Cocaine Exposure History Leads to Distinct Spatial and Temporal Response Patterns to Acute Cocaine Challenge in Rats

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Introduction Repeated drug exposure induces long-lasting neuroadaptations in components of the mesolimbic system that are thought to mediate the reinforcing effects of drugs of abuse and appear to alter subsequent responsiveness to the drug: manifested as tolerance (1) or sensitization (2). We hypothesize that such neuroadaptations should give rise to distinct temporal and spatial patterns in fMRI responses to acute cocaine challenges in animals with a history of cocaine self-administration (SA), which could shed light on the mechanisms of drug-induced neuroadaptations.

Animal Training Male Long-Evans rats were trained to self-administered (SA) either I.V. cocaine (n=10) or oral sucrose (n=13) for 20 days using a long-access exposure regimen (6-h sessions), followed by 30 days of abstinence. A third untreated group (naïve rats, n=10) served as a control.

Imaging Procedures On the test day, rats were anesthetized with propofol (35 mg/kg/h, IV), intubated for artificial ventilation and catheterized for blood pressure monitoring and drug delivery. CBV-weighted fMRI using an iron-oxide contrast agent (iron dose: IV 20 mg/kg) was performed on a Bruker 9.4T scanner. A conventional gradient-echo sequence was used. Scan parameters: TR/TE = 310/6.00 ms, FOV = 3 × 3 cm^2, matrix size = 96 × 96, 13 slices, slice thickness = 1 mm. Five minutes after the scan initiated, animals received a saline injection (0.3 ml IV) followed by two cocaine injections (IV, 0.75 mg/kg per injection), which were initiated 10 and 35 min after the scan started. The fMRI scan lasted for 60 min.

Data Analysis Individual animal images were registered to a common space. Raw CBV-weighted time courses were converted to a percentage of the baseline CBV signal. Data from all 3 groups were combined, a group independent Component Analysis (ICA) was applied to identify the cocaine response pattern plus patterns related to respiration, cardiac, and scanner noise that were subsequently removed from the data. The time course patterns identified by ICA were used to model fMRI responses quantitatively with a General Linear Model (GLM) in AFNI. A one-way ANOVA ($p < 0.05$) was applied to identify significant regional responses. Neuronal firing rates changes following cocaine occur within 15 min, therefore the fMRI time courses were divided into 2-min bins. Fractional fMRI responses within individual intervals were compared across groups. Sliding the bin windows allowed an unbiased identification of the spatial and temporal patterns across groups in this model-free analysis.

Results Consistent with previous findings (3), acute cocaine challenge produces wide-spread activation across the brain in naïve animals; but the fMRI response in cocaine-SA rats demonstrated less activation (Fig. 1). Time-dependent changes in the 2-4 min bin window difference maps between cocaine-SA and naïve rats in response to acute cocaine challenge are illustrated in Figs. 2**a-c**. Cocaine SA rats show significantly less activation in the anterior cingulate cortex (ACC), prelimbic cortex and part of the ventral striatum as illustrated in the averaged time courses (Figs. 2**d-e**), indicating the presence of protracted tolerance.

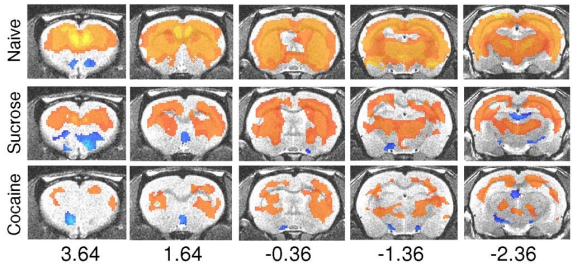

Figure 1. Statistical maps showing cocaine-treated rats are activated to a lesser degree than naïve rats and sucrose-treated rats. Numbers are coordinates relative to bregma.

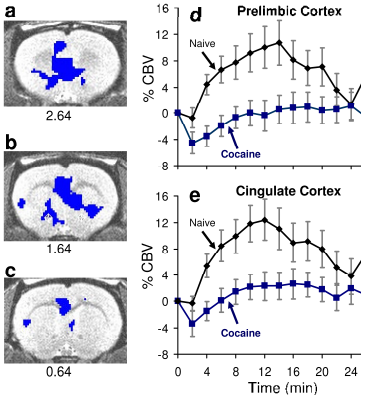

Figure 2. ***a-c*** show cocaine-treated rats demonstrated significantly reduced response in the 2-4 min bin window after an acute cocaine injection. ***d-e*** averaged time courses in the prelimbic cortex and the cingulate cortex binned into 2-min interval. Note the early *negative* CBV response and a greatly reduced positive response in cocaine treated rats relative to naïve rats. Error bars are SEM.

Discussion A major finding of this study is that rats with 20 days repeated cocaine SA followed by 30 days withdrawal demonstrate significantly reduced response to an acute cocaine challenge. In particular, in such regions as the prelimbic cortex, the infralimbic cortex and the ACC, cocaine SA rats have *negative* fMRI response, in contrast to *positive* response in cocaine naïve rats. Neuroanatomically, the prelimbic and infralimbic cortices are major components of the mesolimbic system. They have reciprocal connections with the ventral tegmental area and project to nucleus accumbens core and shell, respectively; they also project to the premotor cortex and have reciprocal connections with the mediodorsal thalamus (4). Thus, the prelimbic and infralimbic cortices involve the translation of motivational stimuli into adaptive motor response.

Considering the fact that fMRI signal reflects mostly afferents into and local processing within a specific region, the reduced and negative fMRI response in prelimbic and infralimbic cortex suggests that the afferents from VTA, mediodorsal thalamus and/or local processing inside the PFC are modulated by the cocaine SA regime. Further work is needed to elucidate underlying mechanism of this phenomenon.

References 1. Koob GF et al. Neurosci Biobehav Rev. 2004;27:739-49. 2. Robinson TE, Berridge KC. Brain Res. Rev. 1993 ;18 :247-91. 3. Marota JJ et al. Neuroimage 2000; 11:13-23. 4. Kalivas PW et al. in Limbic Motor Circuits and Neuropsychiatry. 1993; p237-87.