White Matter Changes in Chronic Cocaine Users Revealed by Voxelwise Group Analysis of Diffusion Tensor Imaging

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Introduction

Neuroimaging studies have shown significant changes in metabolism, functional activity and/or gray matter density in several brain regions including prefrontal cortex, anterior cingulate cortex, ventral striatum, and meso-temporal lobes of human cocaine addicts (1-3). However, whether chronic use of cocaine affects the neuronal pathways connecting these regions is not known. Previous diffusion MRI studies (4-5) were based on region-of-interest (ROI) analysis, leading to a lack of information on whole brain white matter changes associated with cocaine abuse. In the present study, we test the hypothesis that white matter integrity is altered in cocaine addicts compared to healthy controls using a voxelwise group analysis on diffusion tensor imaging (DTI) data.

Methods

Data Acquisition. An EPI-based spin echo pulse sequence was used to acquire diffusion-weighted MRI images from 12 cocaine dependent individuals and 12 healthy controls on a Siemens 3T Allegra scanner. The user group and control group were matched for gender, age, and years of education. For each subject, 35 axial images were prescribed to cover the whole brain with a 128×128 in-plane matrix at a resolution of 1.719×1.719×4 mm^3. Beside the non-diffusion reference image, 12 directions were used to apply the diffusion sensitive gradients at a *b* factor of 1000 s/mm^2. For EPI, TR/TE = 5000/87ms and BW= 1700Hz/Pixel, NEX=4. T1 weighted anatomical images and field maps were also acquired at the corresponding slices.

Data Processing and Analysis. All EPI images were geometrically corrected based on the field map information, and then transformed to Talairach space. Fractional anisotropy (FA), mean diffusivity (MD), and 3 eigenvalues (λ_1, λ_2, and λ_3) of the diffusion tensor were calculated in each voxel. A 3-D nonlinear registration procedure (6) was performed on all FA data sets in order to achieve aliment of white matter tracts across the 24 subjects. All data sets were resampled to 1 mm^3 resolution, and aligned again to a standard Talairach anatomical image. The average FA map was used to generate a white matter mask to restrict the region of analysis. A voxelwise 2-sample *t*-test was used to assess significant differences of FA values between the cocaine users and normal controls. The regions of significant changes were selected by thresholding the *t*-score maps at $p < 0.05$, and a 3-D clustering was used to exclude few spots smaller than the original voxel size of 15 mm^3.

Results

A number of regions demonstrated an FA reduction in cocaine addicts compared with control subjects, and theses regions generally appeared in a bilateral pattern. In Talairach coordinates (LPI), significant reduction of FA was found in pontine crossing tract [+4, -34, -33], substantia nigra [+8, -14, -10], subcallosal gyrus [-12, +18, -12], superior cerebella peduncle [-4, -35, -11], anterior cingulate [-14, +34, +4], middle temporal gyrus [-50, -41, -9], inferior frontal gyrus [+34, +28, +5], medial frontal gyrus [-18, +45, +3], superior frontal gyrus [+20, +18, +3], anterior limb of internal capsule [+15, +4, -2], amygdala [+21, -9, -9], parahippocampal gyrus [+18, +45, +3], corpus callosum [-14, -40, +13], precentral gyrus [+40, -5, +29], and superior occipital gyrus [-26, -76, +28]. A few regions of FA increase were also found, including in middle cerebella peduncle [-9, -17, -31], posterior limb of internal capsule [+18, -17, +5], superior temporal gyrus [-39, -32, +5], middle occipital gyrus [-34, -72, +6] and angular gyrus [-38, -54, +36]. Meanwhile, a global MD increase was found in the cocaine users. The regions of FA reduction generally showed an increase in eigenvalue λ_1 and λ_2, whereas the regions of FA increase showed a decrease of λ_2.

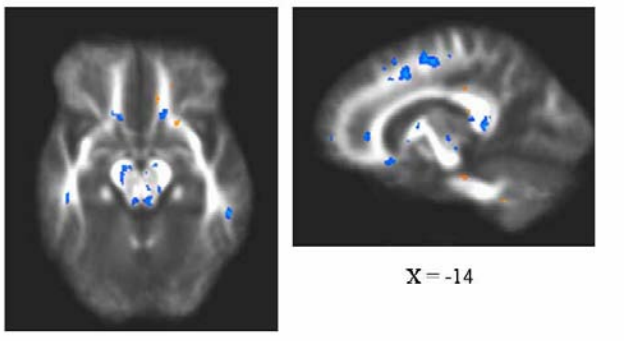

Fig.1 Group *t*-score maps ($p < 0.05$) on background of average FA map. Blue and red regions correspond to the decrease and increase of FA in the cocaine users, respectively

Discussions

Cocaine dependence has been previously reported to lead to reduced orbitofrontal metabolism, impaired cognitive functions and reductions in presumptive gray matter size as revealed by VBM (1-3). Using voxelwise DTI group analysis, we have been able to demonstrate white matter integrity changes in neuronal pathways between brain regions previously associated with cocaine addiction. The reduced FA in substantia nigra, pontine crossing tracts, parahippocampal gyrus, corpus callosum, inferior /medial /superior frontal gyrus, and precentral gyrus may help explain the functional activity and/or connectivity reductions previously reported in prefrontal cortices, anterior cingulate cortex, thalamus, striatum and meso-temporal lobes, and provide *in vivo* histological indications of brain deficits and neuronal dysfunction or degeneration associated with chronic cocaine addiction. It will be of interest to determine if and when these neuronal pathway alterations are reversed during prolonged abstinence and treatment.

References

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