Imaging Cocaine-Induced Changes in BOLD, CBF and Oxygen Consumption

Z. M. Liu[1], Q. Shen[1], K. M. Sicard[1], M. Febo[1], C. F. Ferris[1], E. A. Stein[2], T. Q. Duong[1]

[1]Ctr for Comparative Neuroimaging, Psychiatry, Univ Massachussett Med Sch, Worcester, MA, United States, [2]NIDA, National Institute of Health, Baltimore, MD, United States

INTRODUCTION Pharmacological fMRI (phfMRI) of cocaine administration using the BOLD technique could potentially be contaminated with physiological effects such as cocaine-induced changes in blood pressure, respiration rate, and vasoconstriction. These non-neural effects could drastically affect the BOLD signals. Although some physiological effects can be reduced using mechanical ventilation in anesthetized and paralyzed animals [1], they can not be completely eliminated. Both cocaine-induced positive and negative BOLD changes had been observed, which raises the question "does negative BOLD indicate reduced neural activity in phfMRI?" The BOLD signal arises from an intricate interplay between oxyen metabolism and oxygen delivery by increased CBF. BOLD fMRI may not reliably or accurately reflect neural activity if there was a loss of linear coupling between changes in CBF and neural activity, and/or the presence of non-neural contribution to the BOLD signals.

Our lab recently demonstrated that stimulus-evoked changes in $CMRO_2$ could be reliably measured following electrical somatosensory stimulation in spontaneous breathing rats [2]. *Simultaneous* measurements of BOLD and CBF were made using the continuous arterial spin-labeling technique with multislice echo-planar imaging acquisition. The temporal dynamics of the $CMRO_2$ were calculated pixel-by-pixel using Davis's biophysical BOLD model [3]. $CMRO_2$ changes ranged from 14-43%, depending on stimulation currents. We utilized this technique to investigate the BOLD, CBF and $CMRO_2$ responses following cocaine administration, with the aim to *deconvolve the cocaine-induced neural and non-neural effects.*

METHODS Nine naïve male SD rats (300-375g) were studied. A femoral vein and artery were catheterized for cocaine administration (1mg/kg, ~0.25cc over ~10s, iv) and for continuous monitoring of respiration rate (RR), heart rate (HR), and mean arterial blood pressure (MABP). During imaging studies, rats were anesthetized with 1.1% isoflurane and breathed spontaneously without mechanical ventilation. Blood gases were sampled once during the imaging study. Prior to cocaine administration, hypercapnic (5% CO_2) challenge experiments (repeated twice), were performed for calibration (*i.e.*, to derive the M map) [2,3].

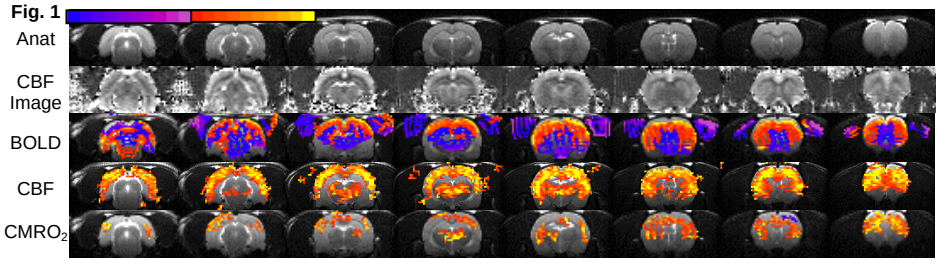
Combined CBF and BOLD measurements were made on a 4.7T Bruker scanner using the continuous arterial spin-labeling technique with single-shot, gradient-echo, echo-planar-imaging (EPI) acquisition. An actively decoupled surface coil (2.3-cm ID) was used for brain imaging and a neck coil for perfusion labeling. MR parameters were: data matrix=64x64, FOV=2.3x2.3cm^2, eight 1.5-mm slices, TE=15ms, and TR=2s. For hypercapnic challenge, 30 pairs of images (2mins) were acquired during baseline and 60 pairs during hypercapnic challenge. For cocaine administration, 4 mins were acquired during baseline, cocaine was administered and an additional ~11 mins of data were acquired (continuous acquisition of 15 mins). High-resolution anatomical images (128x128, RARE) were also acquired.

BOLD images were derived from the control data set of the CBF measurements. T-test was performed between 4 mins baseline and ~4 mins stimulation (starting 30 s after injection) to derive BOLD and CBF percent-change maps. $CMRO_2$ calculation used the biophysical BOLD model of Davis *et al.* [3]. $CMRO_2$, CBF and BOLD signals are related by $\Delta BOLD/BOLD_o = M\{ 1-(CMRO_2/CMRO_{2|o})^{\beta} (CBF/CBF_o)^{\alpha-\beta} \}$, where parameters with subscript zero indicate baseline values. M maps were calculated from the hypercapnic data by setting $CMRO_2/CMRO_{2|0}$ to one since mild hypercapnia does not alter $CMRO_2$ (8). β of 1.5 [3] and α of 0.38 [4] were used. ROI analysis without activation-map mask was performed on the sensory cortex, thalamus, striatum, prefrontal cortex (PFC), nucleus accumbens (NA), substantia nigra (SN), and ventral tegmental area (VTA). Caution must be exercised when interpreting signals in SN and VTA due to susceptibility and partial-volume effect.

RESULTS & DISCUSSIONS MABP increased from a baseline of 113±14 mmHg (mean±SD) to 137±33 mmHg (lasted for 13±3s, P<0.05 relative to baseline) during injection and remain elevated 1-2 min after injection (119±15 mmHg, P<0.05). Respiration rate increased from a baseline of 81±7 bpm to 89±8 bpm (P<0.05) during injection and further increased to 103±16 bpm (P<0.05) 1-2 min after injection. Heart rate dipped slightly from a baseline of 405±49 bpm to 394±39 bpm (P=0.13) during injection and increased slightly to 419±42 bpm (P<0.05) 1-2 mins after injection. The extent to which these physiological effects have on BOLD is unknown.

Figure 1 shows representative anatomical images, CBF images, BOLD, CBF and $CMRO_2$ activation maps from one rat (red-yellow bar: BOLD=1-10%, CBF=50-200%, $CMRO_2$=30-150%. Blue-purple bar: the same except negative). Substantial negative BOLD pixels were detected in the central and ventral part of the brain as well as the temporal muscles outside the brain, consistent with a previous study [1]. In marked contrast, only positive changes (with essentially no negative changes) in CBF and $CMRO_2$ were observed. Group-average percent changes from different brain regions are summaried in **Table 1**. The BOLD responses showed large uncertainty (especially in the PFC, NA and VTA) due to both negative and positive BOLD responses observed cross rats. In contrast, ΔCBF was consistently positive and the *relative* uncertainty was small (compared to that of BOLD). ΔCBF was the highest in the cortex followed by the prefrontal cortex, consistent with cocaine-induced changes in CBV measured using MION contrast agent [2] and CBF measured using autoradiography [5]. $\Delta CMRO_2$ was also consistently positive and the *relative* uncertainty was also small. The largest $\Delta CMRO_2$ was in the prefrontal cortex and smallest $\Delta CMRO_2$ in the cortex although the latter showed the highest ΔCBF.

Fig. 1



% ± SEM	BOLD	CBF	$CMRO_2$
Sensory cortex	6.3±1.2	148±20	28±14
Thalamus	4.6±1.6	90±17	50±17
Striatum	1.7±0.8	67±13	33±13
PFC	2.6±1.9	117±26	98±26
NA	-0.05±1.5	66±17	49±20
SN	2.9±3.1	81±7	30±18
VTA	0.08±3.4	79±12	53±37

CONCLUSIONS The current PET imaging technique for measuring $CMRO_2$ has relatively poor spatiotemporal resolution and is arduous. MRI-derived $\Delta CMRO_2$ offers a unique potential because it is relatively straightforward and can be done on a single subject in a single settting. This preliminary study demonstrated the simultaneous measurements of cocaine-induced BOLD, CBF and $CMRO_2$ changes on a pixel-by-pixel basis. *Dynamic* $CMRO_2$ imaging on a pixel-by-pixel basis is possible and had been demonstrated [2,3]. Cocaine induced substantial and heterogeneous negative and positive BOLD responses. However, ΔCBF and $\Delta CMRO_2$ were almost always positive, suggesting that the BOLD techniques may not reliably and accurately reflect neural activty in cocaine phfMRI due to the presence of non-neural contribution to the BOLD signals and/or loss of linear coupling of BOLD and neural activity. It should be noted that $\Delta CMRO_2$ reflects changes in oxidative metabolism; substantial non-oxidative metabolism could exist in cocaine stimulation and can be evaluated by combined MRI and 2DG studies. Nonetheless, imaging oxygen consumption has the potential to *deconvolve the neural and non-neural component of cocaine-induced stimulation.*

REFERENCES [1] Luo et al, MRM 2003, 49:264. [2] Liu et al. 2003, submitted. [3] Davis et al. PNAS 1998, 95:1834. [4] Grubb et al. 1974, 5:630. [5] Stein & Fuller, Brain Res 1993, 626:117l. J Pharm Exp Therap 1992, 262:327.