The Effects of Cocaine Abuse on Functional Connectivity within the Mesolimbic Pathway

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Introduction

With an estimated 1.5 million chronic cocaine users in the U.S., cocaine abuse is a considerable public health concern (Bolla *et al.*, 2004). The mood elevation and euphoria associated with cocaine use is the result of the inhibition of the reuptake of dopamine in the mesolimbic "reward" pathway. Chronic cocaine use produces a number of distinctive biochemical adaptations within structures in this pathway, and has been the focus in numerous studies (Berhow *et al* 1996).

A decrease in functional connectivity (i.e. the level of correlation in neural activity between distinct brain regions) in the primary motor and visual cortexes has been shown to be an acute effect of cocaine intake (Li *et al* 2000). The long-term effects of chronic cocaine-use on functional connectivity between structures in the mesolimbic pathway, however, has never before been investigated.

Resting state functional magnetic resonance imaging (fMRI) enables researchers to observe and analyze spontaneous neural activity since the subject is not performing a task. An index of resting state functional connectivity can be created by cross-correlating activity patterns between each of the brain regions of interest (ROIs).

Methods

Subject Recruitment: Raw data from the resting state fMRI scans of 26 chronic cocaine users (6 females, age: mean = 39.7, SD = 6.5) and 25 healthy controls (5 females, age: mean = 38.3 yrs, SD = 7.4) were obtained from an ongoing study run by the Center for the Study of Impulsivity in Addiction (CSIA) at the University of Minnesota. All subjects met DSM-IV criteria for substance abuse disorder, and controls were matched with probands by gender, age, and level of education.

fMRI Scanning Sequence: Participants underwent a 6 minute resting-state fMRI scan and were instructed to be as still as possible, keep their eyes closed, and stay awake. Images were collected using a Siemens Trio 3T scanner (Erlangen, Germany). Sequence parameters: gradient-echo echo-planar imaging (EPI), 180 volumes, 34 axial slices, repetition time (TR) = 2s, voxel size = 3.4 x 3.4 x 4.0 mm, matrix = 64 x 64.

Pre-processing: These obtained data were pre-processed using tools from Oxford Centre for Functional Magnetic Resonance Imaging of the Brain's Software Library (FSL version 4.0). The following prestatistics processing was applied: slice-timing correction, motion correction, bandpass filtering (0.01-0.08 hz), and 6mm full-width half-max spatial smoothing. Additionally, the data underwent grand mean scaling and realignment to the MNI152 average brain using a 12 degree-of-freedom linear registration. The first 3 of the 180 time-points were removed to allow for magnetic equilibration

Analysis: Nine 6mm radius spherical ROIs were created and placed within structures known to make up the mesolimbic pathway (Figure 1). A cross-correlation analysis was then conducted to determine an index of functional connectivity among these regions. A matrix consisting of all possible cross-correlations (r-values) of the 9 ROIs was created for each subject (36 total correlations). All r-values were transformed to z-values using the Fischer R-Z transformation, in order to correct for the non-normal distribution of r-values. The z-values were used for group-wise analysis, which consisted of determining the mean of each ROI x ROI cross-correlation and a t-test on the equality of the means between groups.

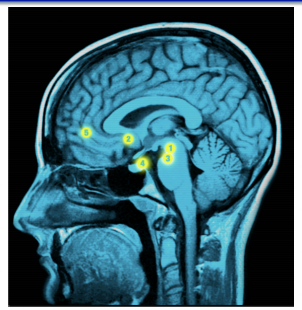


Figure 1 (left): Crude map of the placement of the ROIs within the major structures that make up the mesolimbic system.

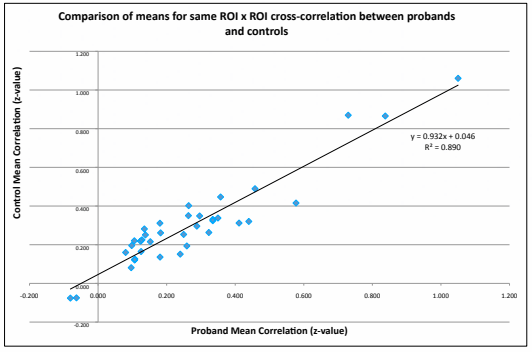
1- **Ventral Tegmental Area** (VTA):
2 ROIs placed in left and right VTA
2- **Nucleus Accumbens** (Nacc):
2 ROIs placed in left and right NAcc
3- **Hippocampus** (HPC):
2 ROIs on left and right side encompassing of part hippocampus and parahippocampal gyrus (PHPC)
4- **Amygdala** (amyg):
2 ROIs placed in left and right amygdala
5- **Orbital Frontal Cortex** (OFC):
1 ROI placed in medial OFC

*Note: this is a 2-dimensional representation of the placement of the ROIs. For 1-4, the actual placement of the left and right ROIs were on either side of what is shown on the map.

Table 1 (below): Results of the correlation analyses and t-tests on the equality of means between groups.

ROI 1 x ROI 2	Proband Mean Correlation	Std. Dev.	Control Mean Correlation	Std. Dev.	Combined Mean	T-test for Equality of Means
L NAcc x L amyg	0.124	0.35	0.218	0.28	0.170	0.29
L HPC/PHPC x L amyg	0.357	0.38	0.447	0.35	0.401	0.39
L HPC/PHPC x L NAcc	0.323	0.35	0.263	0.39	0.294	0.57
L VTA x L amyg	0.250	0.49	0.253	0.46	0.251	0.98
L VTA x L NAcc	0.440	0.31	0.320	0.37	0.381	0.22
L VTA x L HPC/PHPC	0.577	0.49	0.416	0.40	0.498	0.20
L VTA x L amyg	0.106	0.32	0.220	0.28	0.162	0.18
L NAcc x mOFC x L NAcc	0.288	0.39	0.296	0.23	0.292	0.93
L HPC/PHPC x mOFC x VTA	0.060	0.31	0.160	0.28	0.119	0.34
R amyg x L amyg	-0.081	0.41	-0.076	0.32	-0.078	0.96
R amyg x L NAcc	0.838	0.41	0.866	0.44	0.851	0.82
R amyg x L HPC/PHPC	0.181	0.34	0.136	0.30	0.159	0.62
R amyg x L amyg	0.350	0.48	0.338	0.30	0.344	0.92
R amyg x L VTA	0.125	0.60	0.165	0.35	0.145	0.78
R amyg x mOFC	0.096	0.32	0.196	0.27	0.146	0.24
R NAcc x L amyg	0.152	0.28	0.216	0.30	0.183	0.44
R NAcc x L NAcc	1.050	0.44	1.060	0.31	1.055	0.92
R NAcc x L HPC/PHPC	0.259	0.30	0.194	0.37	0.227	0.49
R NAcc x L VTA	0.411	0.32	0.312	0.32	0.363	0.28
R NAcc x mOFC	0.296	0.35	0.349	0.23	0.322	0.53
R NAcc x R amyg	0.107	0.32	0.121	0.29	0.114	0.87
R HPC/PHPC x L amyg	0.294	0.41	0.492	0.35	0.332	0.20
R HPC/PHPC x L NAcc	0.128	0.35	0.225	0.34	0.176	0.32
R HPC/PHPC x L HPC/PHPC	0.458	0.53	0.490	0.52	0.473	0.83
R HPC/PHPC x L VTA	0.135	0.45	0.282	0.35	0.207	0.20
R HPC/PHPC x mOFC	0.107	0.28	0.126	0.32	0.117	0.82
R HPC/PHPC x R NAcc	0.263	0.40	0.350	0.35	0.306	0.41
R HPC/PHPC x R NAcc	0.138	0.36	0.251	0.37	0.193	0.27
R VTA x L amyg	0.240	0.41	0.151	0.48	0.196	0.48
R VTA x L NAcc	0.335	0.35	0.324	0.36	0.329	0.92
R VTA x L HPC/PHPC	0.182	0.46	0.261	0.47	0.221	0.55
R VTA x L VTA	0.730	0.44	0.870	0.34	0.798	0.21
R VTA x mOFC	-0.063	0.34	-0.075	0.29	-0.069	0.90
R VTA x R amyg	0.097	0.57	0.081	0.36	0.089	0.91
R VTA x R NAcc	0.335	0.36	0.331	0.31	0.333	0.97
R VTA x R HPC/PHPC	0.180	0.37	0.311	0.39	0.245	0.23

Figure 2 (below): This scatter plot compares the mean correlations of the same ROI x ROI pair between probands and controls. The highly linear distribution and the created trend-line ($y = 0.932x + 0.046$; $R^2 = 0.890$) suggested that there was little difference between the two.



Results

The results revealed no significant differences ($p > 0.05$) in the cross-correlations of probands and controls (Table 1). The largest difference between mean correlations was for the left VTA and left hippocampus/parahippocampal gyrus ($\Delta = 0.161$; $p = 0.20$). The mean of all ROI x ROI correlations was slightly higher in controls (0.301) than in probands (0.274).

Highest cross-correlations were mostly between the same ROIs across hemispheres (e.g. R NAcc x L NAcc = mean of 1.055). Also high were correlations between ROIs that were close to each other (e.g. L VTA x L HPC/PHPC= .498). The only negative means were both the left and right VTA with the mOFC; the 2 ROIs furthest apart.

Conclusions

Chronic cocaine use does not appear to affect the functional connectivity within nodes in the mesolimbic pathway. This was intriguing since reward-related dopamine release from the VTA– a short-term effect of cocaine-use– has been shown to be directly correlated with neural activity within the structures of the pathway (Schott *et al* 2008). So even though chronic cocaine-use produces a number of characteristic adaptations within these structures, these preliminary results suggested that intrinsic functional connectivity between the structures is not significantly affected.

This observed trend of no significant difference between probands and controls, however, might be due to experimental error– e.g. motion during scans, placement of ROIs, sample size. The fact that there was not a single significant difference between probands and controls out of 36 ROI x ROI correlations (lowest p-value was 0.18) in the created functional connectivity index, however, was supportive of there being no effect– particularly since analysis was unadjusted for multiple comparisons. Future studies could examine the functional connectivity of other parts of the brain, focusing on interhemispheric connectivity as a result of this study.

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FSL: http://www.fmrib.ox.ac.uk/fsl

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