QUALITATIVE DIFFERENCES IN THE BRAIN ACTIVATION EFFECTS OF COCAINE AND MDMA DETERMINED WITH BOLD FMRI IN RHESUS MONKEYS

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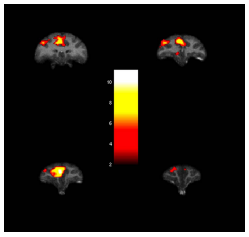
Introduction

Both cocaine and methylenedioxymethamphetamine (MDMA) are drugs that show a high propensity for abuse. However, these drugs have distinct effects. Specifically, cocaine functions as a selective psychomotor stimulant whereas MDMA exhibits stimulant-like and hallucinogenic properties. The effects of psychomotor stimulants primarily include sympathomimetic effects, arousal, changes in cognition, increased locomotion, and robust reinforcing effects. These effects have largely been linked to direct or indirect agonism of dopamine receptors (Ref 1.). The effects of hallucinogens primarily include changes in perception and cognition. These effects have largely been linked to direct or indirect agonism of serotonin receptors (Ref 2.). Dopamine and serotonin receptors subserve neural circuitry involved in different processes including those that are the hallmark effects of psychomotor stimulants and hallucinogens. An understanding of the neurobiology of stimulants such as cocaine versus mixed stimulants/hallucinogens such as MDMA will support medication development efforts to reduce abuse of these substances. As such, the aim of the present research was to determine the effects of these substances on changes in blood oxygenation in the central nervous system of fully conscious rhesus monkeys using BOLD fMRI and to relate those changes to the neurochemical and behavioral effects of these drugs.

Method

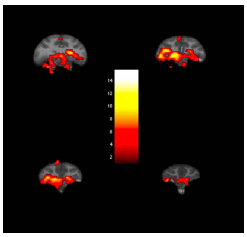
We compared the effects of cocaine (0.3 mg/kg, i.v.) and MDMA (0.3 mg/kg, i.v.) in three adult female rhesus monkeys (*Macaca mulatta*). Each monkey had been previously trained to undergo fMRI scanning while fully conscious using a custom procedure and apparatus. Scans were conducted in a Siemens (Siemens Healthcare, Erlangen, Germany) Trio 3 Tesla magnet with 90cm bore using a standard Siemens CP extremity coil. Anatomical images were acquired using a 3D single shot magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence optimized for T1 contrast. BOLD images were collected utilizing a gradient echo single-shot echo planar imaging (EPI) sequence; collected after a standard second order shim These 2D T2*-weighted images were acquired with the following parameters: 47 slices, TR = 4 seconds, TE = 40ms, 64 x 64 data matrix, 96mm FOV, 1594 Hz per pixel Bandwidth, and 90 degree flip angle yielding a final isotropic resolution of 1.5mm. Field inhomogeneities were mapped using a standard Siemens phase and magnitude image collection sequence for later correction of any single-shot EPI image distortions. Analyses were carried out using SPM5 (Wellcome Trust Center for Neuroimaging, London, UK) supplemented by custom software written in the matrix based programming environments IDL (ITT, Boulder, CO) and MATLAB (MathWorks, Natick, MA). Preprocessing of the images included placement of both the anatomical and functional images in AC-PC alignment and in gross registration to one another, motion correction using a 6 parameter rigid body algorithm, geometric distortion correction using the collected field maps, spatial segmentation of gray matter, white matter, and bias corrected images, spatial normalization and spatial smoothing using a kernel with a full width at half max equal to two times the native resolution of the image (i.e. 3mm). Whole brain analysis was carried out on a pixel by pixel basis using a parametric general linear statistical model. Motion parameters were used as covariates within this model to remove the influence of subject motion on the subsequent results. Multiple comparisons corrections were carried out such the probability of a type I error was maintained at less than 5%.

Figure 1



Significant changes ($p < 0.05$, corrected) in blood oxygenation following cocaine (0.3mg/kg, i.v) in subject RRg4

Figure 2



Significant changes ($p < 0.05$, corrected) in blood oxygenation following MDMA (0.3mg/kg, i.v) in subject RRg4

Results

The effects of cocaine (Figure 1) were localized to the dorsal regions of prefrontal cortex (PFC) whereas the effects of MDMA (Figure 2) were localized to the ventral regions of PFC. Neither drug induced significant activation of subcortical regions. Specifically, changes in blood oxygenation in response to cocaine administration were localized to the anterior cingulate and dorosolateral PFC. MDMA elicited a response in orbital and medial PFC. Statistical maps are thresholded to show activations after correction for multiple comparisons and scaled to the maximum t-value.

Conclusions

The effects of cocaine are consistent with previous studies from our laboratory using PET imaging of changes in blood flow or cerebral metabolism. Furthermore, these effects are localized to prefrontal cortical regions that show the strongest dopaminergic input. However, the effects of MDMA are distinct and appear to the related to serotonergic input. The dorsal regions of PFC have relevance for cognitive control and can be grouped into a broad categorization of reward circuitry whereas the ventral regions of PFC are involved in emotional and perceptual processes. Therefore, the neural circuitry engaged by these compounds appears to regulate their behavioral effects. As such, the use of fMRI allows for a novel approach to determine the mechanism of drugs of abuse and novel pharmacotherapeutic agents designed to diminish the abuse liability of these drugs.

References:

1. Howell L. and Kimmel H. Biochem Pharmacol. 2008;75(1):196-217.
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