Functional Connectivity Analysis of Heroin Addicts Using the Ventral Tegmental Area as a Seed

A. D. Cohen[1], C. Xie[1], W. Li[1], Z. Yang[2], L. Ma[3], and S. Li[1,4]

[1]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Cognitive Research Laboratory, Beijing Institute of Basic Medical Sciences, Beijing, China, People's Republic of, [3]Radiology, PLA 301 Hospital, Beijing, China, People's Republic of, [4]Psychiatry and Behavioral Medicine, Medical College of Wisconsin

Introduction: The ventral tegmental area (VTA) is a group of neurons located at the center of the brain. It is a key part of the mesolimbic reward pathway, which links the VTA, nucleus accumbens (NAc), and prefrontal cortex (PFC). The VTA releases dopamine neurons and is activated by pleasure-producing activities including the use of addictive drugs such as cocaine and heroin. Functional connectivity MRI (fcMRI) is a growing field that uses fMRI to look at correlations between spatially distinct neurophysiologic events. A few fcMRI studies have investigated functional connectivity in human drug addicts (Li 2000, Daglish 2003), but to date there have not been any resting-state fcMRI heroin studies in humans. We hypothesize that heroin users have decreased VTA functional connectivity in comparison with nondrug users.

Methods: This study looked at resting-state fMRI data for both nondrug users and heroin users. Twenty-one heroin users and 15 control subjects were scanned with the single-shot EPI sequence at a 3T GE scanner with imaging parameters of TR of 2000ms, TE of 25ms, flip angle of 90°, FOV of 24 cm, matrix of 64×64. Thirty slices were acquired with slice thickness of 5mm for 6 min. High-resolution SPGR images also were acquired for registration. The region of the VTA was drawn according to the Talairach space coordinates and used as a seed region for functional connectivity analysis. Then, the data was motion corrected and linearly detrended. Heartbeat and respiration were monitored during the scan and regressed out of the data. Finally, single-subject, general linear modeling was applied to eliminate motion-related signals, as well as white matter and CSF signal. Whole-brain functional connectivity analysis was then performed. Cross-correlation maps were obtained for each subject, transformed to a standard space (Talairach Space), converted to z values, and then blurred using a Gaussian kernel with FWHM 6 mm. An intergroup *t*-test was performed on the z values and then corrected for multiple comparisons using a Monte Carlo Simulation and AFNI's AlphaSim program with FWHM of 6 mm, cluster connection radius of 8 mm, and individual voxel threshold probability $p \leq 0.05$. This resulted in a cluster size of 2,910 mm^3 for a significance level p of 0.05.

Results: Statistically significant differences in functional connectivity ($p<.05$ and cluster size = 2910 mm^3) were found in the PFC, cingulate gyrus (CG), and postcentral gyrus (PCG). The heroin addicts showed a decrease in connectivity between the VTA and both the PFC and CG. An increase in connectivity was found between the VTA and the PCG in the heroin addicts. These results are illustrated in Fig. 1.

Discussion: It has been shown that drug addicts have a long-term decrease in dopamine release and a reduction of D2 DA receptors. This is linked to reduced activity in the CG and the dorsolateral PFC (dlPFC). Reduced activity in these regions has been shown to be associated with decreased availability of D2 DA receptors in the ventral striatum (Volkow 2008). The VTA and NAc (located in the ventral striatum) are linked via dopamine in the mesolimbic reward pathway. These findings suggest that a decrease in dopamine release in the VTA also may be associated with decreased activity in these regions and the lack of functional connectivity between the VTA and these regions. These results show intrinsic differences in brain organization between heroin users and nondrug users; the decreased VTA functional connectivity may be underlying the addictive behaviors. It is suggested the fcMRI method could be utilized to study neurobiological mechanisms of addiction and monitor treatment efficacy in the future.

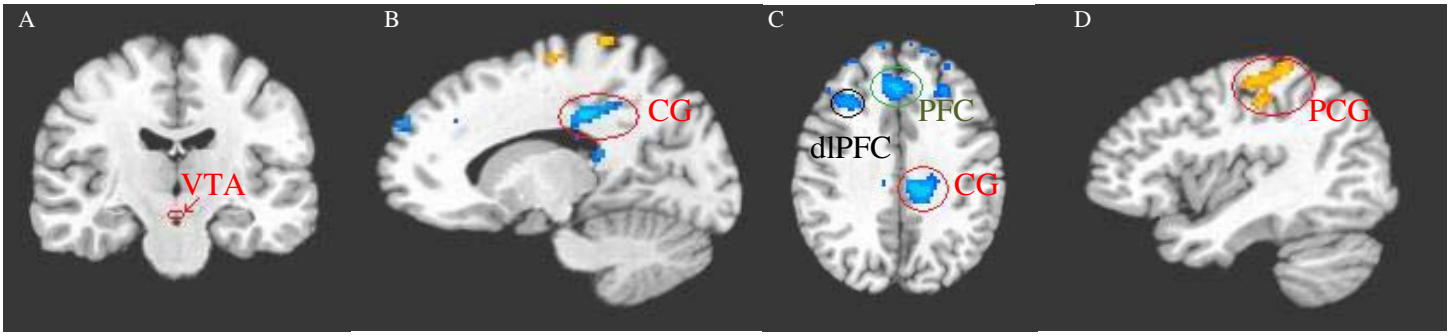

Figure 1. Differences in functional connectivity between heroin users and nondrug controls. (A) Representation of the VTA used as a seed for analysis. (B) Decreased connectivity in the CG. (C) Decreased connectivity in the PFC and CG. (D) Increased connectivity in the PCG. Blue colors indicate a decrease in connectivity and orange colors indicate an increase in connectivity in heroin users compared to the controls.

References:

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