Identification of Hyperactive Intrinsic Amygdala Network Associated with Impulsivity in Abstinent Heroin Addicts

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Introduction: Neuropsychological and neuroimaging studies concerning addiction have demonstrated that the amygdala is instrumental in the regulation of drug reward, craving, and impulsive control [1,2]. However, little is known about the neural correlates of the impulsivity network in heroin user subjects. In this study, we utilized resting-state functional connectivity MRI (fcMRI) to investigate the relationship of the alteration in the amygdala functional connectivity (AFC) network and impulsive control in abstinent heroin users.

Methods: fMRI measurement: Twenty-four heroin-dependent subjects and 17 age-matched healthy control subjects participated in this study. Written consent was obtained from each subject. Impulsive behavior was measured by the Barratt Impulsive Scale (BIS, version 11); MRI scans were conducted at a GE 3.0T Signa LX scanner. 3D high-resolution anatomical images were acquired prior to functional scans. The fMRI data were obtained by using single-shot EPI sequence (TE=25ms, TR=2000 ms, FOV=24×24 cm, matrix=64×64, flip angle=90°, slice thickness=5 mm, space=1.0 mm). 180 imaging volumes were acquired in each functional scan run. **Data preprocessing**: The fMRI datasets were analyzed with AFNI. The first five data points of each dataset were discarded to obtain the stable state. Physiological motion correction, volume registration, and head motion correction were performed to correct tolerable motions during the scan. The resulting datasets were normalized to a standard Talairach image space, and resampled to the resolution of 2×2×2 mm^3. Further preprocessing steps, such as third-order detrending, low-pass temporal filtering of frequencies [0.015, 0.1], and deconvolving the white-matter, CSF, and global signals were executed using General Linear Model (GLM). The Fisher's Z-transformation formula also was employed for skewness reduction and normal distribution normalization. **Functional connectivity analysis:** The seed ROIs located in both sides of amygdala were selected based on anatomical distribution. The cross-correlation coefficient (CC) maps of individual subjects were generated by cross-correlating each voxel time course with the average time course of seed voxels. To identify the significance of AFC in control and heroin subjects, the one-sample *t*-test was utilized. For group statistical analysis, a two-sample t-test was used to detect any significant difference of functional connectivity between the heroin and the nondrug users groups. In addition, to investigate the brain activity behavior relationships, a whole-brain voxelwise linear regression analysis across heroin subjects was implemented by combining the CC values for individual subjects with impulsive scores.

Results: Compared to the nondrug users group (Fig. 1A), the alteration of AFC in the heroin user group has been observed in the prefrontal and limbic networks (Fig. 1B) (one sample *t*-test, $p<0.001$, corrected). Based on the group *t*-test comparison, the heroin users showed remarkably decreased anticorrelation AFC network in left precuneus (close to zero), increased anticorrelation AFC network in right inferior frontal gyrus, and positive AFC network in the right insula and bilateral thalamus (far away from zero); a reversed pattern of the AFC network was also found in right precuneus. The AFC network strengths correlated with the impulsive scores in the HD group that were positive in right subcallosal gyrus, insula, thalamus and posterior cingulated cortexes, and negatively correlated regions in left fusiform area; whereas in the CN group, the left pre-somamotor area-amygdala connectivity was positively correlated, right orbital frontal cortex-amygdala and precuneus-amygdala connectivity were negatively correlated with impulsive scores.

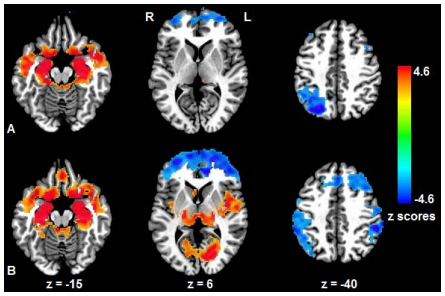
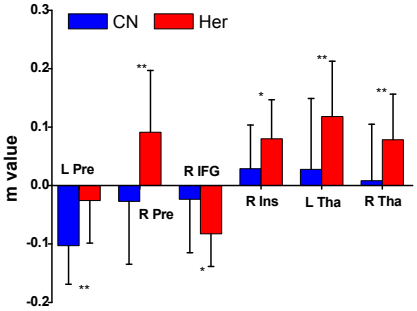
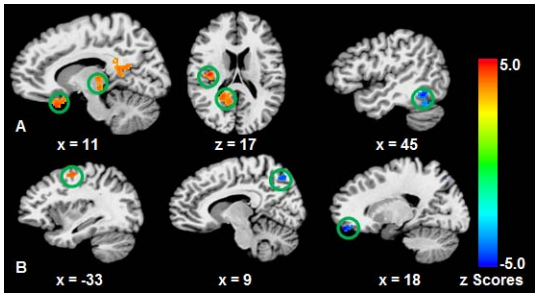


Fig. 1 Brain regions that are significantly connected with amygdala in **A)** control subjects and **B)** heroin users.

Discussion and Conclusion: The high-order cognitive behavior was determined by the neurocognitive network with a high-degree connectivity pattern among discrete brain regions [3]. The observed altered AFC network activity in HD subjects may represent the phamacolopathological damage that may underlie the neurobiological mechanism for the addiction. Our study found different constructs of impulsive network in HD and CN subjects. This further facilitates our understanding of the neural underpinnings of impulsive control dysfunction on addiction.



(Left) Fig. 2 Significantly altered AFC network in heroin group compared to control group. Significant level was set at: *, $p < 0.05$; **, $p < 0.01$. Error bar was presented with standard deviation.



(Right) Fig. 3 Robust linear regression analysis between the AFC network strength and impulsive scores in distinct regions in the heroin users **(A)** and control subjects **(B).**

References: 1, Nikos et al. Neuron. 2004. 44: 729-740. 2, Bechara A. Nat Neurosci 2005; 8(11):1458-1463. 3, Mesulam et al., Neuron.2009; 62(1):1-3.

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