Widespread White Matter Integrity Abnormalities in Cocaine Use Disorder Assessed by High Resolution dMRI and Tractography

Rafael O'Halloran[1], Nelly Alia-Klein[2], and Rita Z Goldstein[2]
[1]*Radiology, Icahn School of Medicine at Mt Sinai, New York, NY, United States,* [2]*Psychiatry, Icahn School of Medicine at Mt Sinai, NY, United States*

TARGET AUDIENCE – Researchers and clinicians working in the area of addiction, specifically in cocaine use disorder.

PURPOSE – In previous MRI studies of **cocaine use disorder (CUD),** fractional Anisotropy (FA) reductions localized in several brain regions were reported[1-4]**. In these studies, there was no clear consensus on the regions affected. The aim of this study is to examine the effect of CUD on white matter integrity using more powerful modern diffusion-weighted MRI (dMRI) acquisition and analysis methods.**

METHODS – *MRI:*. dMRI was performed on 19 healthy controls (age 42±7yrs, a measure of intelligence using the matrix reasoning scale of the WASI 11±3, 4 female) and 21 subjects with cocaine use disorder (CUD) (age 47±6yrs, WASI 10±3, 4 female). Groups were also matched for ethnicity. The acquisition was performed with a high-angular-resolved single shot spin echo EPI sequence with monopolar diffusion encoding [TR/TE = 407200/81.462 ms, 1.8 mm isotropic resolution over the whole brain and multi-band factor of 3 (R=3)[5] without in-plane acceleration]. Paired acquisitions with reversed phase encoding in the LR/RL direction were acquired, each with 64 matched diffusion-encoding directions (b=1200 s/mm2) and 5 un-weighted (b=0) scans. The total scan time for each acquisition was ~5 min. T1-weighted MP-RAGE at 0.8 mm isotropic resolution was obtained for segmentation and anatomical reference.

Analysis: Pre-processing of the diffusion-weighted data was performed using a modified version of the Human Connectome Project pipeline[6] and FSL[7]. The corrected images were fit to a tensor model to obtain Fractional Anisotropy (FA) maps in FSL. Voxelwise statistical analysis of the FA data from all 40 subjects was carried out using Tract-Based Spatial Statistics (TBSS) in FSL. TBSS projects all subjects' FA data onto a mean FA tract skeleton, before applying voxelwise cross-subject statistics. A corrected *t*-statistic was obtained for the test that the FA of the CUD subjects was less than the FA of the controls (given prior reports, the opposite direction was also tested). Connectivity matrices for each subject were computed between 100 anatomical locations with free software (BrainSuite[9], v14b). A group comparison of the connectivity matrices was performed using MATLAB and the Network Based Statistics package of the Brain Connectivity Toolbox[10]. Track visualization was performed with MRTRIX[11].

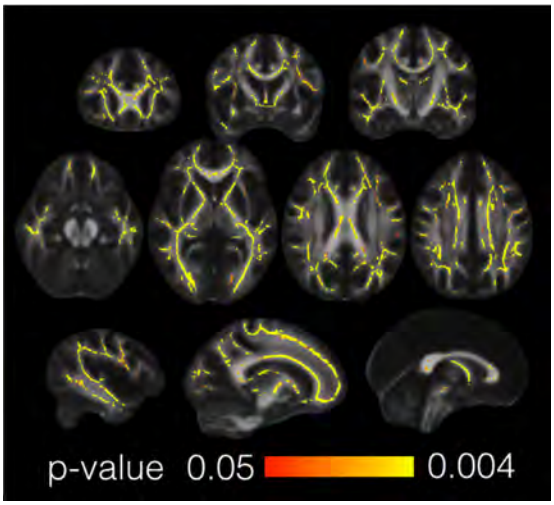

Fig. 1 – The FA of the CUD subjects is significantly lower than that of controls in many of the large white matter tracks.

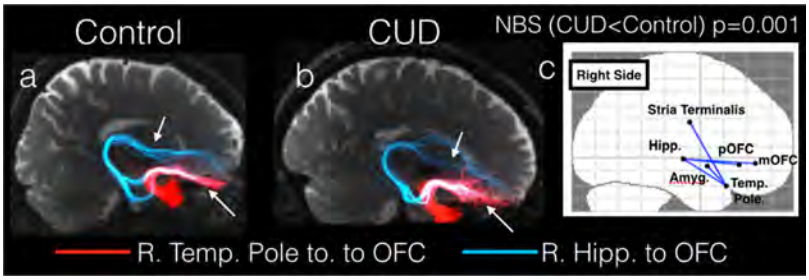

Fig. 2– Tracks from the Temporal pole to the OFC (red) and the Hippocampus to the OFC (blue) in a healthy control (a) and a subject with CUD (b) and the most significantly less connected network in the CUD than controls identified by NBS (c).

RESULTS– A map of *p*-values for skeletonized FA in which the FA of CUD subjects was less than the FA of controls for several representative coronal, axial, and sagittal slices is shown in Figure 1. This map demonstrates that the FA is reduced in CUD subjects over a wide range of white matter tracts including the corpus callosum, the cingulum, internal capsule, frontal white matter, posterior corona radiata, and anterior commissure (there were no significant differences between the groups in the opposite direction, i.e., CUD>controls). Figure 2 shows the most significantly different networks identified by network-based statistics (Threshold t=3.5, p=0.001) comprised of the hippocampus, amygdala, striatum, posterior and medial orbitofrontal cortex (pOFC, mOFC), and temporal pole (Fig 2c). Example tracks from a control and CUD subject are given in Fig 3a,b. Tracks from the right temporal pole to the right OFC are shown in red while tracks from the right hippocampus are shown in blue.

DISCUSSION and CONCLUSIONS – In this study, an analysis of group FA differences between healthy controls and subjects with CUD revealed significantly lower FA in subjects with CUD in many white matter areas. In contrast to previous studies that showed focal regions of decreased FA, and in groups matched for age, gender, ethnicity, and level of intelligence, these results seem to indicate a more widespread effect of CUD on white matter integrity. While many network tracks were found to be significantly lower in the CUD subjects, for simplicity in this brief presentation only the most significant group differences were shown. The compromised integrity of the white matter tracks terminating in the OFC, and encompassing other limbic subcortical regions, extend previous results showing grey matter and functional (task activity and resting-state connectivity) abnormalities in the striatocortical mesolimbic dopaminergic pathway in cocaine addiction. Future work will be focused on correlations between network measures and severity of CUD as well as differences between subgroups such as abstinent and active cocaine users.

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