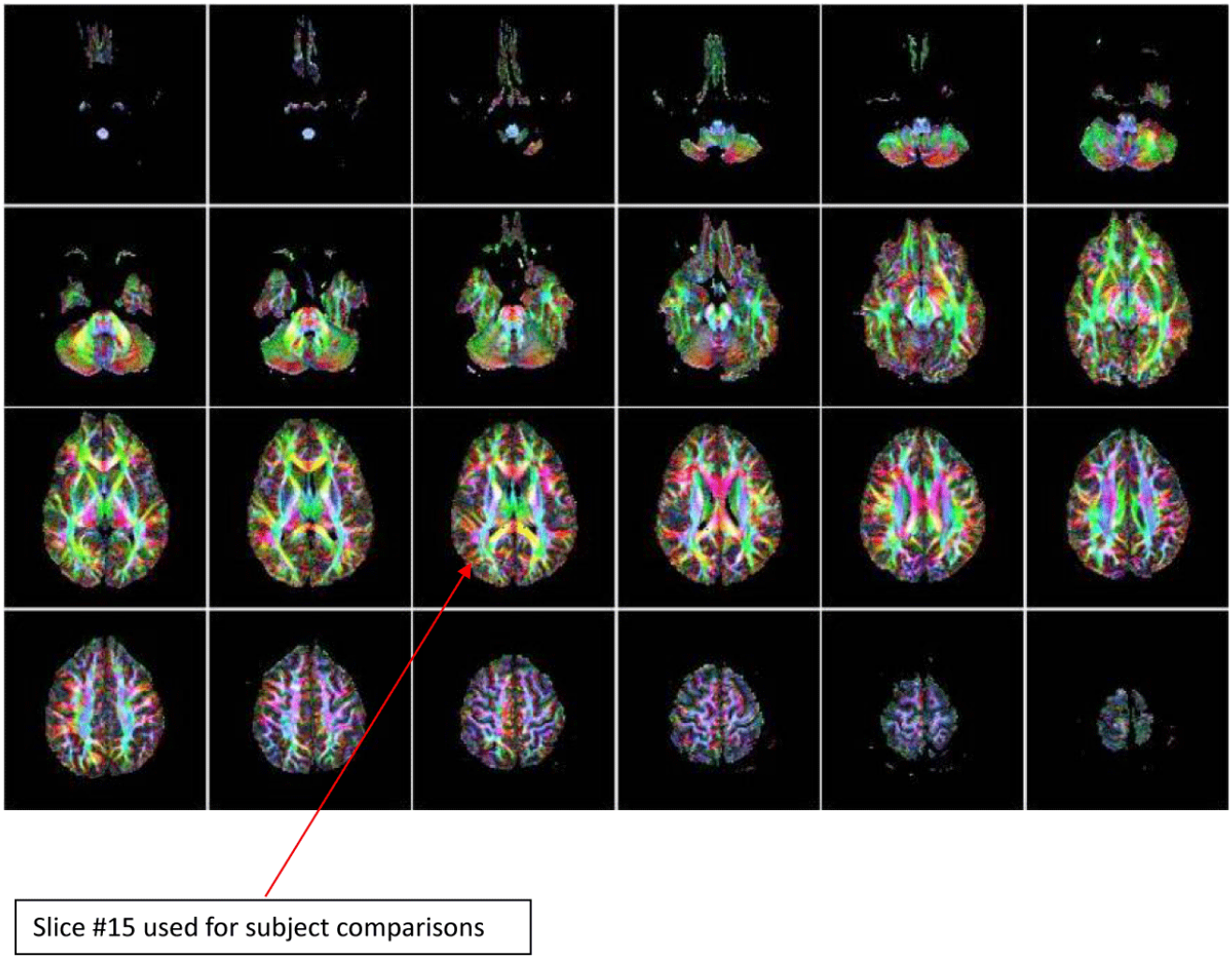

Figure 1: Female Healthy Control, Multiple Axial Whole Brain DTI Tractography Views

This test phase was important as persons with bipolar disorder with stimulant dependence are characteristically hyperactive. Thus, parameters were adjusted to accommodate a 60-minute scan time. As Figure 2 illustrates, the MRI sagittal and DTI axial tractographic views of the whole brain in this control show a healthy brain with multiple connections as outlined in Wakana et al. [9].

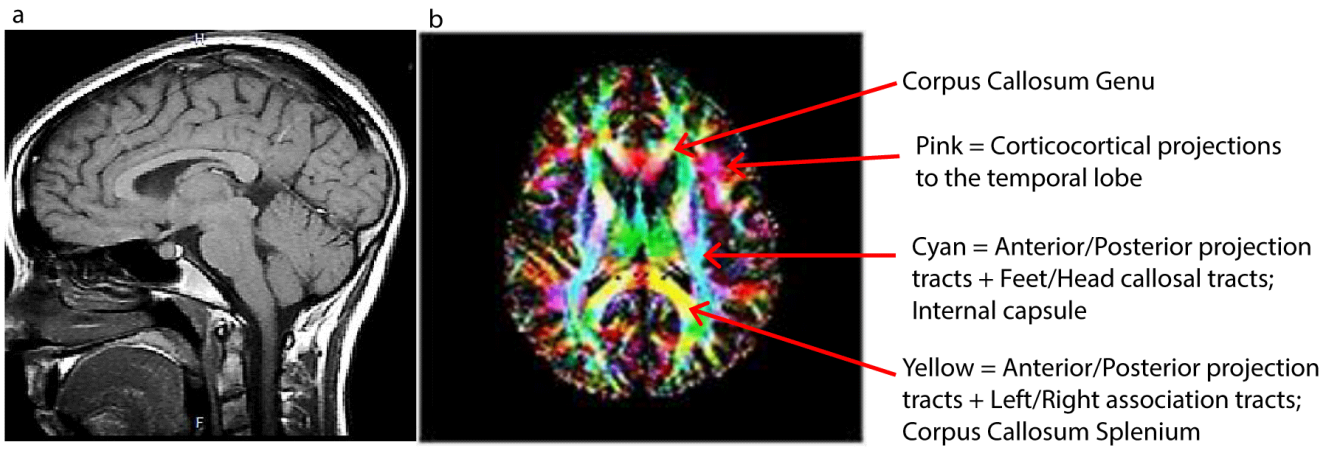

Figure 2: Female Healthy Control, (a) Sagittal MRI, (b) Axial Whole Brain DTI Tractography Slice #15

Figure 3 illustrates a 44 year old female subject with co-occurring disorders who had an age of onset for bipolar I disorder at 8-years old and had a 16-year history of cocaine dependence. She had been receiving 50 mg of quetiapine and 100 mg of bupropion nightly for the past 6-weeks, was euthymic, and was in early partial remission with 140-days abstinence at the time of imaging.

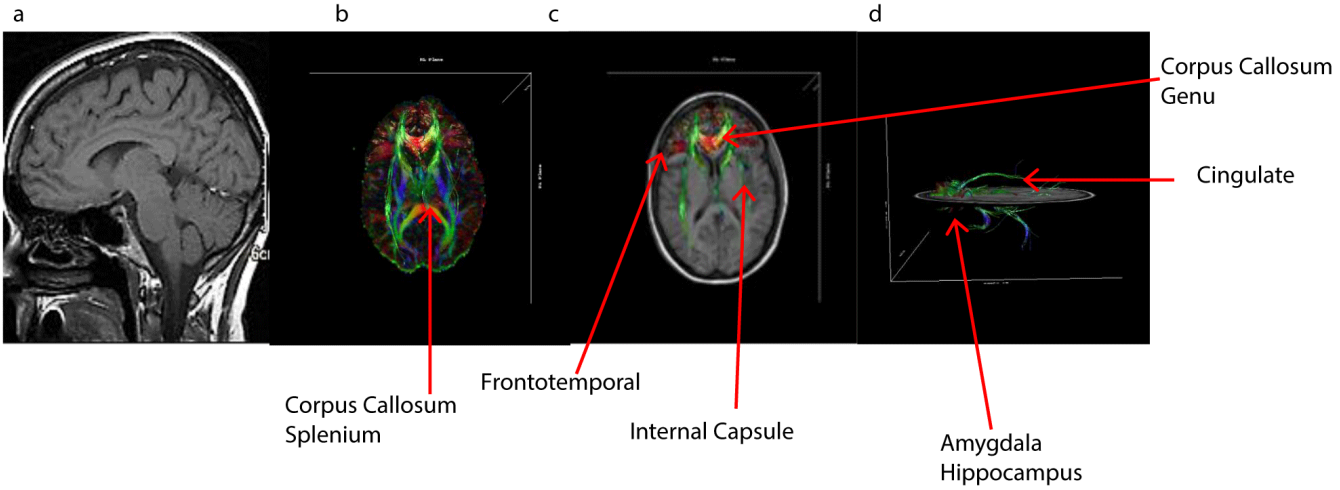

Figure 3: 44-year old Female with Co-Occurring Disorders, (a) Sagittal MRI, (b) Axial Whole Brain DTI Slice #15, (c) Axial Slice Frontotemporal Tractography, (d) 3D Transverse View: a,b,c

Figure 4 shows a 39-year old male subject with co-occurring disorders who had an age of onset for bipolar I disorder at 11-years old and had a 7-year history of cocaine dependence. He had been receiving 400 mg of quetiapine nightly and 500 mg of valproic acid for the past 6-weeks, was in a mixed mood state and had been abstinent from cocaine for 15-days at the time of imaging.

Technical difficulties prevented us from acquiring the axial slice frontotemporal tractography and the 3D transverse views in the healthy control, although these images were obtained for both subjects with co-occurring disorders. The sagittal MR images do not show noticeable gray matter differences among the healthy control and subjects. However, the whole brain DTI connectivity coloration map illustrated by the healthy control in Figure 2 suggests that both co-occurring disorder subjects (Figures 3 and 4) have fewer left/right association (red), anterior/posterior projection (bright green), and feet/head callosal (blue) fiber tracts than the healthy control.

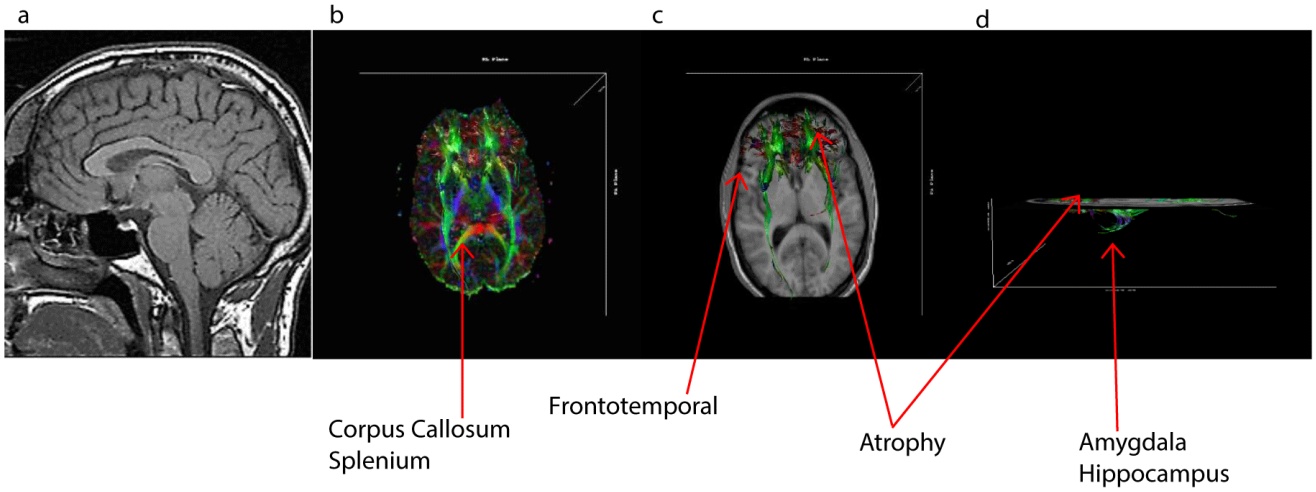

Figure 4: Male with Co-Occurring Disorders, (a) Sagittal MRI, (b) Axial Whole Brain DTI Slice #15, (c) Axial Slice Frontotemporal Tractography, (d) 3D Transverse View:a, b,c

Specifically, red and yellow coloration in the areas of genu and splenium corpus callosi are scarce in the both subjects in comparison to the healthy control. Compared to the female subject in early partial cocaine remission, the association fiber tracks in the genu and splenium corpus callosi are barely visible in the male brain with 15-days of cocaine abstinence. Fewer densities of yellow along the external capsule and optic radiation are also observed in the male brain suggesting a paucity of integrated projection and association fibers necessary for connecting the cortex to other cortical areas and transmitting cortical information.

Pink colored fiber tracts are not as prominent in either subject in comparison to the healthy control suggesting atrophied callosi, frontal, and temporal lobe connections. The axial DTI slice #15 focusing on prefrontal and frontal cortical connectivity is predominately magenta and green in the male subject and starkly contrasts the observed mix of yellow, green, and red in the female subject. Moreover, the complete lack of cingulate, frontal, and uncinate fascicule fibers not seen in the male subject's 3D transverse image is striking and may indicate profound fiber atrophy and/or disconnection.

Discussion

To our knowledge, these images are the first to use DTI tractography to illustrate white matter connectivity differences in those with co-occurring bipolar disorder with cocaine dependence in comparison to a healthy control and as a function of days of abstinence. Currently available DTI images in the literature are generally not pathway specific, but rather densely blurred voxel images. In contrast, the images presented here show distinct pathway connectivity.

In terms of pathway anomalies found in bipolar illness, these results somewhat reflect the findings by Nortje et al. [3] who reported fronto-limbic pathway atrophy in bipolar disorder. In addition, these images align with Barysheva et al. [4] and Thomason and Thompson [5] who also reported atrophy in callosum and cortical association fibers in euthymic patients with bipolar disorder. Specifically, the lack of connectivity in the genu and splenium corpus callosi and in the frontal areas shown in this case series mirror the available data [3-5] and suggest that DTI may help to neurologically characterize bipolar illness.

Nevertheless, whether or not these images can be associated with cocaine dependence or days of abstinence is unclear. Moeller et al. [6] found that in comparison to healthy controls, cocaine dependent subjects without a psychiatric illness also had atrophied fiber tracks in the genu area of the corpus callosum that connects to prefrontal cortex. However, the subjects in Moeller et al. [6] were allowed to be polydrug abusers, whereas substance dependence other than cocaine was an exclusion criterion for enrollment in the present study reported here.

In contrast to Moeller et al. [6], Lim et al. [7] examined cocaine dependent subjects and found no white matter atrophy in the genu corpus callosum, but found significant atrophy in the orbitofrontal cortical area. Unlike Moeller et al. [6], Lim et al. excluded subjects with polydrug abuse. Thus, the combination of frontocortical and corpus callosum fiber atrophy found in the present study may reflect these data and better describe neural anomalies in those with co-occurring bipolar disorder with cocaine dependence.

This study was designed to explore DTI as a suitable technology to better neurologically characterize those with co-occurring bipolar disorder with cocaine dependence. These results are similar to those currently available in the literature. In the real world, those with co-occurring disorders represent a clinically difficult population to treat pharmacologically due to multiple mood symptoms that mimic addiction behaviors and vica versa. Thus, recognizing pathway connection atrophy and anomalies that may be unique to those with co-occurring disorders may inform drug development. However, these images should be viewed with caution due to the obvious limitations of a case series. A weakness of this report is the lack of additional data sets to allow replication of this study. A matched controlled DTI study examining this target population versus those bipolar disorder alone versus cocaine dependence alone is needed to further examine potential fiber tract differences prior to making data interpretations.

Acknowledgements

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