Decreased Functional Connectivity in the Brodmann Area 10 Network in Heroin Users

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Introduction: Functional connectivity MRI (fcMRI) using seed ROI approach has been widely used in current neurological research (e.g. in depression, schizophrenia, and Alzheimer's disease). However, a dearth of literature has been published on heroin-related studies. The purpose of this study is to investigate the changes of functional connectivity (FC) changes between non-heroin participants and heroin abusers. Based on the results from Voxel-Based Morphometry (VBM), we focus on how the decreased gray matter concentration in the region of Brodmann Area (BA) 10 could affect the FC in the brain of heroin users.

Methods: A total of 27 male subjects (age 32.17 ± 3.83 yrs) were recruited for this study. Two of the heroin subjects were excluded due to large motion during MR scans. Thirteen of the subjects were heroin abusers and the remaining twelve were normal control subjects. The heroin subjects met the criteria for opiate addiction in the Diagnostic and Statistical Manual of Method Disorders IV (DSM-IV-TR, American Psychiatric Association 2003). All heroin subjects recruited had undergone two weeks of drug abstinence. All subjects provided written informed consent. ***MRI Protocol:*** Two 12-min scanning runs were conducted on each subject, one for the neutral cue and another for the heroin cue. Each run had three sections: 3 min black screen, 4 min film cue (either heroin or neutral cues), and 5 min black screen. MRI scanning was performed on a GE 1.5T Signa LX scanner. High-resolution anatomical images were acquired, using 3D spoiled gradient echo (SPGR) sequence with 136 continuous axial slices for VBM analysis. Functional MR images were obtained by using a single-shot EPI sequence (TR/TE/FOV/FA/thickness/matrix size = 2000ms/30ms/24cm/90°/5mm/64x64) with 25 sagittal slices. After scanning, subjects were asked to complete a self-report form (Likert Scale). ***Data Analysis:*** VBM was performed using SMP5 software (http://www.fil.ion.ucl.ac.uk/spm) on a Matlab 7.0 platform and AFNI software (http://afni.nimh.nih.gov/afni). First, the gray matter (GM) of all subjects was segmented from the anatomical brain using SPM5, and transformed to Talairach space for further statistical analysis in AFNI. Logit transform was also used to reduce inter-subject variations. Next, every image was smoothed with a 6mm Gaussian kernel and grouped into heroin user group and control group respectively. A group comparison was then performed between these two groups to see the changes in GM concentration [1]. Regions of Interest (ROIs) were defined through the results of VBM. For this study, BA 10 was selected for the seed ROI to further analyze the brain FC of heroin and control subjects (Fig.1) [2]. All fcMRI analysis was carried out using AFNI. The residual portion of the data was derived from the event-related fMRI data by deconvolving the motion and BOLD responses using General Linear Model (GLM). The average time series of the preprocessed fMRI were then calculated at the seed ROI to cross-correlate with each voxel time course across the entire brain individually. The average cross-correlation coefficients (CC) maps were obtained and, for group statistical comparison, a two-sample t test was used to determine the FC-change between heroin and normal subjects (Fig. 2).

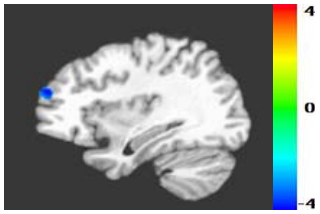

Fig. 1 Decreased GM concentration at BA10 in the heroin group.

Table 1. *Brain regions showed significant change in GM concentration*

			Talairach (mm)				
Anatomical Region	BA	Side	x	y	z	t-value	GMc
Middle Frontal Gys	8, 9	L	28	-21	43	-5.3824	-
Precuneus		L	24	61	27	-4.2566	-
Red Nucleus		R L	-1	18	1	3.8893	+
Supramarginal Gys		L	28	49	32	4.9517	+
Lingual Gyrus	18	R L	-3	86	-5	4.2534	+
Middle Frontal Gys	9	R	-23	-29	31	-4.2853	-
Superior Temporal Gys	40	R	-54	49	19	-4.0073	-
Superior Frontal Gys	38	L	21	-13	-34	-4.2952	-
Superior Frontal Gys	9	L	30	-40	32	-3.4353	-
Superior Frontal Gys	10	R	-34	-51	21	-4.1574	-
Middle Frontal Gys	9	R	-40	-30	38	-5.7404	-
Lingual Gys	17	R	-21	97	-10	3.3045	+

Note: GMc, Gray Matter Change; BA, Brodmann Area; Gys, Gyrus.

Results and Discussion: GM concentration in heroin subjects was significantly decreased compared to that of control subjects, according to the results of VBM analysis. The brain regions showed significance included: bilateral middle frontal gyrus (BA 6, 8, 9), right superior frontal gyrus (BA 10), left superior frontal gyrus (BA 38) , left precuneus, and right superior temporal gyrus (BA 40) ($p < 0.01$, corrected) (Table 1). Using BA 10 as the seed cluster for fcMRI analysis, left precentral gyrus (BA 6), bilateral postcentral gyrus (BA 2), bilateral cingulate gyrus (BA 24), left superior and middle temporal regions (BA 13, 19, 22, 39), and bilateral precuneus (BA 7) were found to be functionally related to BA 10. The cingulate gyrus (BA 24) in particular has been known to be closely associated with emotion, cognitive process and control system [4, 5]. Furthermore, FC in heroin subjects was significantly lower than that of control subjects (Fig. 2, $p < 0.05$, corrected) indicating that the correlation among different brain regions was remarkablely reduced. These results have suggested that FC decrease in heroin addicts may be crucially linked to loss of control, which leads to the main cause of relapse in addiction. It is suggested that the determination of FC could characterize the severity of heroin abuse and be a marker to evaluate treatment efficacy for drug abuse.

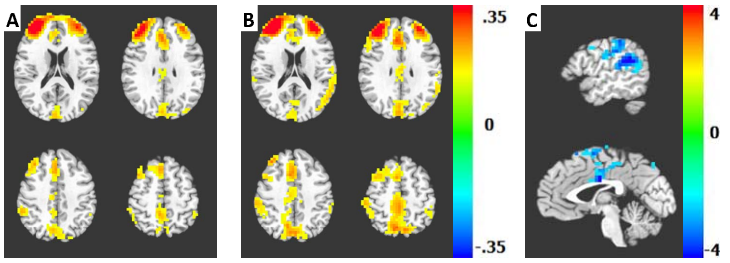

Fig. 2 A and **B** are the average correlation maps for heroin and normal group, respectively. **C** is the difference between the two groups after a two-sample t test and *AlphaSim* clustering ($p<0.01$).

References: **1**: Ashburner J, Friston KJ. Neuroimage. 2000 Jun; 11(6 Pt 1):805-21. **2**: Ramnani N, Owen AM. Nat Rev Neurosci. 2004 Mar;5(3):184-94. **3**: Damein A. Fair, et al. NeuroImage 2007. **4**: Bush G, Luu P, Posner MI. Trends Cogn Sci. 2000 Jun; 4(6):215-222. **5**: Volkow ND, Fowler JS, Wang GJ. J Clin Invest. 2003 May; 111(10):1444-51.

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