

# Mapping the cerebral blood volume response to cocaine with pharmacological MRI in mice at 7 T

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## Introduction:

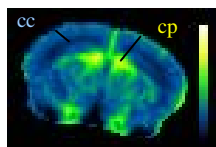
Pharmacological magnetic resonance imaging (phMRI) is used to monitor specific neuroactivation caused by CNS targeted drugs in vivo. As with functional MRI using sensorial or motor stimuli, the blood oxygen level dependent (BOLD) signal, cerebral blood flow and blood volume (CBV) can be used as non-invasive surrogate markers for neuroactivity in experimental animals and humans. In spite of the growing number of knock-out and transgenic mouse models of neurological disorders, relatively few phMRI studies have been reported in mice [1, 2] due to the technical challenges involved in performing in vivo MRI in very small animals. In this study, the feasibility of mapping CBV changes in response to cocaine administration in anesthetized mice using a steady state  $T_2^*$  weighted technique [3] with a superparamagnetic blood pool contrast agent was investigated.

## Method:

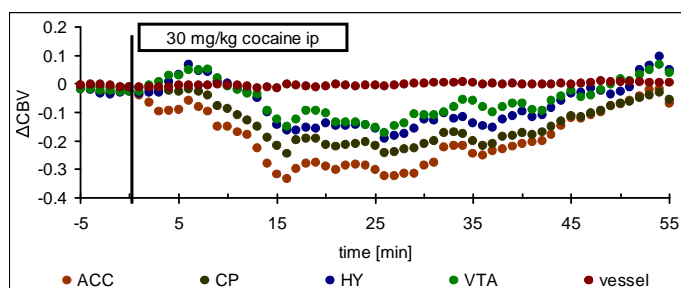
All animal experiments were approved by the institution. Five drug-naïve female C57BL/6J mice (19 - 21 g) equipped with an intraperitoneal (ip) and a tail vein catheter were imaged in a Bruker 7 T Biospec small-animal MR scanner. A custom-made mouse head birdcage radiofrequency coil was developed for this project. The mice were anesthetized with 1.6% isoflurane in  $N_2/O_2$  70%/30% and heated with a continuous flow of warm air. Rectal temperature, respiration and heart rate were monitored throughout the experiment. Fourteen contiguous 0.75 mm slices with an in-plane resolution of  $0.18 \times 0.18$  mm<sup>2</sup> were acquired using a 2D multi-gradient-echo (MGE) sequence ( $N_{\text{echoes}} = 3$ , TE = 2.5, 6.0 and 9.5 ms, TR = 600 ms, total acquisition time per repetition = 1 min). An intravenous bolus of 35 mg/kg MION was injected after acquisition of 20 pre-contrast repetitions, followed by 20 post-contrast repetitions. Equal volumes (10  $\mu$ l/g body weight) of cocaine hydrochloride (30 mg/kg) (Sigma-Aldrich, MO) and acetazolamide (ACTZ, 160 mg/kg) (Diamox<sup>®</sup>, Bedford Laboratories, OH) in normal saline solution were injected ip in the same mouse 20 min and 100 minutes after MION injection, respectively, and the hemodynamic response for each drug was monitored for 80 minutes. For analysis, the 3 echo images were averaged (effective TE = 6 ms) and coregistered using Automated Image Registration (AIR) software [4] for each slice over the time series. The baseline signals averaged over 15 minutes prior to and after MION injection were used to compute  $\Delta R_2^*$ -maps [5] which are proportional to the relative CBV. The drug induced CBV change ( $\Delta$ CBV) was quantified as described in [3, 5, 6].  $\Delta$ CBV-maps were generated in 5 minutes intervals after drug administration, and the  $\Delta$ CBV response from selected regions of interest (ROIs) was analyzed for time to peak, peak amplitude and response duration.

## Results:

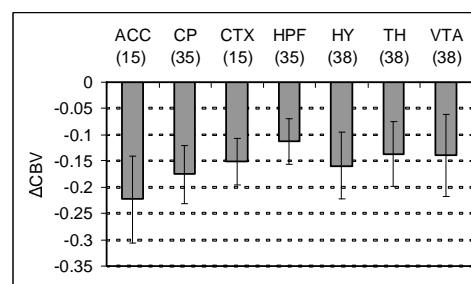
The average SNR in cortical regions was  $40 \pm 9$  and  $25 \pm 5$  before and after MION injection (43% signal drop), respectively. On the relative CBV map (Fig. 1), low and high CBV can be distinguished in the white matter of the corpus callosum and the choroid plexus, respectively. A steady state MION concentration in blood with negligible washout was achieved over the duration of the experiment (Fig. 2). The heart and respiration rate did not change upon injection of either drug. Contrary to the findings in rats [7], the CBV started decreasing within 5 minutes (Fig 2) and reached its peak amplitude at 15 to 40 minutes after cocaine injection (Fig. 3). The maximal duration of the cerebrovascular response was 60 minutes. The CBV change after ACTZ was more variable in amplitude and duration, but always positive.



**Fig. 1:** relative CBV ( $\Delta R_2^*$ ) map of a representative coronal mouse brain slice (blue = low CBV, yellow = high CBV), cc = corpus callosum, cp = choroid plexus



**Fig. 2:** time dependent regional CBV changes ( $n = 1$ ) within 4 brain and a vascular ROI



**Fig. 3:** histogram of peak  $\Delta$ CBV response after Cocaine injection ( $n = 5$ ), time from injection in minutes is given in parentheses

(ROIs: ACC = nucleus accumbens, CP = caudate putamen, CTX = cortex, HPF = hippocampus, HY = hypothalamus, TH = thalamus, VTA = ventral tegmental area)

## Discussion:

By averaging the signal from three echoes, we were able to retain high sensitivity to hemodynamic changes (long TE) while improving the SNR and partially overcoming (short TE) the problem of signal dropout due to susceptibility artifacts. Although the reason for a negative CBV response to acute cocaine administration in mice needs to be further investigated, this finding is congruous with the observed decrease in glucose metabolism in mice [8], monkeys [9] and humans [10].

## Conclusion and perspectives:

We studied the CBV changes in the mouse brain following Cocaine and ACTZ injection aiming to find a method to establish robust maps of neuroactivity. Using this method, a systematic study aimed at exploring the cerebrovascular reactivity to cocaine in genetically modified mouse models involving the monoamine neurotransmission is underway.

## References:

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