Diffusion Tensor Markers of the Neurobiology of Cocaine Addiction

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Introduction: Stimulant drugs like cocaine may be neurotoxic when used chronically. However, reliable identification of neurotoxicity in human drug users is complicated by many factors such as subject gender, age, addiction history and polydrug abuse **(1).** Identifying valid quantitative neuroimaging markers of neurotoxic effects of abuse stimulants is an important application that may pave the way towards therapeutic clinical interventions **(1).** Previous functional MRI studies reported reduced activation in cocaine-dependent (CD) relative to age-matched healthy control (HC) subjects in gray matter (GM) regions such as insula, striatum, thalamus and cingulate **(2, 3, 4).** Here, we applied atlas-based methods to identify macro and microstructural correlates of cocaine dependence, incorporating white matter (WM) connections in addition to the limbic-thalamic-striatal-cortical regions previously reported **(2).** Our current study indicates that GM mean diffusivity of the cingulate cortex and thalamus may serve as early biomarkers; and may be present subsequent to longer-term effects of cocaine on WM pathways.

Subjects and Methods: The inclusion criteria of the HC and CD cohorts were described previously **(2).** The participants included 12 neurologically healthy controls without drug abuse history (6 females; age range = 19-54 years; 35.4 ± 12.2) and 19 CD patients (3 females; ages 24-52 years; 40.8 ± 8.4 years). The two cohorts were not significantly different on age (p=0.15). All MRI studies were performed on a 3T Philips Intera scanner. The diffusion-weighted imaging (DWI) data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with 21 non-collinear encoding directions, b=1000 sec mm^{-2}, T_R/T_E = 7000/65 msec. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; FOV=256x256 mm^2:DWI data were prepared for processing as described previously **(5)**. Whole brain CSF (wbCSF) was segmented into ventricular (vCSF) and non-ventricular or sulcal CSF (sCSF). Whole brain GM and WM were segmented using a DTI-ICBM atlas-based approach **(6, 7)**. The tissue segmentation utilized contrast between CSF and brain parenchyma on the mean diffusivity (MD) and fractional anisotropy (FA) maps **(6).** The approach provided volume and corresponding DTI metrics such as FA, mean, radial and axial diffusivities. The brain tissue was segmented further into deep/corpus callosum and cortical/lobar which was parcellated into frontal, temporal, parietal, limbic and insular zones according to the DTI-WM atlas **(6).** As a representative of deep non-callosal tissue we focused on the anterior (ATR) and posterior thalamic radiations **(PTR),** cingulate/cingulum, insular WM/GM, deep GM (caudate, putamen), hippocampus and amygdala**.** Regional and global volumes were normalized to the intracranial volume of each subject **(7).** Comparisons of regional and global mean values between groups were conducted using analysis-of-variance. Generalized linear regression was used to analyze the scatter of data with age.

Results: Volume-to-ICV percentages were not different in regional and global CSF, GM and WM. Ventricular and sulcal CSF volumes increased with age in both HC and CD. As expected, neocortical GM volume decreased with age at comparable rates in both groups (**Fig. 1A**). As a data quality assurance measure, the scatter of MD vs. FA is provided in **Fig. 1B**. The MD of the thalamus (**Fig. 1C**; p=0.004), anterior and posterior cingulate (**Fig. 1D**, $p < 0.05$) were elevated in CD. The ATR, PTR, insular and cingulum WM were not statistically different (**Fig. 1D**).

Discussion: The measured regional and global age trends of CSF, WM and GM in healthy controls are consistent with published and predicted trends and assure that the methods used are sensitive to capture changes due to age and potential neurotoxicity (**7**). The thalamic and cingulate diffusivity is elevated in the GM of CD, but not in the white matter connections, hinting that alterations in the GM precede changes in WM. Both thalamus and cingulate are regions with high perfusion and high density of dopamine neurotransmitters (**8**). The elevated thalamic diffusivity in CD subjects is consistent with previous reports on the sensitivity of this relay station to the effects of other neurotoxins **(9,10).** Our findings may reflect the potential role of cocaine in disrupting dopamine neurotransmission and a subsequent alteration of GM integrity, due possibly to neuronal or cellular apoptosis following microvascular constriction (**3,4,8**). The application of our methods to CD patients scanned serially to study therapy effects is underway.

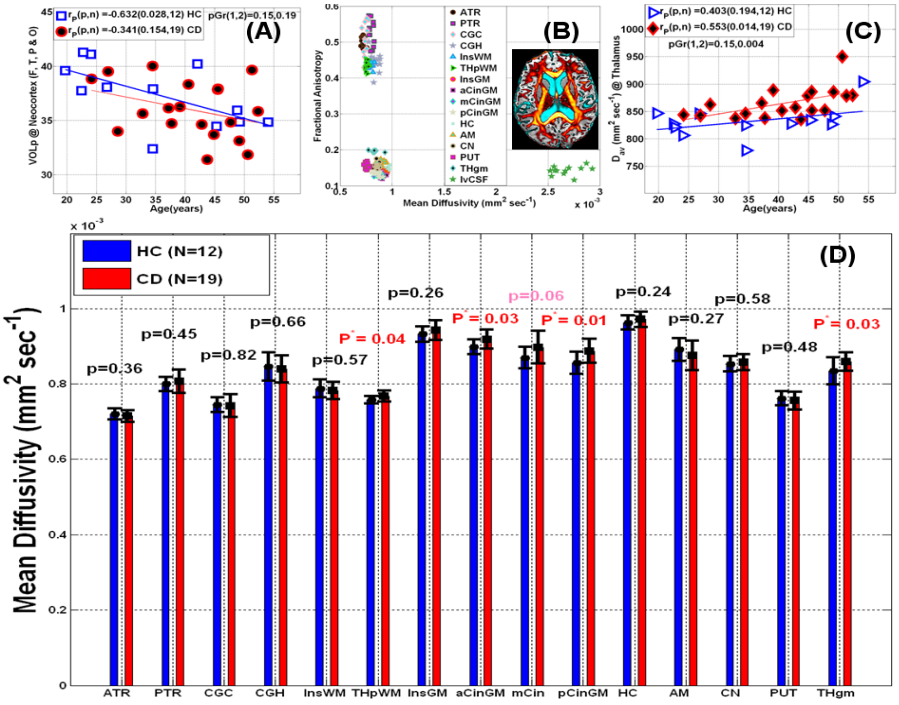

Figure 1. Representative scatter plots of **(A)** neocortical GM volume **(B)** a representation of the a host of WM, GM, and lateral ventricle (CSF) in the FA vs. MD space, **(C)** a scatter of thalamus diffusivity with age in both cohorts and (D) group differences between HC and CD**.** Note that the cingulate GM and thalamus are the only regions with significant elevation of mean diffusivity in cocaine-dependents.

References

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