

# Disrupted midbrain-thalamus functional connectivity in cocaine abusers

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**INTRODUCTION:** Chronic cocaine use decreases brain dopamine activity<sup>1</sup>, however the functional effects of this disruption are largely unknown. We used fMRI and seed-voxel correlation analyses to study brain activation to a cognitive-emotional drug-Stroop-like (DS) task<sup>2</sup> and the functional connectivity (fcMRI) between midbrain and forebrain. Based on previous research<sup>1,3,4</sup>, we hypothesized that compared to healthy control subjects, cocaine abusers would have lower DS activation in and lower fcMRI between the thalamus and midbrain than controls.

**METHODS:** Twenty chronic cocaine abusers (17 men; age =  $41.4 \pm 5.0$  years; education =  $13.1 \pm 1.3$  years; verbal IQ =  $98.8 \pm 9.4$ ; cocaine use onset =  $23.9 \pm 5.7$  years; cocaine duration =  $15.3 \pm 4.9$  years; frequency of cocaine use =  $3.9 \pm 2.2$  days/week; mean  $\pm$  SD), and 20 age-, gender-, and education-matched healthy control subjects participated in this study. All subjects performed a verbal DS task button-pressing to identify the displayed color of drug vs. matched neutral words<sup>2</sup> in a 4Tesla MRI scanner while a single-shot gradient-echo EPI sequence (TE/TR = 20/1600 ms, 4 mm slice thickness, 1-mm gap, 35 coronal slices, 64x64 matrix size, 131 time points) was used to measure blood oxygenation level dependent (BOLD) signals. Image post processing included motion correction, spatial normalization to the Talairach frame ( $3 \times 3 \times 3$  mm<sup>3</sup> voxel size), and spatial smoothing (8-mm Gaussian). BOLD contrast maps were calculated for each subject using a box-car design and the general linear model in SPM2. Connectivity maps reflecting the fcMRI of midbrain with forebrain were estimated from individual blocked fMRI datasets<sup>5</sup> and normalized using the Fisher transform and IDL. Individual BOLD contrast maps were uploaded in a two-way repeated measures ANOVA (random-effects) model in SPM2 for group analyses of brain activation. Similarly, individual fcMRI maps were uploaded in the same random effect SPM2 model for statistical analyses of fcMRI. Complementary ROI analyses, using in-house IDL code, were used to validate the SPM2 findings.

**RESULTS:** There were no significant performance differences between the groups in accuracy or reaction time (main or interaction effects) during the DS task. Compared to a fixation baseline, the DS task activated a bilateral network including prefrontal (PFC) and parietal cortices, thalamus, dorsal striatum, midbrain, and the cerebellum and deactivated the parahippocampus, precuneus, amygdala, insula, and the perigenual anterior cingulate cortex (ACC) ( $p_{\text{corr}} < 0.001$ , cluster-level corrected for multiple comparisons; Fig 1 left panels). Brain activation in the PFC, thalamus, putamen and cerebellum was higher for controls than for cocaine abusers, but deactivation of the ACC was higher for cocaine abusers than for controls ( $p_{\text{corr}} < 0.05$ ; Figs 1 and 2). The fcMRI of midbrain and superior pons (where the noradrenergic locus ceruleus, LC, is located), thalamus, and cerebellum was higher for controls than for cocaine abusers [ $p_{\text{corr}} < 0.001$ ; Fig 1(right) and Fig 2]. By contrast, midbrain showed negative fcMRI with ACC for cocaine subjects but not for controls. Importantly, the fcMRI between midbrain and LC was linearly associated with BOLD-fMRI responses in the ACC for controls but not for cocaine abusers ( $R = 0.50$ ,  $p = 0.02$ ; Fig 3).

**CONCLUSIONS:** Here we show that during processing of drug and matched neutral words, cocaine abusers had lower BOLD-fMRI activation in subcortical brain regions (LC, thalamus, and cerebellum), which is similar to previous findings in cocaine abusers when tested with working memory and visual attention tasks<sup>3,4</sup>. We further show that these brain regions (including the LC) have lower fcMRI with midbrain in cocaine abusers than in controls. Increased deactivations and enhanced fcMRI with midbrain in the perigenual ACC for cocaine abusers more than for controls may be indicative of compensatory responses. These findings suggest that lower recruitment of subcortical resources and larger recruitment of cortical resources are mediated by abnormal fcMRI of catecholamine (dopamine and noradrenaline) pathways in cocaine abusers.

**REFERENCES:** 1- Volkow (2007) *Arch Neurol* **64**: 1575-1579; 2- Goldstein (2007) *Neurosci* **144**: 1153-1159; 3- Tomasi (2007) *Bran Res* **1171**: 83-92; 4-Tomasi (2007) *Psychiatry Res* **155**: 189-201; 5- Fair (2007) *Neuroimage* **35**: 396-405.

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Fig 1: Statistical maps highlighting (Left) the thalamic hypo activation and (Right) the hypo functional connectivity of the thalamus with midbrain for cocaine abusers (N=20) compared with matched healthy controls (N=20)

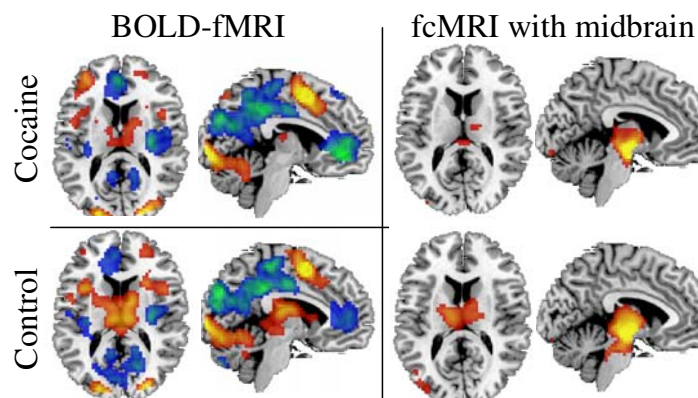


Fig 2: Region of interest analyses quantifying the functional abnormalities in cocaine abusers compared with controls.

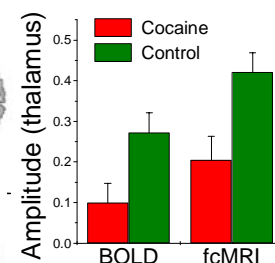


Fig 3: Scatter plot showing the association of ACC deactivation and fcMRI between midbrain and LC in controls but not in cocaine abusers.

