# Cocaine-Induced BOLD in Lower Human Brain is Related to Subjective Euphoria and Craving Ratings

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**INTRODUCTION:** Cocaine induces both euphoria and a drive for further consumption in human addicts, often leading to a binge [1]. Cocaine-induced BOLD responses have been shown to be feasibly obtained in the nucleus accumbens (NAcc) and related brain areas [2,3], which may correspond to the "high" and "craving" experienced by dependent subjects during the experiment. Scaled ratings given by self-administering subjects have been shown to provide reliable descriptions of drug-taking behavior [4]. This study related the local functional changes in NAcc-related circuitry, measured by FMRI during and after intravenous adminstration of cocaine, to affective ratings given by addicted subjects throughout the experiment. We hypothesized that cocaine-induced BOLD responses in the NAcc, ventral tegmental area (VTA), orbitofrontal cortex (OFC) and other regions of interest were measureable and correlated to either the reported euphoria or craving measurements.

**MATERIALS AND METHODS:** 14 right-handed regular cocaine abusers participated in this study. An IRB-approved consent form was obtained from all subjects before any FMRI experiments were conducted. Throughout each experiment, the subject's heart rate and blood pressure were monitored electronically and by a present physician.

*FMRI Experiments:* All experiments were performed on a 1.5 T scanner (GE Medical Systems, Milwaukee, WI), running the MESBAC sequence [6] to compensate for high susceptibility gradients present in the inferior brain. Each subject received infusions of cocaine and saline in separate runs; data from cocaine runs and the saline runs were order controlled. Each run lasted for 15 minutes, during which four axial slices of the inferior brain were imaged every 12 seconds (flip angle = 50 deg, TE = 30 ms, 76 reps, 5 mm slice). After four minutes, a single 20mg/70kg dose of cocaine was infused intravenously over thirty seconds. In one of the two runs, a dose of saline was substituted. Subjects were informed before each run whether saline or cocaine was to be administered. Affective ratings were recorded by the subject with a joystick (Figure 1), moving a cursor along a visal analog scale (VAS) to respond to a cycle of prompts. VAS ratings for *high, craving, sour, pleasant* and *nervous* were sequentially collected every minute. After the FMRI runs, high-resolution whole-brain $T_1$-weighted anatomical images were obtained.

*Data Analysis:* Among the 14 participants, the FMRI data from seven had interpretable VAS data and FMRI data (after motion detection). Of the interpolated VAS rating time series, only those for *high* and *craving* ratings had significant variation (maximum change > 10% of baseline value in at least 5 of 7 subjects). The BOLD responses of the cocaine runs and the saline runs were spatially smoothed (3 mm radius) and related to *high* and *craving* ratings by multiple regression (including a linear noise model). The maps of regression coefficients were assessed individually (partial F-statistic) and compared across subjects (*high* vs. *craving*, paired t-test of absolute coefficients) after transformation of data into common Taliarach space.

**RESULTS AND DISCUSSION:** The VAS ratings for *high* and *craving* during the cocaine runs sustained postinfusion increases above their respective preinfusion baselines, with the *high* rating falling after 4-5 minutes (Figure 2). The postinfusion response in the mesolimbic system (VTA, NAcc) is associated with the *high* rating ($p < 0.05$, 1.5 uL clusters), but other paralimbic areas, such as the insula, correspond to the *craving* rating ($p < 0.05$). Figure 3 displays a representative map of regression coefficients in the OFC: positive associations exist in the medial OFC and negative associations in the lateral OFC, but *high*- and *craving*-related BOLD responses are differently localized. One explanation for compulsive repeated use of drugs such as cocaine is that addicts experience a potent "wanting" for the drug that is separate from "liking," and that these processes are related to the pharmacological effect of cocaine on the NAcc and connected brain regions [6]. This experiment demonstrates that cocaine "liking" and "wanting" are separate cognitive processes that are not only consciously perceived by subjects after cocaine administration, but also correspond to the BOLD response in NAcc-related brain areas to different degrees.

**REFERENCES:** 1. Cami and Farre, NEJM 2003. 2. Breiter et al., Neuron 1997. 3. Kufahl et al., Proc. ISMRM 11:9, 2003. 4. Fischman and Foltin, Brit J Addiction 1991. 5. Li Z et al., MRM 2002. 6. Robinson and Berridge, Ann Rev Psychol 2003.

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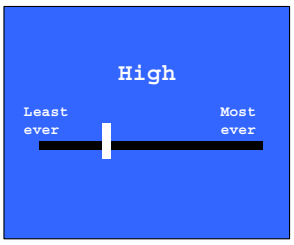


**Figure 1. Visual Stimulus for FMRI Experiments.**

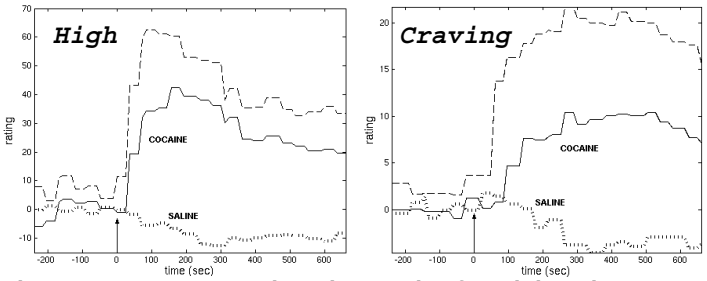


**Figure 2. Mean VAS Rating Time Series for *High* and *Craving*.** Measured relative to preinfuson baseline (solid line: mean, dashed: mean + standard deviation), both increase after cocaine infusion (arrow at t = 0).

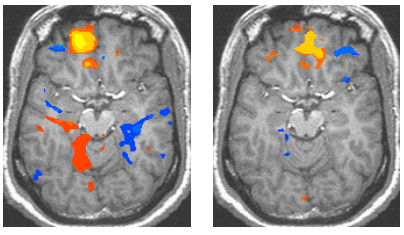


**Figure 3. Regression Coefficients (left is left).** Correlated (red, orange) and anticorrelated (blue) voxels in the OFC (Bonferroni $p < 0.01$, F-test).