Mapping Negative and Positive Signal Sources in CBV Following Cocaine Treatment

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Introduction.

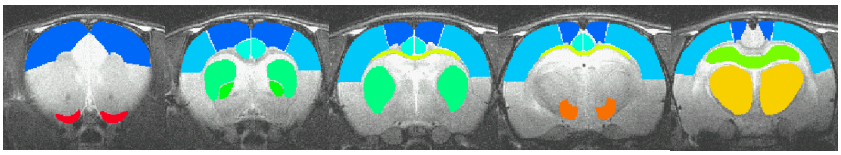
A unique region specific and dose dependent sharp negative BOLD signal was observed seconds after cocaine administration in urethane anesthetized rats [1]. The mechanisms responsible for this negative BOLD signal are not clear. Two mechanisms have been hypothesized: one, a putative mechanism similar to "initial early dip" seen in a functional visual study on cat brain associated with increased metabolic activity [2]; two, secondary cerebral vascular constriction induced by elevated norepinephrine levels after cocaine infusion [1]. In the present study, we tested the notion that data from CBF and CBV measurements in the same animal could help delineate between the two mechanisms and improve functional mapping of cocaine-induced changes in brain activity.

Materials and Methods.

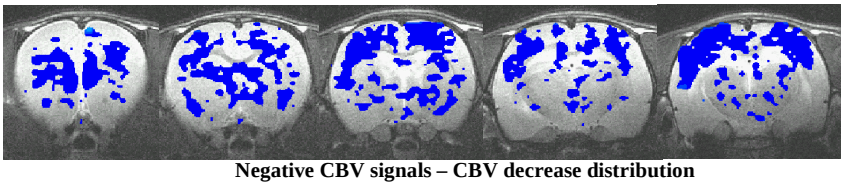
Animal Preparation: Nine male Sprague-Dawley rats weighing between 250-300 g were used for cocaine (1.0mg/kg) challenges. Under urethane anesthesia (1.2g/kg), all rats were artificially ventilated with room air at a tidal volume of 3.2 ml and respiration frequency of 55 Hz to maintain normal physiological status. Body temperature was maintained at 37 ^{o}C with a water circulated heat pad. The right femoral vein was cannulated (PE-50) for contrast delivery. *Hypercapnia challenge:* all rats underwent hypercapnia challenge with a CO_2 concentration of 5% to ensure normal cerebral vascular response pre drug exposure. *fMRI experiments:* fMRI experiments were performed on a Bruker Biospec 4.7T/40cm scanner with a 20-G/cm field gradient. Continuous arterial spin-labeling techniques were used for CBF measurement. Paired images with a single-shot, gradient-echo EPI were acquired alternately: one with arterial spin labeling and the other without, using a custom-built actively decoupled surface coil (2.3-cm inner diameter) for brain imaging and a neck coil for perfusion labeling. The MR parameters were: FOV=3.0 cm, slice thickness=1.5 mm, image matrix=64 x 64, giving an in-plane image resolution of 470 x 470 µm, TR=2 sec, and TE=18.7 ms. Continuous arterial spin labeling used a 1.7 sec square RF pulse to the labeling coil in the presence of 1.0 G/cm gradient along the flow direction, such that the condition of adiabatic inversion was satisfied. Monocrystalline iron oxide nanocolloid (MION) was introduced into the same CBF imaging setting excluding neck labeling at a proper dose for CBV measurement, such that the baseline SNR is reduced to approximately e^{-1} of the value prior to injection. CBF measurement followed by CBV measurement was performed on 5 rats in response to cocaine challenge. Each rat was challenged twice with cocaine with a 90-min interval. Only CBF or CBV measurements were performed on another 4 rats under two doses of cocaine challenges with more than 90-min interval. *Data analysis:* After CBV time courses were calculated based on pre- and post-MION baseline signal intensities, two non-linear model fitting analysis were performed based on CBF and CBV time courses. A differential exponential (Diff-Exp) model or a Beta model was used for fitting the negative or positive signals on a pixel by pixel basis [1]. The percentage changes of CBF and CBV signals were calculated using AFNI software package. Significant CBF and CBV perturbations ($p<0.05$) by cocaine were compared in ten ROIs. Ten ROIs were defined from the five slices (interaural 12.20 mm - 6.2 mm): motor cortex (Mor-dark blue), somatosensory cortex (Som-moderate blue), cingulate gyrus (Cin-light blue), caudate putamen (Cpu-light turquoise), nucleus accumbens (Nac-moderate turquoise), hippocampus (Hip-green), corpus callosum (Cca-yellow), thalamus (Tha-orange), hypothalamus (Hyp-dark orange) and olfactory tubercle (Olf-red).

Results.

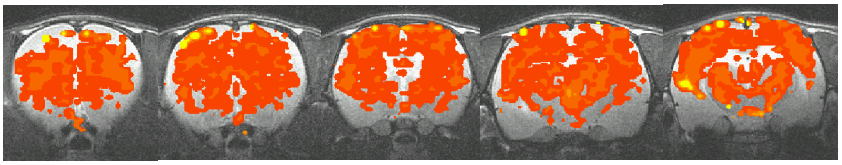
Both increase of CBF and CBV was observed in all rats under hypercapnia challenges. Insignificant difference of CBV or CBF perturbation was found between first dose and second dose of cocaine challenges. A clear "initial dip" was found in CBV with a time window of 30-120 sec immediately after cocaine injection followed by a prolonged CBV increase (Fig. 1). CBF increase was also detected by arterial spin labeling techniques, however with significant less detection power than CBV methods on signal decrease (table 1). A more regionally specific mapping on cocaine's effect was observed using the negative CBV signal sources than positive ones (Fig 1).



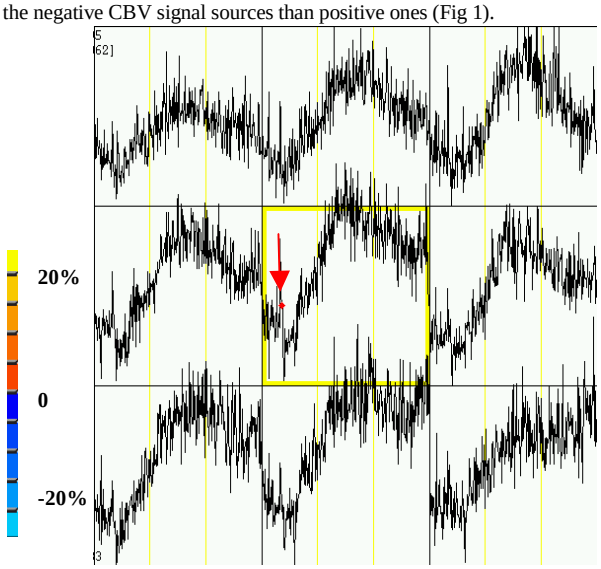
Anatomay and 10 ROIs



Negative CBV signals – CBV decrease distribution



Positive CBV signals – CBV increase distribution



CBV time course from 9 voxels after cocaine infusion (red arrow)

Fig. 1 Analysis of cocaine induced CBV signal source (right figure) by fitting "initial dip" (left figure, second row) or by positive signal source (left figure third row). Anatomy and ten ROIs was also displayed (left column, first row).

Table 1. Percentage of initial CBV or CBF decrease (M±SD) in 10 ROIs (*: $p<0.05$)

ROIs	Mor	Som	Cin	Cpu	Nac	Hip	Cca	Tha	Hyp	Olf
CBV	-25.6±4.3 *	-26.1±4.1*	-9.9±0.7*	-9.6±0.3*	-9.4±0.5*	-12.1±2.8	-10.1±6.8	-22.7±10.4	-13.8±6.6*	-61.7±61.0
CBF	-3.8±0.9	-6.4±4.8	-3.0±2.9	-3.4±1.5	-1.9±2.6	-8.2±1.4	-10.2±6.8	-2.9±1.4	-0.4±0.3	-5.4±5.9

Discussion.

A global CBV increase was observed after cocaine infusion and this pattern corroborates the data of Marota et al., [3]. A more region specific CBV decrease was also observed localized primarily to the cortical-mesolimbic dopamine system pathways, including prefrontal cortex, caudate/putamen and nucleus accumbens. The negative signal profile in CBV followed by a positive signal was comparable to that observed in BOLD studies using the same anesthetic preparation [1]. The major finding of this study was that CBV measurement using MION can detect an initial decrease in CBV, which lasted 30 – 120 sec. Presumably, this initial decrease in CBV is due to cerebral vasoconstriction as reported in human studies using MR angiography [4]. The increase in arterial vascular resistance may cause a reduction in capillary blood volume and decreased venous capacitance. However, given the unique pattern of negative signal it is unlikely that the initial CBV distribution is entirely due to a cocaine-vascular intereaction, but probably involves a more complex yet unknown interactive mechanism between parenchyma and blood vessels.

References.

[1] Luo F, *et al.* MRM 2003; 49: 264-270. [2] Duong TQ, *et al.* MRM 2000; 44:231-242. [3] Marota JJ, *et al.* Neuroimage 2000; 11:13-23. [4] Kaufman MJ, *et al.* JAMA 1998; 279:376-380.