

# Neural underpinning from goal-directed drug seeking to dysfunctional stimulus-response habit: Increased Nucleus Accumbens – Caudate Connectivity in Heroin Addicts

A. D. Cohen<sup>1</sup>, C. Xie<sup>1</sup>, W. Li<sup>1</sup>, T. T. Zhang<sup>1</sup>, Z. Yang<sup>2</sup>, and S. Li<sup>1</sup>

<sup>1</sup>Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, <sup>2</sup>Beijing Institute of Basic Medical Science, Beijing, China, People's Republic of

**Introduction:** The nucleus accumbens (NAc) has been shown to mediate the reinforcing effects of drugs, including heroin (Koob 1992, Volkow 1997). Recent research has begun to point out the role of the dorsal striatum in drug addiction. Haber et al. describe a dopamine-dependent ascending spiral pathway linking the NAc to progressively more dorsal regions of the striatum via the substantia nigra (SN) and ventral tegmental area (VTA) (Haber 2000). Furthermore, Belin and Everitt showed cocaine seeking depends on connectivity between the ventral and dorsal striatum in rats (Belin and Everitt 2008). Functional connectivity MRI (fcMRI) is a rapidly growing field using functional MRI to look at correlations between spatially distinct neurophysiologic events. Currently there have not been any fcMRI studies specifically looking at the NAc – striatum connection in human drug addicts.

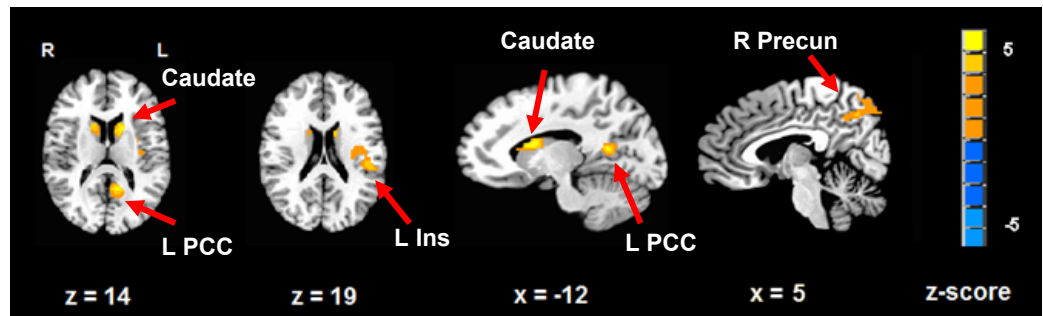
**Methods:** This study looked at resting state fMRI data for both heroin addicts and non addicts. In total 23 heroin addicted and 15 control subjects were scanned in a 3T GE scanner with TR = 2000ms, TE = 25ms, flip angle = 90 degrees, slice thickness = 5mm with a 1mm skip, and a matrix of 64 × 64. Using the NAc as a seed, functional connectivity was compared between groups. Thirteen brain regions attributed to the addiction network (Everitt, Robbins 2005) were selected as seed regions. Functional connectivity between the NAc and the other 12 regions was calculated in each individual and then a group comparison was conducted. The data was motion corrected and linearly detrended. Heartbeat signal and respiration signal were monitored during the scan and then regressed out. Single subject general linear modeling was applied to eliminate motion related signal, white matter and CSF signals, global signal, and high frequency signals (band-pass filtering <0.1 Hz). 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 = 6mm. 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 = 6mm, cluster connection radius = 8mm, and individual voxel threshold probability = 0.05. Minimum cluster sizes varied for each ROI.

**Results:** A between group 2 sample t-test analysis yielded significant differences in several brain regions. Increased positive correlation was seen in the left insula, left precuneus, left posterior cingulate cortex, and bilateral caudate body in heroin subjects vs. controls. This is shown in Figure 1. No significant decreases in correlation were seen in heroin subjects compared to controls.

**Discussion:** Drug addiction is characterized by a compulsive need and uncontrollable urge to obtain drugs coupled with a decreased response to natural rewards. Initially drug seeking behavior is goal-directed (Belin and Everitt 2008). However, after prolonged use, drug seeking behavior becomes mediated by a dysfunctional stimulus-response (S-R) habit (Everitt and Robbins 2005, Belin and Everitt 2008). Studies of rats and non human primates show an increased role of the dorsal striatum is coupled with increased drug seeking habits (Belin and Everitt 2008). This study showed increased NAc – caudate connectivity in heroin addicts vs. controls. These results suggest increased NAc – caudate connections could underlie the shift from goal directed to habitual behavior in drug addiction.

## Figure 1. NAc Difference Map.

Difference between heroin and control connectivity using the NAc as a seed. Orange colors indicate heroin connectivity > control. Blue colors indicate heroin connectivity < control. Maps were generated by a 2 sample t-test of the smoothed, normalized correlation values from the control group and heroin group. Significance threshold is set to  $p < 0.05$ .



## References:

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