

# Latency of Cocaine-Induced BOLD Response in Human Subjects Distinguishes Regions within the Orbitofrontal Cortex

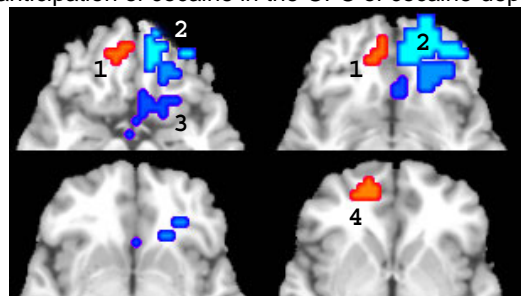
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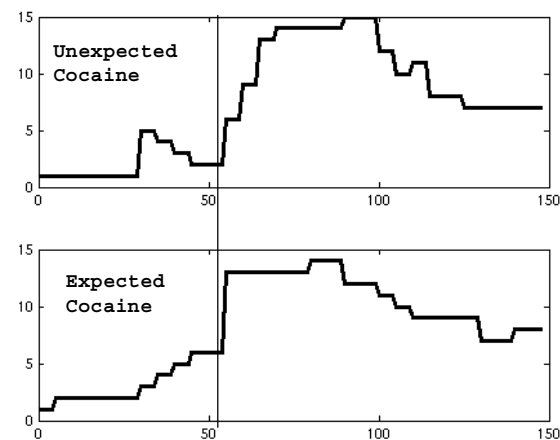
**INTRODUCTION:** The orbitofrontal cortex (OFC), the frontal brain region situated over the orbital bone of primates and humans, has been shown by BOLD fMRI investigation to respond to intravenous cocaine [1]. The cocaine-induced BOLD signal in the OFC was also shown to be related to simultaneously recorded HIGH ratings, as given by the subject via a joystick during the scan [2]. This study, in which human cocaine addicts are given an intravenous dose of cocaine during an fMRI scan under two conditions of expectation (wherein the subject anticipates cocaine during the scan in one trial, and anticipates a control dose of saline in the other trial), dissociates the BOLD responses of the medial and lateral OFC regions by their temporal characteristics.

**MATERIALS AND METHODS:** 22 right-handed regular cocaine abusers participated in this 2-day, 4-scan study. Experiments were performed as in previous acute cocaine fMRI investigations [1,2], in which the BOLD response in the brain was recorded at 1.5 Tesla while the subject received an intravenous dose of 20mg/70kg cocaine or saline. Infusions were for 30 sec, 7 min into the 20 min scan. Data were collected with a hybrid MESBAC-EPI sequence [3] to compensate for high susceptibility gradients present in the inferior brain (TR = 8 sec, matrix = 128 x 64, slice = 5mm, TE = 30 ms, 150 time points). Each day, the subjects received one cocaine infusion and one saline infusion. In each scan, the infusion was preceded by a "cocaine is coming" or "saline is coming" message, which was projected onto a screen 4 min into the scan. On one of the days, the subject received the cocaine infusion after the "saline is coming" message. HIGH and CRAVING ratings were given by the subject via joystick, following visual prompts that appeared on the screen throughout the scan. Among the 22 participants, the data from 13 were used after motion detection and correction procedures.

**RESULTS AND DISCUSSION:** Significant BOLD response was determined by nonlinear fitting to a pharmacokinetic model, as in previous experiments [1,2]. Four activated regions for the cocaine infusion trials were found in the OFC (Figure 1): left medial orbital gyrus (region 1), right orbital gyrus (region 2), right posterior orbital gyrus (region 3) and left frontal pole (region 4). The HIGH ratings recorded in 11 of the 13 subjects indicate a postinfusion shift earlier in the cases in which the subject expects cocaine (Figure 2, top chart) than in those in which the subject expects saline (Figure 2, bottom chart). Average BOLD timecourses for regions 2 and 3 suggest a correspondingly delayed response for unanticipated cocaine, as well as an enhanced postinfusion response in region 4 (Figure 3). These results demonstrate regionally-specific sensitivities, in BOLD response polarity and latency, to cocaine and the anticipation of cocaine in the OFC of cocaine-dependent subjects.



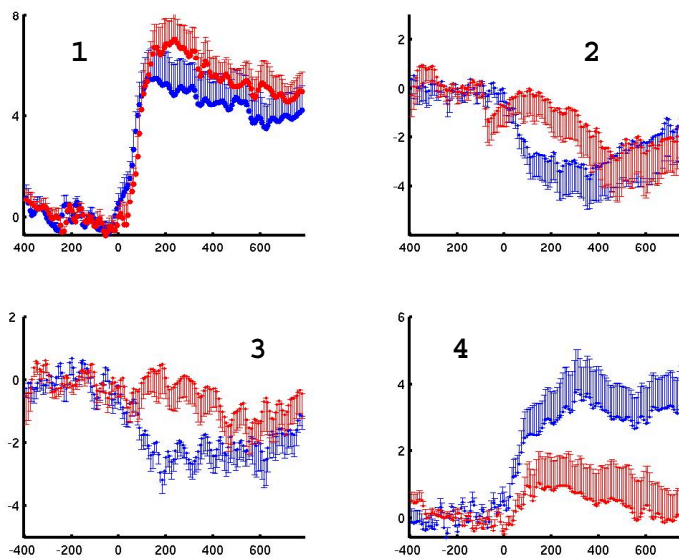
**Figure 1. OFC activation pattern for cocaine infusion** (t-test vs. no effect, cluster-wise  $p < 0.05$ , 13 subjects). Left is left. Regions are numbered: 1) left medial orbital gyrus 2) right orbital gyrus 3) right posterior orbital gyrus 4) left frontal pole.



**Figure 2. HIGH ratings during cocaine infusion runs for one subject.** Infusion time shown by vertical line. HIGH ratings shown in arbitrary units.

**REFERENCES:** 1. Kufahl et al., ISMRM 2003. 2. Kufahl et al., ISMRM 2004. 3. Li Z et al., MRM 2002.

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**Figure 3. Regional average plots across subjects (regions enumerated as in Figure 1).** Red timecourses are the average BOLD response during the unexpected cocaine trial (cocaine infusion at time zero, following the "saline is coming" message), and blue timecourses represent the expected cocaine trial (cocaine infusion following the "cocaine is coming" message). Errorbars denote one standard deviation. Horizontal axis is time (sec) relative to cocaine infusion, and vertical axis is % BOLD signal relative to preinfusion baseline.