Effects of Chronic Cocaine Self-Administration on Cognition and Cerebral Glucose Utilization in Rhesus Monkeys

Supplemental Information

[^{18}F]-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) Analysis

For the behavioral data, two-way analyses of variance were conducted to compare number of trials completed and number of pellets earned between the two FDG sessions. Additional *t*-tests were conducted to compare the number of trials completed and % accuracy between groups in the post-acquisition intradimensional stage and the % accuracy during extradimensional shift performance on FDG days. For all analyses, significance threshold was *p* < 0.05. T1- weighted magnetic resonance images were acquired on all monkeys for co-registration with the PET data using a 3.0T MR scanner (GE Medical Systems) under ketamine-induction (10 mg/kg) and 1.5% isoflurane-maintained anesthesia. The PET data were analyzed using the methods derived by Porrino and colleagues (1,2). The concentration of FDG in blood over time for each subject (blood input function) was determined by scaling a population-averaged FDG blood curve by the subject's blood FDG concentration at T = 45 minutes. The individual blood input curves and glucose values were then applied to respective PET data to generate images of cerebral metabolic rates of glucose (MRGlu) using the "MRGlu (FDG Autorad)" model based on Huang *et al.* (3) implemented in the pixel-wise modeling tool in the PMOD image analysis software (PMOD Technologies, Zurich, Switzerland). Subsequent manipulations and analyses were conducted on the PET MRGlu data using the Statistical Parametric Mapping (SPM5) software (University College London, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/) in conjunction with MATLAB (MathWorks, Natick, MA, United States). Using this software, PET MRGlu data were co-registered to respective individual structural MR images and then normalized to a standard rhesus macaque template (4). Proportional normalization and grand mean scaling were applied to account for differences in

global activity. Finally, images were smoothed using a 2 mm isotropic Gaussian kernel with a voxel size of 1 x 1 x 1 mm.

Response and Pellet Retrieval Latencies

There was not an overall main effect of group on average response latency but there was a main effect of group ($F_{1,6} = 9.348$, $p < 0.05$) on pellet retrieval latency during the stimulus discrimination and reversal components; there was not a significant difference across either stage following post-hoc testing.

There was an overall main effect of group ($F_{1,24} = 4.428$, $p < 0.05$) on average response latency during the set-shifting task. The mean (± SEM) group response latencies across all stages were 2.13 ± 0.29 sec vs. 1.60 ± 0.35 sec for the cocaine-naive and cocaine-experienced groups, respectively. Similarly, there were significant group differences in average pellet retrieval latency ($F_{1,24} = 30.196$, $p < 0.001$), with cocaine-naive monkeys taking 1.17 ± 0.04 sec compared to 0.62 ± 0.19 sec for cocaine-experienced monkeys. *Post-hoc* testing showed significant differences between groups in pellet retrieval latency across all stages (simple discrimination, compound discrimination, intradimensional shift, extradimensional shift, all $p < 0.05$).

Table S1. Task performance prior to and during FDG incorporation

	Monkey	Baseline Purple[1] Box	Total Trials / Errors					ED (40 Min)[1]		% Correct
			SD	CD	ID	ID (Post Acq)	% Correct	Trials	SR	
Coc-Exp	1374	195	9 / 3	46 / 18	9 / 1	144 / 6	95.9	222 / 84	138	62.2
	1375	182	243 / 102	14 / 4	16 / 5	134 / 37	72.4	223 / 86	137	61.4
	1377	175	108 / 55	89 / 40	157 / 83	196 / 64	67.3	249 / 73	176	70.7
	1381	144	144 / 73	315 / 161	63 / 30	178 / 87	50.8	223 / 108	115	51.6
Mean		174	126 / 58.3	116 / 55.8	61.3 / 29.8	163 / 48.5	71.6	229.3* / 87.8	141.5*	61.5
Coc-Naive	1681	150	67 / 34	268 / 131	138 / 61	187 / 81	56.7	207 / 98	109	52.7
	1682	185	37 / 14	30 / 8	27 / 6	149 / 50	73.2	212 / 82	130	61.3
	1683	171	58 / 20	118 / 49	120 / 54	148 / 29	80.4	224 / 93	131	58.5
	1696	199	258 / 127	73 / 31	330 / 127	140 / 41	70.7	217 / 95	122	56.2
Mean		176.3	105 / 48.8	122.3 / 72	153.8 / 62	156 / 50.3	70.3	215* / 92	123.0*	57.2

[1]Behavior during FDG incorporation

* significantly more trials were completed yet fewer reinforcers earned (e.g. correct responses) by both groups during the ED session compared to their respective baseline (BL) sessions but there were no differences between groups. Note: trials completed and reinforcers earned are identical in the BL condition, no "incorrect" response could be emitted.

Acq, acquisition; CD, compound discrimination; ED, extradimensional shift; ID, intradimensional shift; SD, simple discrimination; SR, reinforcers.

Table S2. Differences in relative glucose utilization between cocaine-naive and cocaine-experienced monkeys (*n* = 4/group).

Condition	Brain Region	Hemisphere	Standard z-score[1]	Cluster size (# of voxels)
Cocaine-naive > Cocaine SA				
	precentral/ postcentral gyrus	Left	3.32	87
Cocaine SA > Cocaine-naive				
	inferior occipital/ fusiform gyrus	Left	3.63	150

[1] p< 0.05; corrected for search volume
SA, self-administration.

Supplemental References

1. Porrino LJ, Daunais JB, Rogers GA, Hampson RE, Deadwyler SA (2005): Facilitation of task performance and removal of the effects of sleep deprivation by an ampakine (CX717) in nonhuman primates. *PLoS Biol.* 3:e299.

2. Deadwyler SA, Porrino L, Siegel JM, Hampson RE (2007): Systemic and nasal delivery of orexin-A (Hypocretin-1) reduces the effects of sleep deprivation on cognitive performance in nonhuman primates. *J Neurosci.* 27: 14239-14247.

3. Black KJ, Koller JM, Snyder AZ, Parlmutter JS (2004): Atlas template images for nonhuman primate neuroimaging: baboon and macaque. *Methods Enzymol.* 385:91-102.

4. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE (1980): Noninvasive determination of local cerebral metabolic rate of glucose in man. *Am J Physiol.* 238: E69-82.