Anticipation Modulates the Acute Cocaine Effect in Human Paralimbic and Executive Cortical Regions: an FMRI Study

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INTRODUCTION: The activation of human paralimbic brain regions following cocaine administration has been documented in FMRI studies of human addicts [1,2]. Higher cortical centers sensitive to psychostimulants, including the orbitofrontal cortex (OFC), have recently been shown in a PET investigation to be more responsive to the drug stimulus when that stimulus is anticipated by the subject [3]. We studied the difference in the cocaine-elicited BOLD response in the whole brain of cocaine-dependent human subjects imposed by active anticipation of cocaine infusion.

MATERIALS AND METHODS: 22 right-handed regular cocaine abusers completed this study. An IRB-approved consent form was obtained from all subjects before any FMRI experiments were conducted. Throughout each experiment, the subjects' heart rate and blood pressure were monitored both electronically and by a physician. ***FMRI Experiments:*** All experiments were performed on a 1.5 T scanner (GE Medical Systems, Milwaukee, WI), running a hybrid MESBAC-EPI sequence [4] to compensate for high susceptibility gradients present in the inferior brain. Each subject received 2 separate runs on each of 2 days; data from the cocaine runs and saline runs were order-controlled. Each run lasted for 20 min, during which the entire brain was imaged every 8 sec (flip angle = 50°, TE = 30 ms, 150 reps). After 4 min, a green bar appears across the bottom of the screen with the message "20 mg cocaine is coming" or "saline is coming" and gradually shrinks from left to right (Fig. 1). After 7 min, when the green bar vanished, a single 20mg/70kg dose of cocaine was infused intravenously over 30 sec. In one of the runs on each day, a dose of saline was substituted. After the FMRI runs, high-resolution whole-brain anatomical images were obtained with a spoiled-GRASS pulse sequence. ***Data Analysis:*** Among the 22 participants, the data from 13 were used after motion detection and correction procedures. The BOLD responses of the cocaine and saline runs were spatially smoothed (4 mm radius) and fitted to a difference-of-exponents model based on the single-dose two-compartment pharmacokinetics of cocaine [5], including a linear noise model. 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 voxelwise paired t-tests. Figure 2 displays the %AUC response for the unanticipated cocaine infusion (after "saline is coming" is shown on the screen) relative to anticipated cocaine infusion (after the "cocaine is coming" message), with a cluster threshold at the $p < 0.05$ level (voxel threshold at $p < 0.04$, minimal cluster size = 705 uL).

RESULTS AND DISCUSSION: Four cocaine-sensitive regions of interest (ROI) were shown to be more responsive, in terms of postinfusion %AUC, to cocaine when anticipated by the subject (see Table). BA47 and BA10 of the OFC are thought to be part of an integrated control circuit, which the subject may engage during drug-elicited cocaine craving [3]. The anterior cingulate cortex (ACC), highlighted in Figure 2, has been associated with reward expectancy in monkeys [6] and cocaine-dependent humans [7]. Other regions (nucleus accumbens, insula, amygdala, vermis) were also sensitive to cocaine and anticipation state, but did not pass the cluster size threshold. These results demonstrate that subject anticipation modulates the cocaine BOLD response in paralimbic and executive brain regions, and a dependence of the corresponding drug-induced neural activity on preinfusion expectation state is implied.

REFERENCES: 1. Breiter et al., Neuron 1997. 2. Kufahl et al., ISMRM 2003. 3. Volkow et al., J. Neurosci. 2003. 4. Li Z et al., MRM 2002. 5. Stein and Risinger, in *Functional MRI.* Springer, 1999. 6. Shidara and Richmond, Science 2002. 7. Peoples, Science 2002.

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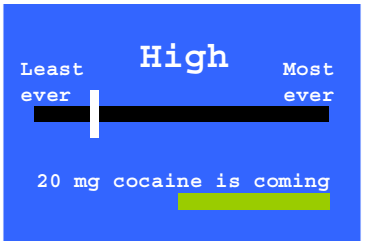

Figure 1. Visual stimulus for FMRI experiments. Subject watches a screen throughout each run. Subject responds to prompts ("High", "Craving", etc.) every 30 sec via joystick to confirm psychoactive effects of the drug infusion.

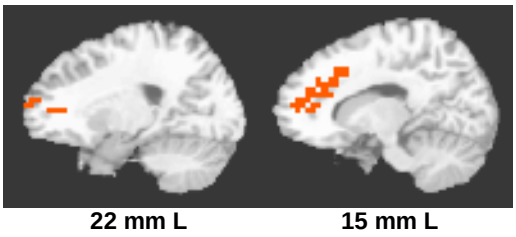

Figure 2. T-test activation map of expected cocaine vs. unexpected cocaine %AUC (t = +3 to –3, N=13, cluster-wise p<0.05). Orange clusters depict a greater postinfusion %AUC for anticipated cocaine than for unanticipated cocaine.

ROI	R/L	A/P	I/S	Vol
OFC: BA47	43	-37	-6	1024
OFC: BA10	18	-52	6	1152
r Parahipp.	-38	14	-19	960
l ACC	15	-44	16	3520

Table. Loci of differential BOLD response between anticipated cocaine and unanticipated cocaine. All listed clusters demonstrated greater post-infusion %AUC for anticipated cocaine. Centroid coordinates are given in standard Talairach space, and volume is in microliters.