Acute Effects of Cocaine in Lower Human Brain: An FMRI Study

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SYNOPSIS: This FMRI study used controlled doses of cocaine to induce BOLD signal changes in the human orbitofrontal cortex and other parts of the lower brain believed to be associated with chronic drug abuse. The MESBAC pulse sequence was used to compensate for signal distortion that had previously made pharmacological FMRI study of the orbitofrontal cortex unreliable. Nonparametric statistical tests showed significant cocaine-induced activation patterns across nine different subjects imaged at 1.5 Tesla.

INTRODUCTION: Several regions in the inferior part of the human brain, including the orbitofrontal cortex (OFC), are of interest in the analysis of compulsive drug abuse [1]. The pioneering FMRI study of acute cocaine effects on a measured BOLD signal in human brain [2] found significant and repeatable activations in the mesocorticolimbic dopaminergic pathway (including the nucleus accumbens and ventral tegmental area) and the basal ganglia, but did not measure the OFC response, due to susceptibility artifacts. This study utilized the recently-developed MESBAC pulse sequence [3] to measure the response of the regions listed above, as well as the OFC, during a single-dose cocaine infusion. Significant BOLD signal changes were expected in what is hypothesized to be the reward circuitry during and after intravenous cocaine administration.

MATERIALS AND METHODS:

Human Subjects: 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.

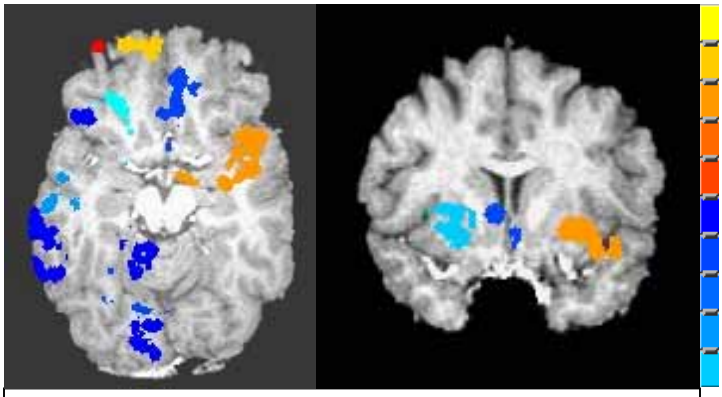

Figure 1. Clustered Wilcoxon analysis of the BOLD response of cocaine injection vs. saline injection (left is left). Red and yellow correspond to a positive relative signal change for cocaine, blue to a negative change.

FMRI Experiments: All experiments were performed on a 1.5 T scanner (GE Medical Systems, Milwaukee, WI) fitted with an end-capped birdcage coil and a water-cooled gradient coil. Each subject received an injection of cocaine and saline in separate runs; data from the cocaine run and the saline run were order controlled. Each run lasted for 15 minutes, during which four axial slices of the inferior brain were imaged every 12 seconds using the MESBAC pulse sequence (flip angle = 50 deg, TE = 30 ms, 76 reps, 64 x 64, 5 mm slice). After four minutes, a single 20 mg / 70 kg dose of cocaine was injected over 30 seconds. In one of two runs, a dose of saline was substituted. Subjects were always informed whether cocaine or saline was to be injected. After the functional imaging runs, high-resolution whole-brain anatomical images were obtained with a spoiled-GRASS pulse sequence.

Data Analysis: Among the 14 participants, the data from nine were used after motion detection and correction procedures. The BOLD responses of the cocaine run and the saline run were fitted to a differential exponent model based on the single-dose two-compartment pharmacokinetics of cocaine [4]. The area under the fitted curve was obtained as a percentage of the signal baseline (AUC%). The AUC% maps were transformed into a common Talairach space for comparison across subjects, and processed with a voxel-wise Wilcoxon test, the non-parametric analogue for paired t-tests. Figure 1 displays the Wilcoxon results for the cocaine injection (treatment effect vs. saline, -3 to +3 relative %AUC), with a threshold at the p = 0.05 level (cluster size = 1.5 uL).

RESULTS AND DISCUSSION: The Wilcoxon analysis found activations of several regions of interest at the p=0.05 level of significance, including sections of the OFC and the nucleus accumbens. These results are summarized in Table 1. Other regions were activated in only some subjects, such as the left amygdala and ventral segmental area (VTA). Consistent activation of regions associated with both reward processing and craving [2] supports the notion that cocaine induces a heterogeneous activation pattern in the OFC that corresponds to the acute cocaine effect as well as drug-induced craving. Both the dopaminergic mesocorticolimbic circuit (VTA, nucleus accumbens and OFC) and striato-thalamo-cortical circuit (striatum, thalamus, OFC) exhibited significant BOLD signal changes, suggesting that regions of the OFC were actively integrating inputs from both subsystems. These results demonstrate that the MESBAC pulse sequence allows feasible study of the acute cocaine effect in many lower cortical and sub-cortical regions of interest.

Table 1. Activated regions of lower brain following cocaine injection

Anatomical region	Side	Tal. origin (mm)			Polarity of Signal Change (post-injection, cocaine)
		R/L	A/P	I/S	
Medial Orbital Gyrus	R	-6	-37	-11	-
Frontal Pole	L	31	-58	-5	+
Lateral Orbital Gyrus	L	22	-29	-10	-
Medial Prefrontal Cortex	Both	-1	38	-1	-
Anterior Cingulate Cortex	Both	-1	38	4	-
Nucleus Accumbens	L	6	-7	0	-
Globus Pallidus	R	-15	4	-2	+
Basal Forebrain	R	-5	-13	-7	-
Putamen	R	-24	0	3	+
Thalamus	R	-12	8	4	+
Inferior Temporal Gyrus	L	56	34	-10	-
Middle Temporal Gyrus	L	57	39	-4	-
Superior Temporal Gyrus	L	51	14	-4	-
Insula	R	-25	7	1	+

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ACKNOWLEDGEMENTS: This work was funded in part by the grants DA10214 and RR00058.