Detection of Cocaine-Induced Neural Activation using Pharmacological Activity Induced Manganese (PhAIM) MRI

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Introduction

Pharmacological fMRI (phfMRI) based on blood oxygen level dependent (BOLD) contrast relies on changes in hemodynamics induced by administration of CNS-active drugs. However, non-neural drug-induced physiological changes could contaminate results obtained using the BOLD technique. Recently, paramagnetic manganese was shown to provide enhanced MR contrast of synaptic activity while being independent of, although co-localized with, the hemodynamic response [1]. During activation extracellular manganese enters neurons via voltage-gated calcium channels, resulting in an increase in intracellular relaxation rates, leading to signal enhancement. Dynamic Activity Induced Manganese (DAIM) MRI was introduced to deconvolve the enhancement due to specific stimuli from enhancement due to non-specific stimuli [2]. Recently, this approach was extended further to imaging neurotransmitter-induced brain activity in a technique labeled Pharmacological Activity-Induced Manganese Dependent Contrast (PhAIM) MRI [3]. It is well known that cocaine inhibits dopamine reuptake resulting in neural activation in several cortical and subcortical structures including nucleus accumbens (NAcc), caudate and putamen (CPu), amygdala (Amyg), anterior cingulate (ACing), ventral tegmental area (VTA), and somatosensory cortex (SS) [4, 5]. The goal of the present study was to determine if regional cocaine induced neural activation could be detected using PhAIM MRI.

Materials and Methods

Four naive male Sprague-Dawley rats (250-350 g) were divided into two groups: an experimental group (n=2) and a control group (n=2). Rats were anesthetized with urethane (1.2 mg/kg) administered IP. Polyethylene catheters (PE-50) were placed in the right femoral artery and vein for mean arterial blood pressure (MABP) monitoring and drug administration, respectively, and in the left external carotid artery for drug administration. A tracheotomy was performed and the animals were mechanically ventilated at 55 strokes per minute (2.5 ml tidal volume) with a 80:20 air:O_2 mixture. Core body temperature was monitored with a rectal probe and maintained at 36.8°C±0.5°C with a circulating water pad placed under the animal. Gallamine (250 mg/kg) was injected IV fifteen minutes before the experiment to induce paralysis and minimize motion artifacts.

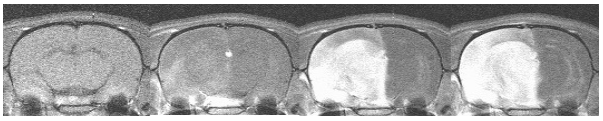

Figure 1a: T1W Anatomical Images of Experimental Rat

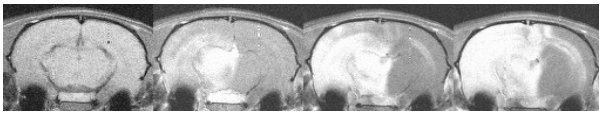

Figure 1b: T1W Anatomical Images of Control Rat

The paradigm for the experiment consisted of 5 intervals as follows: 1) T1-weighted (T1W) MR acquisition, 2) T1W MR acquisition during and after 1.8 ml/min injection of 0.45 μm filtered 25% mannitol (1.0 ml/100g) at 37°C, 3) T1W MR acquisition during and after 1.2 ml/min co-injection of 50 mM $MnCl_2$ (1.0 ml/kg) and 0.9% normal saline (1.0 ml/kg) 10 minutes after mannitol injection, 4) T1W MR acquisition during and after 1.2 ml/min co-injection of 50 mM $MnCl_2$ (1.0 ml/kg) and cocaine (2.5 mg/kg) 45 minutes after mannitol injection, 5) T1W MR acquisition during and after 1.2 ml/min injection of cocaine (2.5 mg/kg) 80 minutes after mannitol injection. For the control group, cocaine was replaced with an equal volume of saline. For intervals 3, 4, and 5, low resolution drug response images were collected for the first 25 minutes of the intervals followed by high resolution anatomical images for the remaining 10 minutes of the intervals.

Acquisition was performed on a Bruker BIOSPEC 30/60 3.0 T horizontal magnet with a homebuilt 20/20/40 G/cm (in x, y, z, respectively) torque-balanced gradient coil and a homebuilt birdcage RF coil. Multi-slice T1W, axial, spin echo drug response images were obtained using the following parameters: field of view = 35 mm, matrix size = 64 x 64, slice thickness = 2.0 mm, NEX = 1, number of slices = 15, repetition time = 550 ms, echo time = 19.3 ms. For anatomical images, the matrix size and NEX were increased to 256 x 256 and 4, respectively. The interface of the hard and soft tissue palette was used to localize slices to the Bregma. All subsequent images were normalized to the control image. A stereotactic rat atlas was used to construct regions of interest (ROI's) of the NAcc, CPu, Amyg, ACing, VTA, and SS for each rat. AFNI was used to calculate average ROI time courses.

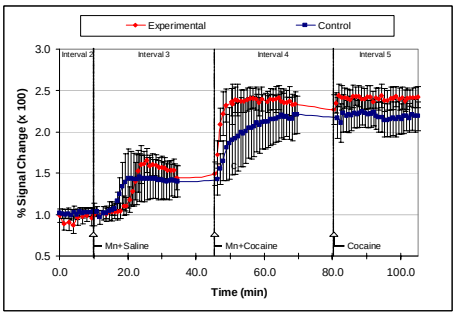

Figure 2a: Normalized NAcc Time Courses

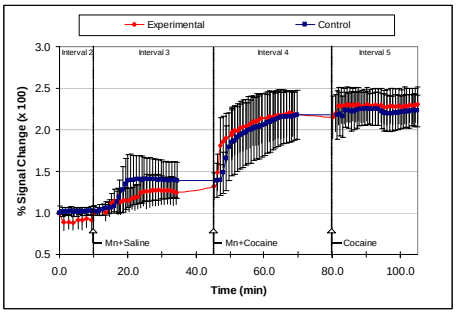

Figure 2b: Normalized CPu Time Courses

Results and Discussion

Figures 1a and 1b display axial T1W anatomical images (Bregma: -6 mm) of one experimental and one control rat, respectively, at intervals 1, 3, 4, and 5 described in Methods. The brains of both experimental and control rats display prominent signal enhancement. Figures 2a and 2b display the normalized time courses averaged over ROIs of the NAcc and CPu, respectively, for one experimental and one control rat. Mannitol was injected at time t = 0 on these figures. The time course of the control rat was found to be similar in both NAcc and CPu. Co-injection of manganese and saline during interval 3 produced a 10 minute ramp that plateaued at a 30% signal increase relative to control scan. Co-injection of manganese and saline during interval 4 produced an unexpected larger ramp that plateaued at a 120% signal increase. Injection of saline during interval 5 had little effect on signal enhancement. In contrast, the time course of the experimental rat was found to differ between NAcc and CPu. Co-injection of manganese and cocaine during interval 4 produced a sharp ramp in NAcc that plateaued at a 130% signal increase but a ramp and plateau similar to control rat in CPu. Injection of cocaine during interval 5 had little effect in NAcc but resulted in a slight enhancement in CPu. There appears to be a significant difference between experimental and control rats during interval 4 in the NAcc, but not in the CPu. The sharp ramp during interval 4 in the NAcc demonstrates that cocaine induced neural activation can be detected using PhAIM MRI. However, the ramp and plateau to 120% during interval 4 in the control rat demonstrates that this signal increase was not due to drug action. This phenomenon could confound the result of neural activity if manganese and drug are given together during interval 4. Therefore, caution must be taken to differentiate manganese effects from drug effects when using PhAIM MRI. This could be accomplished by performing a control study during interval 4.

References

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Acknowledgements

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