

## Pharmacological MRI with T1 Contrast Agents

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### Introduction

The majority of preclinical pharmacological magnetic resonance imaging (phMRI) studies employ contrast-enhanced cerebral blood volume (CBV) imaging using superparamagnetic iron oxide (SPIO) nanoparticles or they measure blood oxygen level dependent (BOLD) signal changes after drug challenge. Neural activity is indirectly measured through regional alterations in T2\* or T2 that can be captured using appropriate multi-slice gradient echo or spin echo sequences<sup>1-3</sup>. However, these current techniques are limited by loss of signal in brain areas with significant magnetic field inhomogeneities. Previously, two rodent paw stimulation-induced cortical fMRI studies took advantage of T1 shortening intravascular contrast agents at lower fields (1.5T, 2T)<sup>4-5</sup>, but otherwise the advantages of using T1 weighted agents to monitor blood volume changes have been little explored. However, T1 agents rely on adequate exchange of water between intravascular and extravascular compartments to spread their effect. The experiments shown here demonstrate the feasibility of whole brain phMRI at 9.4T with the FDA approved T1 contrast agent Magnevist using an optimized 3D acquisition sequence to detect amphetamine-induced brain activity.

### Methods

Adult male Sprague-Dawley rats (220-270g) were scanned in a Varian 9.4T Varian magnet using a Doty Litz 38 coil. Animals were intubated, mechanically ventilated under neuromuscular blockade, and anesthetized with isoflurane (0.9%) delivered in a gas mixture of O<sub>2</sub>:N<sub>2</sub>O (1:2). Heart rate, respiration rate, temperature, and end-tidal CO<sub>2</sub> were continuously monitored. Functional images were acquired using a 3D gradient echo sequence (TR = 29.5 ms; TE = 1.15 ms; flip angle = 11; data matrix = 64 x 64 x 32; field of view 32 x 32 x 32 mm). One brain volume was acquired every 60 seconds. After acquiring a pre-contrast baseline for 10 min, Magnevist (0.6 mmol/kg, i.v) was injected. The post-contrast functional scan consisted of a 10 min baseline, followed by amphetamine (2.0 or 4.0 mg/kg, i.p.) injection, then images were acquired for another 20 min.

### Results

Amphetamine evoked robust, sustained signal increases in the rat brain. Figure 1 depicts activation maps for one slice covering the caudate-putamen, an area rich in dopamine transporters. Voxels are colorized to the mean percent signal change over the last 10 min of the scan relative to the mean baseline signal. Figure 1 also shows the time courses of the drug responses in the caudate-putamen for the two doses. Increasing the psychostimulant dose from 2.0 to 4.0 mg/kg elevated the acquired signal increases from 1.87±0.55% to 4.71±0.33% in the caudate-putamen, demonstrating that the method is sensitive to drug concentration.

### Discussion

Here we show that phMRI can be performed using Magnevist in rats at 9.4T with a 3D acquisition. We optimized parameters for 3D imaging of rodent brain to use as an alternative phMRI acquisition method. We administered amphetamine as the drug challenge as it is commonly used in preclinical models of psychosis/schizophrenia and drug addiction. The brain maps reflect the underlying action of amphetamine in the brain similar to previously published BOLD and SPIO-based CBV phMRI results. However, there are advantages to using T1 agents, e.g., signals increase, rather than decrease as with SPIO nanoparticles, and higher resolution (less distorted) 3D acquisitions are possible. The localization pattern of activation shown here is more precise compared to that of previous BOLD studies. These data validate the utility of using a T1 shortening agent with 3D acquisition for phMRI. This method has potential translation to clinical drug studies using FDA-approved contrast agents.

### References

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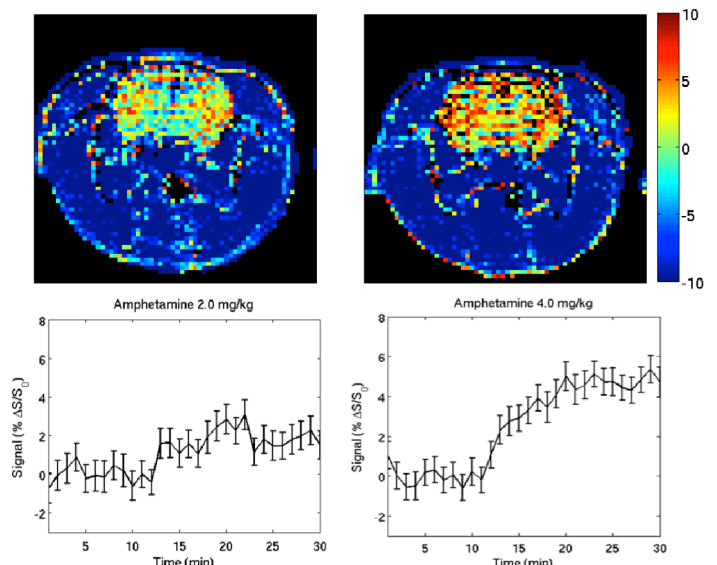


Fig. 1: Activation maps and time courses of the amphetamine phMRI response. Top row: Representative activation maps depict the % signal change (averaged over t=20-30 min) for 2 mg/kg (left) and 4 mg/kg (right) doses. Bottom row: Signal time courses extracted from the caudate-putamen. Data are presented as % signal change  $\pm$  SEM.