Resting-State Functional Connectivity in Fronto-Striatal Networks during Abstinence Predicts Cocaine Consumption after Relapse: Results from a fMRI Study on Awake Non-Human Primates

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Introduction: Cocaine addiction is characterized by alternating cycles of abstinence and relapse and loss of control drug consumption [1]. Identifying the critical determinants of individual vulnerabilities to cocaine addiction is very important for designing therapies. Non-human primates (NHPs) afford distinct advantages in translational neuroimaging studies of drug addiction [2-3]. A fronto-striatal network comprised of frontal brain regions including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, (ACC), and orbital prefrontal cortex (OPFC), and striatal regions including nucleus accumbens (NAcc), anterior aspects of caudate, and putamen, understood to underlie drug-taking [2-3, 4]. Previously, we established a protocol to assess resting state functional connectivity (rsFC) with MRI (rsFMRI) in awake NHPs [5-6], thereby avoiding the impairment of rsFMRI networks [7] that can be engendered by anesthetics conventionally employed in NHP fMRI studies [8]. In this study, we examined three female rhesus monkeys in prolonged abstinence following a long history of cocaine consumption. We assessed rsFC in fronto-striatal networks in these NHPs, under baseline conditions (i..e, during abstinence) and after acute cocaine administration.

Methods: Three adult female rhesus monkeys, in (enforced) prolonged abstinence with a long history (> 5 years) of self-administration to psychoactive compounds [5] 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 [5]. 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 [5], attached to the CP extremity coil. The subjects underwent 10-minute fcMRI scans during which they lay quietly in the scanner with their eyes open [5-6]. FMRI 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 co-registration of the rsFMRI data. FMRI 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). After the FMRI study, the subjects were allowed to once again engage in intravenous cocaine self-administration, and their level of cocaine consumption was noted.

Each rsFMRI 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. Volumes with excessive (> 1.5 mm) motion were removed from the analysis. ROIs of frontal and striatal regions: DLPFC, ACC, OPFC and NAcc were manually segmented. The ROI-averaged time-series served as reference vectors in the cross-correlation analysis, and rsFC of each seed ROI was assessed through the cross correlation coefficient (CC). The relationship between fronto-striatal rsFC and level of cocaine consumption after resumption of drug self-administration was assessed with linear regression. Further, graph theory measures were employed to probe the whole-brain rsFC network. Nodes for graph analysis were formed by rsFMRI voxels resampled to 2mm X 2mm X 2mm resolution. A binary distance matrix was formed by setting edges with CC > 0.3 to 1 and the rest to 0. Summary measures of network connectivity: characteristic path length, average clustering coefficient, and average degree centrality, and small-worldness ratio were obtained, to assess the integrity of whole-brain connectivity networks.

Results & Discussion: The primates exhibited excessive motion (displacement > 2 mm) in less than 5% of the volumes in all of the rsFMRI runs. In the prefrontal cortex (PFC), rsFC of both DLPFC and ACC to NAcc was significantly reduced ($t_3 > 8$; $p < 0.05$) after acute cocaine administration. DLPFC and ACC connectivity to NAcc assesses the integrity of networks associated with outcome valuation, behavioral inhibition, drug craving, and risky decision making [1,2-4]. Thus cocaine intake degrades these fronto-striatal networks and will potentially impair these functions. NAcc's rsFC to other areas in the striatum also went down after acute cocaine administration, but not to the same extent as NAcc to PFC connectivity. Quantitatively, the ratio of NA-PFC connectivity to NA-striatum connectivity decreased with cocaine administration ($t_3 > 6$; $p < 0.05$). These data suggest that cocaine selectively spares the function of the reward circuitry while impairing top-down prefrontal control over these brain areas. Further across the three subjects, baseline rsFC between DLPFC and NAcc was inversely related ($p< 0.01$) to level of cocaine consumption during resumption of drug-taking. This indicates that loss of top-down control over striatal areas related to the motivational and reinforcing properties of cocaine may be a critical determinant of relapse to cocaine consumption following a period of abstinence. Finally, besides fronto-striatal networks, summary graph-based measures of whole brain connectivity also revealed significant reduction of rsFC between regions across the brain. Average degree centrality decreased after acute cocaine administration ($p < 0.05$) and characteristic path length increased after cocaine consumption ($p < 0.05$). Thus cocaine administration can impair a number of different brain functions due to loss of connectivity.

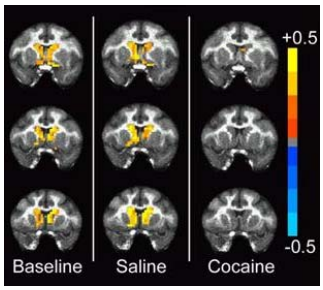

Fig.1: rsFC (CC) map of DLPFC for a representative subject.

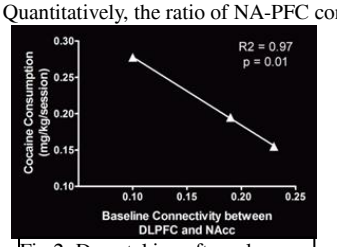

Fig.2: Drug-taking after relapse vs. rsFC of DLPFC to NAcc

Conclusion: In summary, acute cocaine administration robustly decreased whole-brain rsFC and selectively impairs top-down prefrontal circuits that control behavior related to cocaine abuse. Importantly, impaired connectivity between prefrontal and striatal areas during abstinence predicted consumption of cocaine when these subjects were provided renewed access to the drug. Based on these findings, loss of prefrontal to striatal functional connectivity may be a critical mechanism underlying the negative downward spiral of cycles of abstinence and relapse that characterize cocaine addiction.

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