Impaired frontal executive function in abstinent heroin addiction: an fMRI study

L-P. Fu[1], Y. Wang[2], S-J. Li[3], G-H. Bi[1], Z-T. Zou[2], X. Xu[2], E-M. Ye[1], L. Ma[2], and Z. Yang[1]

[1]Beijing Institute of Basic Medical Science, Beijing, Beijing, China, People's Republic of, [2]General Hospital of People's Liberation Army of China, [3]Department of Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Introduction Heroin, like various illicit substances, has a negative impact on the frontal cognitive function after repeated abuse. Recently, there have been several studies on heroin addiction which focus on the neurocognition impairment [2,3], but the research on the long-term effect of heroin use on impulsivity is rare. Moreover, the research that applies neuroimaging fMRI to explore the impulsive control of heroin dependents, particularly the protracted abstinent heroin users, is even more so. In this study, an fMRI method with the Go/NoGo task was employed to detect the neuroanatomic substrates involved in inhibitory response and competition, to probe the frontal neurocognition of abstinent heroin dependents and to explore the impact of heroin on human cognitive function, even after drug abstinence has been achieved for months.

Materials and Methods **Subjects:** Thirty male abstinent heroin dependents (AHD) and 18 male healthy controls (HC) participated in the study after written informed consents were obtained. In terms of age (33.0± 5.9; 29.2± 6.9) and education (10.7± 2.2; 9.9± 2.3), the two groups were matched; the years of addiction and the weeks of abstinence were 6.4±3.4 and 7.6±2.1, respectively, The drug abstinence was determined by the negative presence of morphine in the urine-analysis. **fMRI acquisition:** All subjects received three scans: an SPGR high-resolution, a T1-Flair anatomical scan and a 6:50 fMRI-BOLD scan. All images were acquired at a 3.0 T GE Excite HD scanner using a standard GE head coil. The imaging parameters for SPGR acquisition (TR=10.4 ms, TE=MinFul, Thickness=1.0 mm, Matrix=256×256, FOV=240 mm, 140 slices in axial plane, acquired resolution in plane=0.9×0.9 mm2); T1-FLAIR provided the same localization information as the fMRI images (TR=2300 ms, TE=23 ms, Thickness=5 mm, Slice skip=1.0 mm, Matrix= 256×256, FOV=240 mm, Slices= 20). The whole-brain functional images were acquired using a single-shot echo-planar imaging (EPI) sequence (TR =2000 ms, TE = 25 ms, Bandwidth = 125 kHz, Matrix = 64×64, FOV =240 cm, Thickness=5.0 mm, Spacing=1.0 mm, Slices=20 and 5 dummy scan). **Go/NoGo paradigm**: A block-design paradigm programmed by Presentation Software (0.53 version) was developed to probe executive function, which consisted of 10 alternatives of "Go" and "Go-NoGo" epochs following a 10-sec resting epoch .Subjects were shown a continuous series of 200 letters and instructed to respond, by pressing a button with their thumb of the right hand, to withhold for any letter except "V". Approximately 75% of the trials were targets (characters "U" "M" "W") and all trials presented in pseudo-randomised order. The duration of stimulus was 1500 ms and inter-stimulus interval was 500 ms. Approximately 200 stimuli presented in a 400s period for this task. For every trial, the event and response time were spontaneously recorded by the Presentation software and the reaction times (RT) were obtained from such a formula: RT= (response time-event time)/10000 **Data analysis:** AFNI software was employed to perform all fMRI analyses. Among the 48 participants, the data of 5 were eliminated due to excessive head motion (elimination criteria: translational motion > 1.0 mm and rotation > 1.0°). After temporally and spatially filtering data (Gaussian filter with a 4-mm radius), the first and last five time points were omitted and a general linear model was employed to process the individual data. The signal change percentage maps were transformed into a common Talairach space for further group analysis. A one-sampled *t*-test was used to obtain the subject-specific estimation with a null hypothesis of no activation changes relative to baseline and a voxelwised independent *t*-test was performed to assess the difference of response inhibition between the AHD and HC groups. A cluster threshold at the $P_c < 0.05$ level was used, accounting for multiple comparisons (individual voxel threshold at $P_u < 0.005$, minimum cluster size = 422 μl), which was determined by a Monte Carlo simulation of simultaneous statistical tests based on the brain mask.

Results **Behavioral Data:** The data of two patients and one control could not be used for analysis. The one-way ANOVA analysis (LSD multiple comparisons, Group×Mean RT, $F_{(1,44)}=4.74$, $P=0.035 < 0.05$) revealed that RTs of HC was significantly faster than that of AHD (see Fig 1). **fMRI data analysis:** In healthy controls, neural substances involved in response inhibition were revealed. Significant activation was observed in bilateral medial prefrontal cortex (mPFC) and anterior cingulated cortex (ACC), as well as in the bilateral inferior frontal gyrus (IFG), precuneus and limbic system, et al. In patients, few clusters were activated except for the left superior, middle frontal gyrus and BA 8. Compared to HC, the AHD were significantly hypoactive and deactivation was observed in the bilateral inferior/medial PFC, ACC, right middle temporal gyrus and limbic system, et al. (see Fig. 2).

Discussion and Conclusion The RT of HC was significantly faster than that of AHD, which indicated that AHD required more time to perform tasks and suggested a compromised frontal response executive function. The significant activation of bilateral mPFC, ACC and IFG induced by response inhibition in HC is supported by previous neuroimaging studies [4,5]; the unexpected activation in left superior, middle frontal gyrus and BA 8 of AHD may be due to more frontal resources exerted as a compensation for the diminished mPFC and ACC activation; and compared with HC, the hypoactive state in mPFC and ACC of AHD reflected impaired inhibitory control of frontal, which may be the evidence for the disrupted self-control of heroin addicts. Our results demonstrated midline structure involved in response inhibition and impaired frontal executive function, which lasted even months into abstinence. The disrupted frontal executive cognitive function may be the common dominator for substances abuse, which contributes to the vulnerability of heroin users to the conditioned cues, craving for the drug and leads to relapse at last.

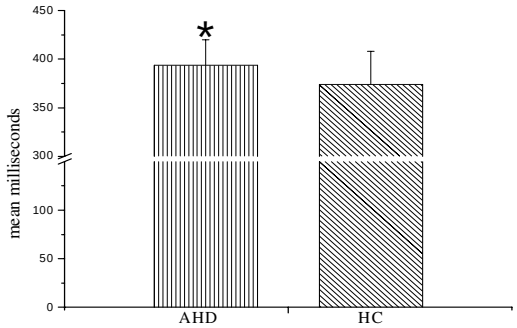

Figure 1. Mean RT for HC and AHD. Vertical capped lines atop bars indicate standard deviation of the RT ($F_{(1,44)} = 4.74$, $P < 0.05$). [1]

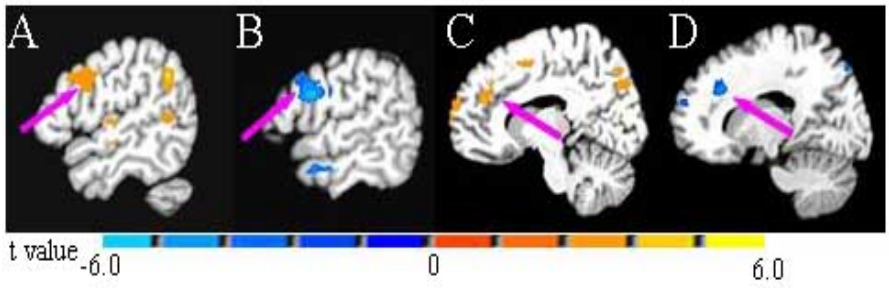

Figure 2. The sagittal statistic maps (A, x = 5 and C, x=10) show significant activation induced by response inhibition in HC; B and D maps (x = 6 and 11) reveal the hypoactive in the corresponding regions in AHD. The pink arrows point to right IFG and ACC (orange and blue). The threshold for statistical significance is set with $P < 0.05$

Reference 1. Baler R.D. and Volkow N.D. (2006). Trends Mol Med. 12:559-566; 2. Lee T.M. and Pau C.W. (2002). Brain Inj. 16:885-889; 3. Lee TM et al. (2005). Neurosci Lett. 382:211-216; 4. Garavan H, et al. (2002). Neuroimage. 17:1820-1829; 5. Hester R and Garavan H, (2004). J Neurosci. 24:11017-11022.