



CONTRAST-ENHANCED fMRI OF COCAINE ACTION IN A WAKE, NON-HUMAN PRIMATE



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Abstract

- Cocaine-induced brain activation has not been measured previously by fMRI in drug-naïve human or non-human primates, nor has it been measured in any awake human or animal model using iron oxide contrast agent.
- The high sensitivity of contrast-enhanced fMRI can help resolve some of the conflicts in the literature regarding cocaine-induced brain activation as measured in human and non-human primates using non-invasive neuro-imaging.
- For studying drug abuse, the **significance** of fMRI in awake macaques is that the animals can be followed **longitudinally as a function of drug exposure** to study neural correlates of processes of addiction, abstinence, and reinstatement of drug.
- These preliminary results demonstrate robust fMRI results in an individual animal in individual sessions in both **awake** and **halothane-anesthetized** states.

BACKGROUND

- The acute effects of cocaine-induced brain activation has been studied by non-invasive neuro-imaging using PET-FDG, PET-CBF, SPECT-CBF, and BOLD-fMRI. However, **there is no agreement on even the general sign of cocaine-induced alterations in cerebral metabolism and blood flow** by these methods, as reviewed by Howell [1], below.

Table 2 Acute effects of cocaine on cerebral metabolism and blood flow

Decreases in cerebral metabolism	
London et al. 1990	Human polydrug abusers; PET imaging - [¹⁸ F]FDG; 40 mg (IV) cocaine
Decreases in cerebral blood flow	
Johnson et al. 1998	Human cocaine-dependent; SPECT - technetium-99m-bicucate; 0.325 and 0.650 mg/kg (IV) cocaine
Pearlson et al. 1993	Human cocaine-dependent; SPECT - technetium-99m-examotazine; 48 mg (IV) cocaine
Wallace et al. 1996	Human cocaine-dependent; SPECT - technetium-99m-examotazine; 40 mg (IV) cocaine
Transient regional increases in cerebral blood flow	
Breiter et al. 1997	Human cocaine-dependent; fMRI (BOLD); 0.6 mg/kg (IV) cocaine
Mathew et al. 1996	Human cocaine-dependent; laser Doppler - 133 xenon; 0.3 mg/kg (IV) cocaine
Howell et al. 2002	Rhesus monkeys; PET - [¹⁵ O]water; 0.3 and 1.0 mg/kg (IV) cocaine

- In the rodent, cocaine induces regionally specific **increases** in cerebral metabolism [2], blood flow [3], and fMRI signals weighted by CBV and BOLD signal [4]. However, glucose metabolism in non-human primates **decreases** regionally as a consequence of cocaine injection [5], a result opposite the rat.

- Differences in results throughout the literature may be due to multiple sources: a lack of sensitivity in techniques, different states of drug exposure, potential species differences, and/or interactions with the state of development. **Longitudinal studies of cocaine exposure can help resolve these issues.**

Animal model

- Male macaque, 3.5 kg
- Trained to self-administer juice/water in magnet; training requires several months
- IV injections (contrast agent, cocaine) into femoral vein after accommodating monkey to catheter & leg wrap

fMRI

- Gradient-echo single-shot EPI, TR/TE = 5000/24
- MION contrast agent, 10 mg/kg
- BOLD imaging for one injection
- Resolution: 1.25 x 1.25 x 1.5 mm³
- FOV: 80 mm x 80 mm x74 mm (whole brain)

Experiments

- awake & visually fixating state, 0.25 mg/kg cocaine x 3 injections with 1 hour spacing, MION contrast
- awake & visually fixating state, 0.50 mg/kg cocaine x 2 injections with 1 hour spacing, BOLD then MION
- halothane-anesthetized state, 0.50 mg/kg cocaine x 1 injection, MION contrast

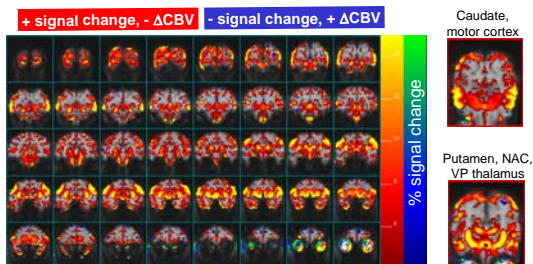
Behavior

- Eye fixation moved off-target after cocaine injection, and then re-established position following cocaine response.
- After obtaining cocaine, body movement reduced significantly (freezing); this response is opposite the rodent (hyper-locomotion) but is well known among primate behavioralists. Motion increased in excess of pre-cocaine baseline after cerebral response resolved to baseline. This response was repeated during serial injections.

BOLD signal

BOLD results were dominated by motion artifact, an unsurprising result given the difficulties of the model and the small size of signal changes. In a GLM analysis, large signal changes were associated with an index of motion provided by AFNI motion correction, but residual BOLD signal changes were not interpretable.

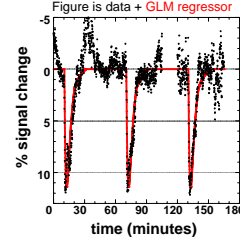
CBV-weighted signal, awake macaque



Like 2-DG results in this model (but opposite results in rodent) [5], CBV changes were predominantly negative). Largest signal changes occurred in putamen, caudate, ventral thalamic nuclei, nucleus accumbens, pontine nuclei, and motor cortex.

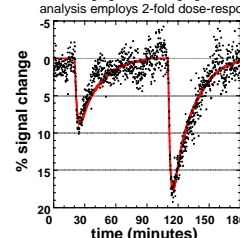
Results

putamen signal for 0.25 mg/kg x 3 injections; awake macaque;



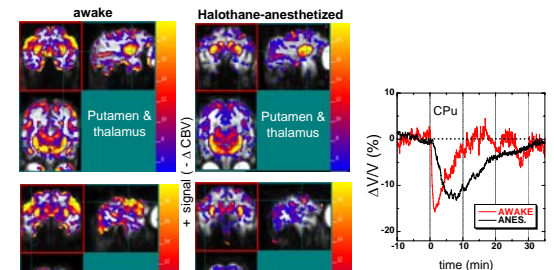
GLM using 2 temporal components; See poster 1512

fMRI signal in nucleus accumbens; Cross-session analysis of awake monkey data; 0.25 mg/kg and 0.5 mg/kg cocaine; analysis employs 2-fold dose-response



awake versus anesthetized state

- remarkable similarity in cocaine-induced functional response
- most pronounced differences are
 - greater "deactivation" of motor cortex in awake state
 - protracted temporal response in anesthetized state



Large reduction in fMRI signal in motor cortex in awake state is consistent with behavioral "freezing" after cocaine injection

Conclusions

- Cocaine-induced brain activation can be measured robustly in individual sessions in awake, behaving non-human primates using exogenous agent.
- Drug-naïve macaques show an opposite sign of the cocaine-induced functional response relative to drug-naïve rodents.
- These results set the stage for longitudinal studies of neuro-adaptations due to chronic cocaine exposure in a primate model.