Reduction of Functional Connectivity in Cocaine Users Revealed by Resting-State Functional MRI

H. Gu[1], W. Zhan[1], T. J. Ross[1], B. J. Salmeron[1], E. A. Stein[1], and Y. Yang[1]

[1]Neuroimaging Research Branch, National Institute on Drug Abuse, Baltimore, MD, United States

Introduction

Neuroimaging studies have shown significant reductions in metabolism, functional activity and/or gray matter density in several brain regions including prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventral striatum, and meso-temporal lobes of human cocaine addicts (1-3). However, whether chronic use of cocaine affects the interactions among these brain regions is not known. Synchronized low-frequency fluctuations in resting-state fMRI signal (4) provide the possibility to assess functional connectivity both in healthy individuals and in various disease states (5,6). In the present study, we use resting-state fMRI to test the hypothesis that system specific functional connectivity is altered in cocaine addicts compared to healthy controls.

Methods

Data Acquisition. Resting-state fMRI data were acquired from 16 cocaine dependent individuals and 16 healthy controls on a 3T Siemens Allegra scanner. The user and control groups were matched for gender, age, and years of education. All participants gave informed written consent prior to study entry. Subjects were instructed to close their eyes and not to think of anything in particular during the scan. Thirty-nine slices were prescribed to cover the whole brain and 180 image volumes were acquired with 2s TR, 27 ms TE and 3.43×3.43×4 mm^3 spatial resolution.

Data Processing and Analysis. All resting-state data were slice-timing corrected, volume registered, linearly detrended, and transformed to Talairach space. The data were then spatially smoothed (FWHM = 6 mm) and temporally filtered (low-pass frequency cutoff = 0.1 Hz). Five spherical ROIs (radius = 3 mm) were selected in left amygdala, hippocampus, ACC, medial dorsal (MD) thalamus, and precentral gyrus/primary motor cortex. Time courses from voxels within these 5 ROIs were averaged to generate five templates. Correlation coefficients (CCs) of each voxel in the brain were calculated between the voxel time course and the templates, which were then converted to z-scores. Assuming low frequency fluctuation (LFF) signals from white matter are less interesting and significant, an average time course was extracted from voxels in white matter, to which the image data were orthogonalized in calculating CC. Two-sample t-tests were performed on z-score maps to assess significant differences between the two groups for each of the five ROIs.

Results

A general reduction in functional connectivity was seen in cocaine addicts compared with matched control subjects. Specifically, when the seed point was in the amygdala, significant reductions in functional connectivity was found in a large area of the medial prefrontal cortex (mPFC), inferior prefrontal cortex (iPFC), orbital cortex, anterior and posterior cingulate cortices (ACC & PCC), and cerebellar tonsil in the cocaine group (Fig.1). Similar brain areas in mPFC, iPFC, ACC and PCC showed decreased connectivity when the seed point was in hippocampus. When the seed was in the dorsal ACC (Brodmann 24), functional connectivity was significantly reduced in the putamen, hippocampus, and ACC (Brodmann 32). Connectivity was decreased in the mPFC, ACC, caudate, nucleus accumbens (NAc), amygdala, and putamem when the seed was placed in MD thalamus. No significant differences were seen in the primary motor cortex when the seed was in precentral gyrus.

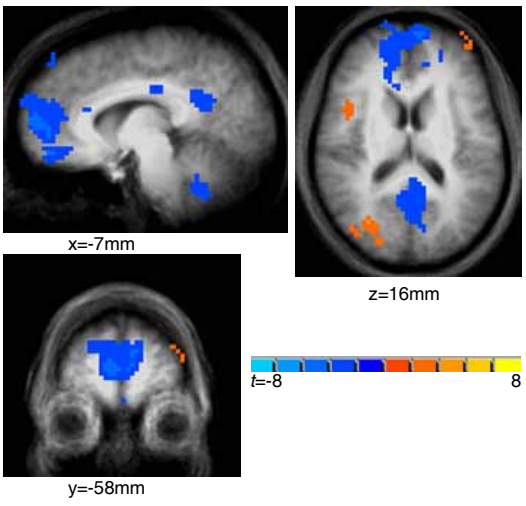

Fig.1 Significant changes in functional connectivity of cocaine users compared to healthy controls ($p < 0.01$) when seed voxels were in amygdala. (Blue – decrease; red – increase)

Discussions

Cocaine dependence has been previously revealed to lead to reduced orbitofrontal metabolism, impaired cognitive functions and reductions in presumptive gray matter size as revealed by VBM (1-3). Using resting-state fMRI, we have been able to demonstrate consistent, system dependent decreases in functional connectivity among brain regions associated with cocaine addiction. The reduced connections among prefrontal cortices, ACC, MD thalamus, striatum and meso-temporal lobes may help explain brain deficits associated with chronic cocaine addiction, and point to a powerful new tool to study cocaine-induced neuronal dysfunction or dysregulation. It will be of interest to determine if and when these putative connectivity alterations are reversed during prolonged abstinence and treatment .

References

1. Volkow et al, Synapse 1993; 14:169-177. 2. Goldstein and Volkow Am J Psychiatry 2002; 159:1642-1652. 3. Franklin et al, Biol Psychiatry 2002; 51:134-142. 4. Biswal et al, Magn Reson Med 1994; 34: 537-541. 5. Greicius et al., PNAS 2003; 100: 253-258. 6. Li et al., Ragiology 2002; 225: 253-259.