Extraction of Pharmacokinetic Parameters from Human Brain Cocaine BOLD Responses

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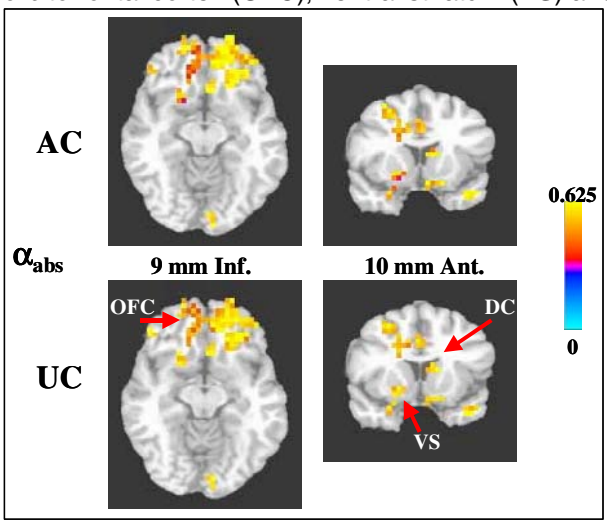
INTRODUCTION: The activation of human paralimbic brain regions following cocaine administration has been documented in FMRI studies of human addicts [1, 2]. Parametric modeling of the cocaine BOLD response is based on a one-compartment pharmacokinetic model with a rapid cocaine absorption rate α_{abs} and a much lower clearance rate α_{elim}, characteristics associated with the addictive potential of the drug [3]. We examined the cocaine BOLD response of 13 cocaine addicts. Subject anticipation was a controlled variable: α_{abs} and α_{elim} parameters were found for AC (anticipated cocaine) and UC (unanticipated cocaine) conditions. Results associated with 3 regions of interest are described: the orbitofrontal cortex (OFC), ventral striatum (VS) and dorsal caudate (DC).



MATERIALS AND METHODS: 13 right-handed regular cocaine abusers completed this study. An IRB-approved consent form was obtained from all subjects. Throughout each experiment, the subject's heart rate and blood pressure were monitored.

FMRI Experiments: Subjects were scanned with a 1.5T scanner on 2 consecutive days. High susceptibility gradients present in the inferior brain were compensated with a specialized EPI acquisition scheme [4]. Each run lasted for 20 minutes, during which the entire brain was imaged every 8 seconds (flip=50˚, TE=30ms, 150reps). Cocaine was administered iv 7 min into the scan. For the AC run, cocaine infusion was preceded by a visual cue predicting cocaine. For the UC run (presented in random order), the cocaine infusion was preceded by a visual cue predicting a control treatment (saline).

Data Analysis: The BOLD responses of the cocaine runs and the saline runs were fit to a difference-of-exponents model based on the single-dose one-compartment pharmacokinetics of cocaine [5], including a linear noise model ($\mathbf{n_0 + n_1 t}$):

$$BOLD = k[e^{-\alpha_1(t-t_0)} - e^{-\alpha_2(t-t_0)}]u(t-t_0) + n_0 + n_1 t + \varepsilon \ ,$$

where **u()** is a step function, $\mathbf{t_0}$ is the time delay to the drug response, **k** is a scaling constant, and **ε** is a Gaussian error term. The estimates for α_1 and α_2 were spatially smoothed (8mm FWHM) and transformed into Talairach space for comparison across subjects. The calculated $\alpha_{abs} = 60\alpha_2$ and $\alpha_{elim} = 60\alpha_1$ were compared with nonparametric ranksum tests. ROI boundaries were determined by statistical procedures (finding cocaine activation) described previously [2].

RESULTS and DISCUSSION: The maximum α_{abs} found in the activated voxels was 0.625 min^{-1}, corresponding to a half-life $t_{1/2abs}$ = 1.1 min. This exceeds the $t_{1/2abs}$ reported for iv cocaine in unanaesthetized rats (0.9 ± 0.1 min for 0.5mg/kg dose, [6]. The standard reference for human pharmacokinetics (smoking) does not report α_{abs} except for one subject (0.052 min, [7]). Despite the uncertainty in measuring α_{abs} resulting from the rapid uptake of iv cocaine and relatively low temporal resolution of the data acquisition, some heterogeneity in α_{abs} is apparent throughout the activated brain for both AC and UC runs (figure). However, the lack of significant changes in α_{abs} between AC and UC data from the same regions (table) implies that the temporal effects found in previous reports of anticipation-modulated drug effects [2, 8] are not entirely explainable as different absorption rates.

The maximum α_{elim} in the activated voxels was 0.031 min^{-1}, corresponding to half-life $t_{1/2elim}$ = 22.2 min. This is less than the half-life range reported in the standard reference for human cocaine smoking ($t_{1/2elim}$ = 48 ± 12 min [6]), and could indicate that the BOLD signal reflects changes in levels of cocaine euphoria and/or craving rather than the clearance of cocaine from the brain or blood supply. As the table indicates, more between-condition (AC vs. UC) variability was found in the α_{elim} data than in the α_{abs} data, possibly a product of better estimation for α_{elim} (more data points) from the model fit.

Pharmacokinetic parameters α_{abs} and α_{elim} (min^{-1}) derived from the BOLD model. Comparisons between AC and UC conditions were made using a nonparametric ranksum test.

ROI	AC: α_{abs}	UC: α_{abs}	$\Delta\alpha_{abs}$	AC: α_{elim}	UC: α_{elim}	$\Delta\alpha_{elim}$
L medial OFC	0.42 ± 0.14	0.45 ± 0.24	N/S (p=0.51)	0.021 ± 0.011	0.025 ± 0.005	0.004 (p<0.02)
L ventral striatum	0.54 ± 0.24	0.55 ± 0.1	N/S (p=0.64)	0.023 ± 0.007	0.025 ± 0.01	N/S (p=0.14)
R dorsal caudate	0.57 ± 0.15	0.55 ± 0.16	N/S (p=0.37)	0.025 ± 0.005	0.021 ± 0.006	0.004 (p<0.006)

REFERENCES: **1.** Breiter et al., Neuron 1997. **2.** Kufahl et al., NI 2005. **3.** Volkow et al., J Pharm Exp Ther 1999. **4.** Li et al., MRM 2002. **5.** Stein, J. Anal Tox 2001. **6.** Booze et al., Neur Tetr 1997. **7.** Jeffcoat et al., Drug Met Dis 1989. **8.** Volkow et al., J Neuro 2003.

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