Years of Prolonged Cocaine Use Alter Brain Activity in Regions of the Anterior Prefrontal Cortex and Orbitofrontal Cortex of Human Brain Detected by fMRI

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Introduction: Drug craving is thought to be a powerful motivational state or incentive salience that 'causes' drug-seeking behavior and drug relapse. Drug craving can be generally elicited by conditioned-cue, drug-cue or stress. It has been hypothesized that the neurobiological basis of drug craving is related to the sensitization of the mesolimbic cortical (MLC) reward system and memory activation of associated learning circuitry. However, it is not clear how years of prolonged cocaine use will alter specific brain circuitry. In this fMRI study, a cocaine-cue film is introduced to stimulate cocaine users in a GE Signa 1.5T scanner and to test our hypothesis that prolonged cocaine use will alter brain activity in the regions of the anterior prefrontal cortex and the orbitofrontal cortex.

Materials and Methods: Twenty-six right-handed regular cocaine users (5 female and 21 male, age 35.5±6.7 yrs) were recruited in this study. An Institutional Review Board-approved consent form was obtained from each subject before any fMRI experiments were conducted. Last cocaine use occurred from one to three days prior to study, which was confirmed by Triage® urine tests. **fMRI Experiments:** Each subject participated in three 12-minute fMRI scans in a GE Signa 1.5T scanner. Each scan consisted of a 3-minute baseline period during which a blue screen with a center fixation was shown, followed by a 4-minute film, and a 5-minute visual-spatial working memory task as a distracter. Three types of film were presented in the three scans in a counterbalanced order: cocaine film in which crack cocaine usage is simulated, neutral film in which everyday activities are presented, and an erotic film. Subjects were instructed by the subtitle of the films to rate their feelings of "craving", "happy", "aroused", "sex turned on" and "anxious" once every minute in a random order. Four axial slices of the inferior brain were acquired in the fMRI scans. A **m**ulti-**e**cho **s**egmented echo-planar imaging with **b**ackground **c**ompensation (MESBAC) pulse sequence (1) was employed to overcome susceptibility artifacts in brain regions that are difficult to image with BOLD-fMRI, but predicted to be involved in drug-relapse behavior. The acquisition parameters were: FOV of 24 cm, slice thickness of 5 mm, matrix size of 128 × 128, TE of 30 ms and an equivalent TR of 12 seconds. **Data Analysis:** Nine of the 26 users were rejected from data analysis due to head motion. The rejection criteria was either rigid head motion exceeding 2° or 2 mm as detected by AFNI *3dvolreg* program, or the motion-enhanced susceptibility effect (2) contributing to >20% BOLD change in a widespread manner. Fifteen of the 17 motion-survived fMRI datasets had their corresponding visual analog scale (VAS) ratings. The first 7 minutes of the fMRI datasets of cocaine users watching cocaine films were analyzed with AFNI and customized Matlab® script. Each voxel time course was fitted to a beta function. The maps of percent of the area under the curve (AUC%) were obtained for individual users, then were converted to standard Talairach space and spatially smoothed with a FWHM of 2 mm Gaussian filter. One sample student t-test with null hypothesis was conducted on AUC% to generate a common activation map across subjects. The mean AUC% in each activated region and the years of cocaine use were correlated across individual subjects. The years of cocaine use for individual subjects also were correlated with the craving % changes obtained from the ratio of average "craving" ratings during film presentation and baseline.

Results and Discussion: A significant negative correlation was found between years of cocaine use and craving % change (Fig. 1). This result indicates that abusers with long cocaine-abuse histories showed less craving in the response to conditional cue. Initially, this result seems against an intuition that the longer the cocaine use, the stronger the craving. Later, we found that our result supports a hypothesis that the drug use is a habitual behavior with automaticity. This hypothesis is further supported by the activation in BA10 as shown in Fig. 2c. Activation in BA10 is known to be the representation of strategy planning, behavior control, and/or decision-making (3). In this study, a significant negative correlation between activation in BA10 and the years of cocaine use ($r = 0.51$, $p = 0.04$) suggests a habitual learning process transitioning from controlled to automatic drug use. For abusers with prolonged abuse history, drug use becomes automatic and requires less activation in the BA10 region. However, in other brain regions as shown in Figs. 2a and 2b, BOLD signals in the bilateral BA47 regions are positively correlated with the years of cocaine use. This positive correlation ($r = 0.52$, $p = 0.03$ for right BA47 and $r = 0.53$, $p = 0.05$ for left BA47) suggests that cocaine-related episodic memory is enhanced and consolidated over the years of cocaine abuse.

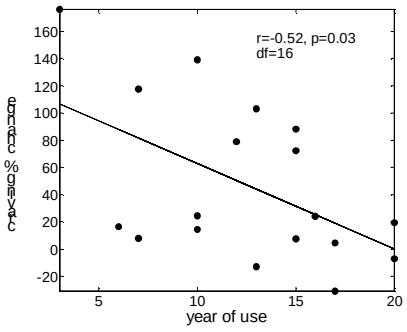
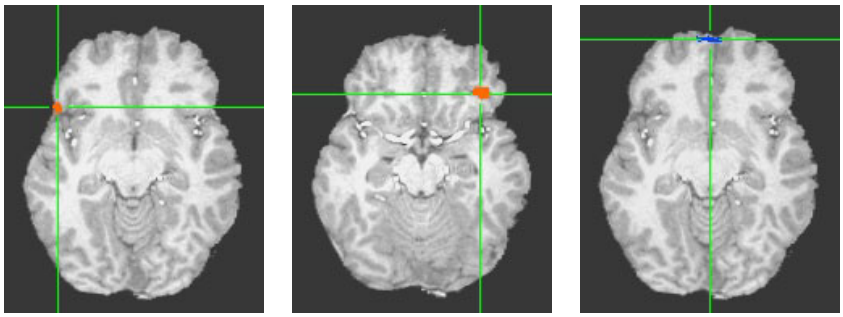


Figure 1. Correlation of years of use vs. "craving" % change



(a) Right BA47 [-46.8, -18.8, -8.3] (b) Left BA47 [37.8, -26.9, -14.1] (c) Medial BA10 [-0.4,-61.0,-10.2]

Figure 2. Significant correlation between year of use vs. mean AUC% in (a) Right BA47 p=0.03; (b) Left BA47 p=0.05; and (c) Medial BA10, p=0.04. Crosshairs are centered at the centroid locations of the regions of interest. (Orange, positive cc and blue, negative cc)

References: **1.** Li Z, et al. MRM 48:312-321, 2002. **2.** Li S-J, et al. ISMRM 11,1792, 2003. **3.** Ramnani N and Owen A. Nature Review Neuroscience, 5: 184-194, 2004.

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