Reduced Prefrontal Cortical Activation Following Repeated Cocaine Exposure: A BOLD fMRI Study In Awake Rats

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INTRODUCTION: Repeated cocaine results in behavioral changes that arise from its effects on neurons of the brain reward system. This system is composed of the ventral tegmental area (VTA) and its neuronal targets the medial prefrontal cortex (PFC) and nucleus accumbens (NA). Functional MRI using the BOLD technique can be used to investigate the effects of acute and long-term cocaine exposure on neural substrates of the reward pathway. Several BOLD studies have shown changes in brain activation in response to an acute cocaine injection [1]. However, results from these studies are hampered by the use of general anesthetics which are know to reduce neuronal activity and cerebral metabolism, as well as affect cerebral blood flow [1]. Recently, we developed methods for imaging the BOLD signal response to cocaine in an awake rat model [2]. Cocaine administration resulted in positive BOLD signal changes in all major areas of the brain reward system [2]. Cocaine's brain activation profile was not observed in vehicle injected controls.

The goal of the present study was to use BOLD fMRI to determine the enduring adaptations within the brain reward system following repeated cocaine exposure. Since repeated cocaine administration produces long-lasting effects on cerebrovasculature function [3], we used hypercapnic (5 %) challenge to assess BOLD contrast before and after cocaine administration to verify differences in cerebrovascular reactivity between drug naive and cocaine pre-exposed rats.

METHODS: Adult male rats (300-350 grams) were given a daily cocaine (15 mg/kg, i.p.) or saline injection on 7 consecutive days, abstained for 7 additional days and re-exposed to cocaine during functional imaging on a final day. This resulted in two groups: 1) rats that received cocaine for the first time during imaging (SAL) and those re-exposed to cocaine during imaging (COC)(n = 5 per group). Prior to imaging studies, rats were anesthetized with 2% isoflurane and a polyethylene (PE-10) tubing was placed into the lateral ventricle and affixed to skull with surgical glue. Studies were performed with a multi-concentric dual-coil, small animal restrainer developed by Insight Neuroimaging Systems, LLC, (Worcester, MA). Experiments were conducted in a Bruker Biospec 4.7-T/40-cm horizontal magnet (Oxford Instrument, Oxford, U.K.) equipped with a Biospec Bruker console (Bruker, Billerica, MA U.S.A) and a 20-G/cm magnetic field gradient insert (ID = 12 cm) capable of a 120-μs rise time (Bruker). Functional images were acquired during a 15 minute session (1 image/2 sec); cocaine was injected 5 minutes into the scan (20 ug/ 10 uL, ICV). Functional scan parameters: Spin echo EPI, TR = 2,000 ms, TE = 55 ms, 90˚ flip angle, 12 slices, 1.2 mm slice thickness, FOV = 30 mm, data matrix 64 X 64. Anatomical scan parameters: Multi-slice fast spin echo, TR = 2,125 ms, TE = 50 ms, echo train length = 8, data matrix = 256 x 256. Rats were given a 1 minute 5 % CO_2 challenge during a 3 minute functional scan 20 minutes prior to and 10 minutes after cocaine injection. ROI analysis for hypercapnia data sets were performed on the cerebral cortex and the general sub-cortical region. ROI analysis for cocaine imaging was performed on frontal cortical brain areas (orbital, prelimbic, and anterior cingulated areas), anterior and posterior thalamic regions, and areas of the mesolimbic (VTA, NA and ventral pallidum) and nigrostriatal systems (globus pallidus, dorsal striatum, substantia nigra). Statistical significance was determined with Stimulate software (Strupp, 1996) using a t-test analysis ($p < 0.05$) comparing baseline to stimulation (cocaine or 5 % CO_2) period. Activated pixels from each rat were overlaid on their corresponding anatomy.

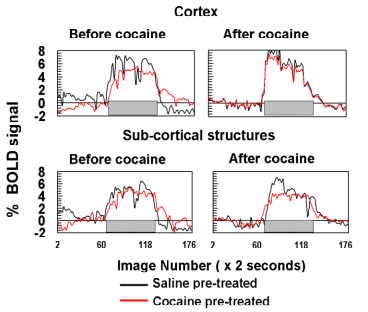

Fig. 1 BOLD response to 5 % CO2 in saline and cocaine pre-exposed rats.

RESULTS&DISCUSSION: The effect of hypercapnia on BOLD contrast was analyzed before and after cocaine injections in cortical and sub-cortical brain tissue. There were no statistical differences in the BOLD response to hypercapnia between SAL and COC rats (One-way ANOVA, $\alpha = 0.05$, $F = 1.5$ $p = 0.3$). Contrast-to-noise ratio calculations (%ΔBOLD/ SD_{CO2}) did not reveal any differences between these groups. **Fig. 1** shows the resulting data for hypercapnia challenge. Rats that received cocaine for the first time (SAL) showed a rapid and robust increase in BOLD signal intensity (+5%) in frontal cortical brain structures **(Fig. 2)**, as well as other sub-cortical areas **(Fig. 3)**. Cocaine administration to rats pre-exposed to the drug (COC) produced BOLD signal changes significantly lower than cocaine naive animals. In particular, frontal cortical brain structures showed +1 to +2% BOLD signal changes, whereas negative BOLD signal changes predominated in anterior thalamic nuclei (-1 to -5%) and NA **(Fig. 3)**. Interestingly, no differences in the BOLD signal response to cocaine were observed in the VTA and dorsal striatum in rats that received single or repeated cocaine.

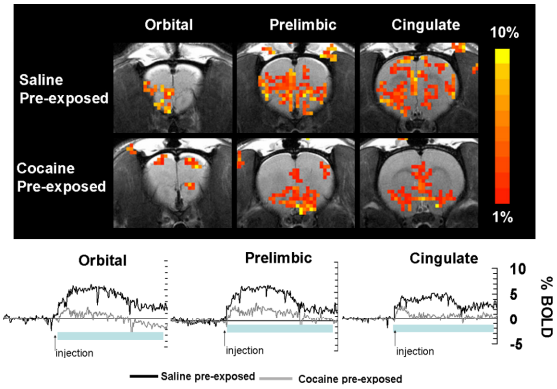

Fig. 2 BOLD response to cocaine in prefrontal cortical areas of naive and drug pre-exposed rats.

CONCLUSION: The present data indicate that rats pre-exposed to cocaine show a reduced BOLD signal response to the drug, as compared to drug naive animals. This 'depressed' response appears to be pronounced in prefrontal cortical areas and anterior thalamic nuclei, which are known to exchange significant amounts of excitatory inputs. Recent studies show that repeated cocaine produces long-term depression of excitatory synaptic transmission [4], and human PET imaging studies report reduced glucose metabolism in the frontal cortex of cocaine abusers [5]. Both scenarios are consistent with our present fMRI results. However, caution must be exercised when interpreting the effects of cocaine on BOLD signal intensity as changes in neuronal activity and completely ruling out its effect on cerebrovascular function, although our present data do not support this **(Fig. 1)**. Future experiments using Davis's biophysical BOLD model to investigate cocaine-induced changes in $CMRO_2$ (Liu et al., ISMRM 2004) may provide further evidence for a depressed neuronal response to cocaine following repeated exposure to the drug.

REFERENCES: [1] Mandeville et al., MRM, 2001 45:443. [2] Febo et al, 2003 submitted. [3] Kaufman et al., JAMA, 1998, 279: 376. [4] Thomas et al, Nat Neuroscience, 2001, 4: 1217. [5] Volkow et al., Am J Psych, 1991, 148: 621.

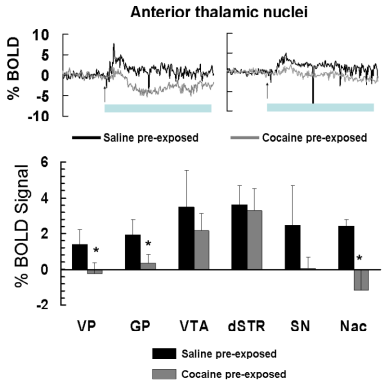

Fig. 3 BOLD response to cocaine in anterior thalamic and sub-cortical areas of naïve and drug pre-exposed rats.