Neural Correlates of Amygdala Functional Connectivity on Abstinent Heroin Addicts

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

Methods: fMRI measurement: Twenty-four heroin-dependent subjects and seventeen age-matched healthy control subjects participated in this study. Written consent informs was obtained from each subject. 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=2000ms, FOV=24×24cm, matrix=64×64, flip angle=90°, slice thickness=5mm, space=1.0mm). 180 imaging volumes were acquired in each functional scan run. All subjects were instructed to keep their eyes closed, relax and move as little as possible. Foam pads were used to reduce head motion during EPI data acquisition. **Data preprocessing**: The fMRI datasets were analyzed with AFNI. The first 5 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 mm3. 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 was also 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 coefficients (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 comparing with zero was utilized. For group statistical analysis, a two-sample t-test was used to detect any significant difference of functional connectivity between the heroin group and the non drug users group. In addition, to investigate the brain activity-behavior relationships, linear regression analysis based on whole-brain voxel-wise across heroin subjects was implemented by combination the CC values for individual subjects with heroin consumption dosage.

Results: Compared to the non-drug users group (Fig. 1A), the alteration of AFC in heroin user group has been observed in prefrontal and limbic networks (Fig. 1B). Based on the group t-test comparison between the heroin users and non-drug users, the significant alternations ($p<0.05$ with cluster size > 5470 mm^3) in AFC were observed in the bilateral cuneus (BA18), precuneus (BA7), posterior cingulated cortex (BA31) and right angular gyrus (BA39), superior parietal gyrus (BA7) (Fig.1C). Statistical maps of linear regression analysis between AFC strength (cross-correlation coefficients) and the amount of heroin usage per day were showed the positive correlation in the regions of bilateral superior, middle and inferior temporal gyrus (BA38,21,20), and those negative correlation in regions of the bilateral medial frontal gyrus (BA8), dorsal lateral prefrontal cortex(BA9,46), angular gyrus (BA39), precuneus (BA7), thalamus, right superior, precentral gyrus (BA6), left insula(BA13), precuneus (BA7), superior and inferior parietal gyrus(BA7, 40) (Fig.2) ($p<0.01$ with cluster size > 1180 mm^3).

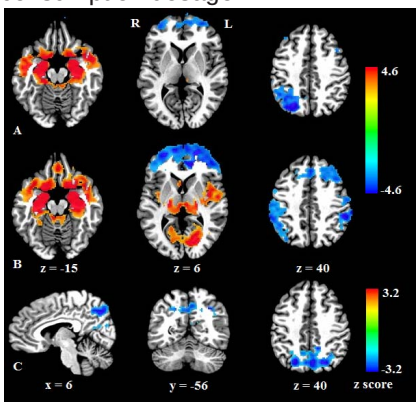

Fig. 1 Brain regions that are significantly correlated with Amygdala in **A)** control and **B)** heroin users ($p<0.001$, corrected). **C)** Brain regions with significantly altered AFC in heroin users. ($p<0.05$, corrected)

Discussion and Conclusion: It has been known that the prefrontal cortex is involved in executive control function. The observed decreased AFC activity in the heroin users may represent the phamacolopathological damage that may underlie the neurobiological mechanism for the addictive behavior – loss of behavioral control. Similarly, the decreased AFC activity in the insular and thalamus also indicated the alteration in the mesollimbic circuitry affected by the heroin consumption [2,3]. It is suggested that the fcMRI method could be applied to evaluate the consequence of heroin use and related alteration in brain circuitry.

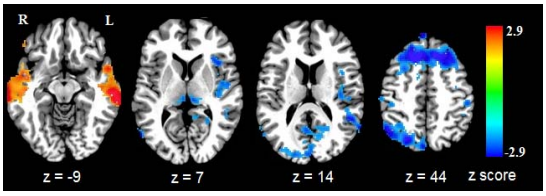

Fig. 2 Linear regression analysis between AFC across heroin subjects and the amount of heroin dosage per day showing both positive and native correlations between the AFC network and the dosage of heroin ($p<0.01$, corrected).

References

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