Decreased Functional Connectivity after Acute Cocaine Administration: a Feasibility Study of Resting-state fMRI in Awake Non-human Primates

Kaundinya Gopinath[1], Kevin Murnane[2], and Leonard Howell[2]

[1]*Department of Radiology & Imaging Sciences, Emory University, Atlanta, GA, United States,* [2]*Yerkes National Primate Research Center, Emory University, Atlanta, GA, United States*

Introduction: Non-human primates afford distinct advantages in translational neuroimaging studies of drug addiction [1-2]. Resting state functional connectivity MRI (fcMRI) is increasingly being used to investigate neurocircuitry in healthy and diseased individuals [3]. To date, fcMRI studies in non-human primates have been exclusively conducted in subjects under anesthesia [4]. However, anesthetics can alter fcMRI networks [5], and thus confound the conclusions made from such data. A fronto-striatal network comprised of frontal brain regions including the anterior cingulate (ACC), medial prefrontal cortex (MPFC), dorsolateral (DLPFC), and orbital prefrontal cortex (OPFC), and striatal regions including anterior aspects of caudate, putamen, and nucleus acumbens (NA) are understood to underlie drug-taking [1-2, 6]. In this study, resting state functional connectivity in these networks were assessed in three awake nonhuman primates under baseline conditions, and after acute cocaine administration.

Methods: Three adult female rhesus monkeys (labeled RBp3, RMv3 and RRg4), with a long history (> 5 years) of self-administration to psychoactive compounds [7] were scanned in a Siemens 3T Tim Trio MRI scanner using a CP extremity coil. Details of animal habituation and MRI setup have been reported elsewhere [7]. Studies were carried out in accordance with the NIH Guide for Care and Use of Laboratory animals and approved by the Animal Care and Use Committee at Emory University. The subjects lay prone in a custom-built restraint cradle optimized for acquiring MRI data from conscious monkeys [7], attached to the CP extremity coil. In the fcMRI paradigm, subjects underwent 10-minute fcMRI scans during which they lay quietly in the scanner with their eyes open. FcMRI scans were acquired with coronal whole-brain gradient echo EPI (TR/TE = 4000/40 ms, FA = 90°, FOV = 96mm x 96mm; in-plane resolution = 1.5 mm x 1.5 mm; 47 slices with thickness 1.5 mm). T1W anatomic images were obtained with a 3d MPRAGE sequence (TR/TI/TE/FA = 2700ms/800ms/3ms/8°). 10 separate MPRAGE acquisitions from different sessions were averaged off-line for each subject to generate the final anatomical image used for coregistration of the functional data. FcMRI scans were acquired during 3 separate conditions, at baseline, after a negative control infusion of the saline vehicle, and after an experimenter-administered intravenous infusion of cocaine HCl (0.3 mg/kg). Each fcMRI time-series was registered to a base volume, co-registered to the T1W anatomic, and spatially smoothed with a FWHM = 2 mm isotropic gaussian kernel. ROI-averaged time-series were obtained from 5mm spherical seeds placed at anatomical locations [1-2,6] in the bilateral caudate, putamen, NA, ACC, MPFC, DLPFC, and OPFC. The ROI time-series served as reference vectors in the cross-correlation analysis, and functional connectivity of each seed ROI was assessed through the cross correlation coefficient (CC). Volumes with excessive (> 1.5 mm) motion were removed from the analysis. Data analysis was performed with AFNI and FSL.

Results & Discussion: The primates exhibited excessive motion (displacement > 2 mm) in less than 5% of the volumes in all of the fcMRI runs. Figure 1 shows the functional connectivity maps (frontal slice) of the right NA seed from the baseline and acute cocaine effects sessions in subject RMv3. Figure 2 shows the connectivity maps of the right DLPFC seed for RMv3. The primates RMv3 and RBp3 exhibited strong functional connectivity between frontal and striatal regions (FDR q < 0.00001) at baseline. There was a marked decrease in functional connectivity between frontal and striatal regions after acute cocaine administration. This decrease was further evident in the average CC between frontal and striatal ROIs during the two sessions (Table 1).

Decreased fronto-striatal functional connectivity after acute cocaine administration may be responsible for the long-term changes seen in these networks in cocaine-dependent individuals [1-2,6,8]. These results are consistent with the increased frontal cortex BOLD activation upon cocaine challenge seen in the same set of monkeys in another study [7], and supplement prior findings with evidence of decreased connectivity to striatal and frontal areas in the neurocircuitry underlying drug-taking [1-2,6]. The results demonstrate the feasibility of acquiring resting state functional connectivity data from awake monkeys, and provide a translational model for studying the acute and chronic changes induced by cocaine.

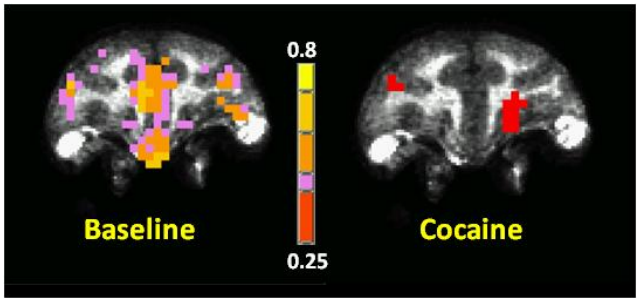

Figure 1: Brain regions functionally connected to right NA: (left) Baseline (CC > 0.4; FDR q < 0.0001); (right) Cocaine (CC > 0.25; FDR q < 0.03).

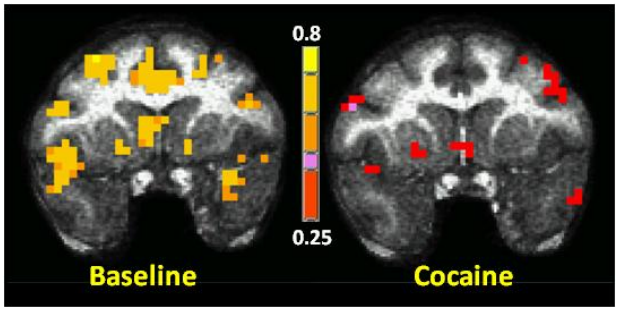

Figure 2: Brain regions functionally connected to right DLPFC: (left) Baseline (CC > 0.5; FDR q < 0.0001); (right) Cocaine (CC > 0.25; FDR q < 0.03)

Table 1: Average of CCs from RBp3 and RMv3 datasets between frontal and striatal ROIs (Bonferroni corrected p < 0.05)

	Left Caudate		**Right Caudate**		**Left Putamen**		**Right Putamen**		**Left Acumbens**		**Right Acumbens**	
	Baseline	***Cocaine***	**Baseline**	***Cocaine***	**Baseline**	***Cocaine***	**Baseline**	***Cocaine***	**Baseline**	***Cocaine***	**Baseline**	***Cocaine***
ACC	**0.68**	***0.41***	**0.64**	***0.38***	**0.41**	***0.26***	**0.49**	***0.33***	**0.49**	***0.26***	**0.55**	***0.36***
LDLPFC	**0.76**	***0.35***	**0.82**	***0.28***	**0.68**	***0.28***	**0.71**	***0.33***	**0.63**	***0.29***	**0.69**	***0.30***
RDLPFC	**0.76**	***0.38***	**0.78**	***0.29***	**0.62**	***0.30***	**0.7**	***0.41***	**0.66**	***0.34***	**0.70**	***0.40***
MPFC	**0.73**	***0.47***	**0.78**	***0.44***	**0.65**	***0.35***	**0.68**	***0.35***	**0.62**	***0.34***	**0.65**	***0.44***
LOPFC	**0.63**	***0.37***	**0.71**	***0.23***	**0.63**	***0.41***	**0.64**	***0.35***	**0.55**	***0.29***	**0.57**	***0.38***
ROPFC	**0.64**	***0.32***	**0.76**	***0.33***	**0.66**	***0.26***	**0.74**	***0.44***	**0.60**	***0.26***	**0.65**	***0.33***

References: [1] Murnane K., et al., Psychopharmacology, 216:153–171, 2011; [2] Howell L., et al., Ann N Y Acad Sci., 1141:176-94, 2008; [3] Rosazza C., et al., Neurol. Sci., 32:773-785, 2011; [4] Oler J., et al., Neuroimage, 61:1059–1066, 2012; [5] Peltier S., et al., Neuroreport, 16:285-288, 2005; [6] Haber S., et al., Neuropsychopharmacology, 35:4-26, 2010; [7] Murnane K., et al., J Neurosci Methods, 191:11-20, 2010; [8] Tomasi D., et al., PloS One, 5:5:e10815.