fMRI of cocaine self-administration in non-human primates

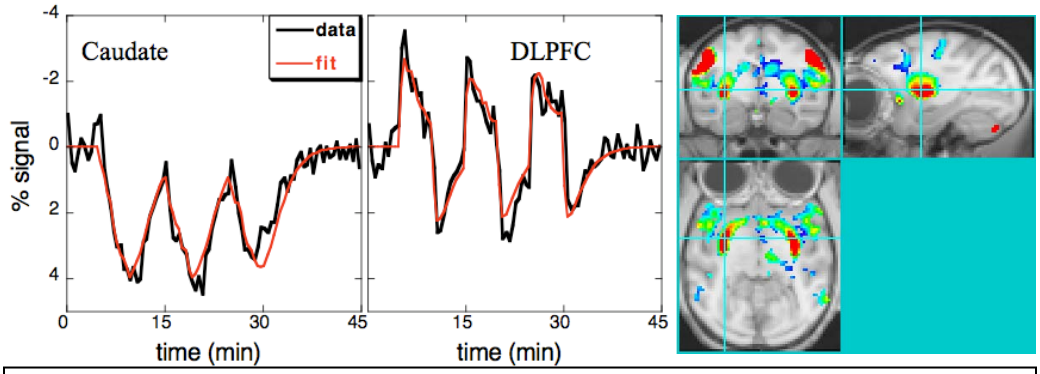
J-K. Choi[1], H. Deng[1], W. Vanduffel[1], W. Vanduffel[1], and J. B. Mandeville[2]

[1]Massachusetts General Hospital, United States, [2]Radiology, Massachusetts General Hospital, Charlestown, MA, United States

Introduction: Human neuro-imaging of cocaine craving has identified a predominantly frontal pattern of cue-associated cortical activation including OFC and DLPFC, but results have been inconsistent across studies [1]. Non-human primates (NHP) enable controlled longitudinal studies of drug exposure, and functional MRI (fMRI) provides a means to evaluate the neural responses to drug and to drug-associated stimuli. Our goal was to develop an fMRI protocol that would enable longitudinal examination of the direct effects of cocaine and the cognitive processes associated with cocaine-seeking behavior during on-going self-administration (SA) of cocaine by NHP in the magnet environment.

Methods: To obtain micro-injections of cocaine (0.015 mg/kg), the tradition "level press" from drug SA was replaced by a task requiring eye saccades and fixation. Color-coded visual cues were presented to the NHPs (n=2), pupil position was monitored by infrared tracking, and a custom-built behavioral system analyzed eye positions and coordinated visual presentation, drug injection, and water reward. The lockout time between successive cocaine cues was dependent upon cue selectivity in previous trials, such that the total amount of injected cocaine was proportional to the fixation percentage upon cocaine cues. A peripheral visual cue differentiated time periods of SA from time periods with no cocaine availability.

The NHP head was fixed in place during fMRI, but the body was free to move at all times. Motion artifacts in the fMRI data were reduced by accelerating the fMRI acquisition using two methods: 2-fold parallel imaging based upon a custom 4-channel phased array of RF coils, and further acceleration enabled by ultra-fast gradients inserted into the bore of the Siemens Trio 3 Tesla scanner. fMRI employed a steady-state exogenous contrast agent (MION) to enhance signal changes.



LEFT: Cocaine produced functional inhibition (decrease of CBV) in basal ganglia. **MIDDLE**: The response in dorsolateral prefrontal cortex was a summation of a direct effect of cocaine (inhibition) and an activation associated with the cocaine availability interval. **RIGHT**: A map of the direct effect of cocaine (inhibition) in putamen (overlay scale 1-4% signal change).

Results: After introducing the NHPs to the task, preference for cocaine cues over neutral cues reached 70-90% after 5-10 training sessions, whereas extinguishing this preference was more gradual (several months) with high intersession variability. Slightly less than 0.5 mg/kg typically was consumed during the 15-minute periods when cocaine was available, and this was repeated 4 times per session. Using this procedure, cocaine SA (as well as non-contingent injection of cocaine) produced functional inhibition (decrease of CBV) in basal ganglia that was particularly pronounced in posterior-ventral putamen. Inhibition of functional signal additionally occurred in motor and premotor cortices. SA also produced focal cortical activation that was not seen by non-contingent administration of cocaine, including activation of Brodmann areas 46 (DLPFC), 8 (FEF), and the most anterior aspect of 6 (PMC). These activations were associated with periods of drug availability, rather than with the drug effects of cocaine. Activation of DLPFC was not observed due to non-contingent cocaine infusion, but it was observed during cocaine SA and during presentation of drug-reinforced cues with the substitution of saline for cocaine.

Discussion: Cocaine induced functional inhibition of fMRI signal in basal ganglia, a result opposite the rat and one in agreement with studies of glucose metabolism in the two species [2]. Pronounced functional activations were observed in frontal cortex including DLPFC during periods of drug availability. However, SA produces a complex functional response pattern, including activity related to visual stimulation, operant behavior, and drug infusion. Not all contributions can be temporally dissociated, but further longitudinal studies including SA, non-contingent infusion of cocaine, and non-operant experiments (classical conditioning) can help clarify the pertinent circuitry associated with cocaine craving and drug-seeking behavior.

References:

1. Wilson SJ et al., Nat Neurosci, 2004. 7(3): p. 211-4.
2. Lyons D. et al., J Neurosci, 1996. 16(3): p. 1230-8.