**Contrast-enhanced fMRI of cocaine action in awake non-human primate**

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## Introduction

Cocaine-induced brain activation in cocaine-abusing humans and drug-naïve or exposed non-human primates has been measured by a number of non-invasive neuro-imaging modalities, including PET-FDG, PET-CBF, SPECT-CBF, and BOLD-fMRI. Despite these measurements, there is no agreement on even the general *sign* of cocaine-induced alterations in cerebral metabolism and blood flow, as reviewed by Howell [1]. This situation may arise from multiple sources: a lack of sensitivity in these techniques, different states of drug exposure, potential species differences, and/or interactions with the state of development.

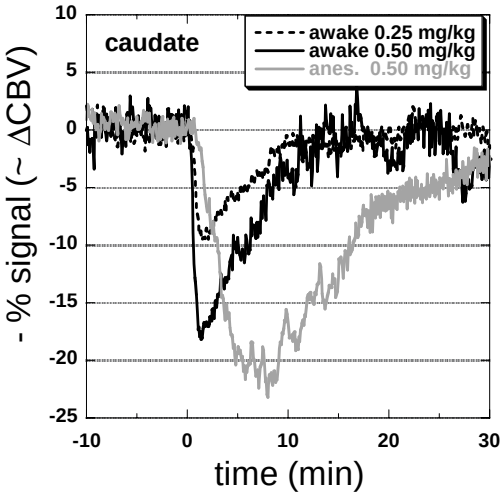
This study reports the first fMRI measurements, to our knowledge, of cocaine-induced brain activation in awake or anesthetize non-human primates, and the first such results in a drug-naïve primate. This non-human primate model is significant because 1) macaques can be trained for awake fMRI with behavioral feedback, including (ultimately) self-administration of drug, and 2) contrast agent can be employed to boost sensitivity, and thus resolve a main limitation of BOLD fMRI.

## Methods

A 3.5 kg macaque was trained to self-administer juice/water reward in a 3 Tesla magnet environment. In the first experiment, 3 IV doses of 0.25 mg/kg cocaine were delivered by experimenters to the awake animal using a separation interval of 1 hour. In the second experiment, the dose was doubled to 0.50 mg/kg for 2 injections; BOLD fMRI measured the response to the 1st injection, and contrast-enhanced fMRI evaluated the 2nd injection. In the 3rd experiment, 0.5 mg/kg was injected in the same subject after induction and maintenance of anesthesia (1% halothane, free-breathing, end-tidal CO2 and heart rate continuously monitored).

## Results & Discussion

As in the rodent [2], "low-field" BOLD results were too insensitive to obtain reliable results in a single session. However, contrast-enhanced fMRI provided robust, symmetric bilateral results in all sessions and all individual injections. A remarkable cross-session reproducibility in functional brain maps was obtained in the awake animal after a two-fold scaling for the dose response. In all regions with significant change of signal, excluding medial prefrontal cortex (MPFC), cocaine *decreased* CBV. Sample results are shown in the figure for the caudate region. MPFC showed a bilateral *increase* in CBV that was reproducible across injections and sessions in the awake state. Cocaine produced a "deactivation" in visual cortex, and the modulated response to the attendant visual stimulus (full field alternating stationary and moving dot pattern) was significantly reduced by this effect. While this interaction is likely to be a neural effect, cocaine-induced behavior (slightly altered fixation, reduced motion) also must be considered.




In the anesthetized condition, the 3D brain map was remarkable similar to the awake state but for MPFC, which was not activated in the anesthetized condition. In the temporal domain, all regional responses were delayed in the anesthetized condition, consistent with a longer half-life of cocaine in the blood due to systemic reduction of metabolism.

Further data are required to relate these results to human studies on cocaine-abusing subjects, and to the large body of literature on rodents. Issues to be resolved include: 1) does drug-exposure history substantially alter the response compared to the drug-naïve state (this study), 2) are cocaine-induced responses different in the adult and juvenile (this study), and 3) is there a species difference between rodents and primates, as suggested by invasive autoradiography [3], or is this difference clouded by the other issues?

1. Howell, L.L. and K.M. Wilcox. Psychopharmacology (Berl), 2002. **163**(3-4): p. 352-61.
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3. Lyons, D., D.P. Friedman, M.A. Nader, and L.J. Porrino. J Neurosci, 1996. **16**(3): p. 1230-8.