Different Microcirculatory Mechanism Governed by Hypercapnia or Cocaine Challenges: implications on CMRO2 mapping on Drug Studies

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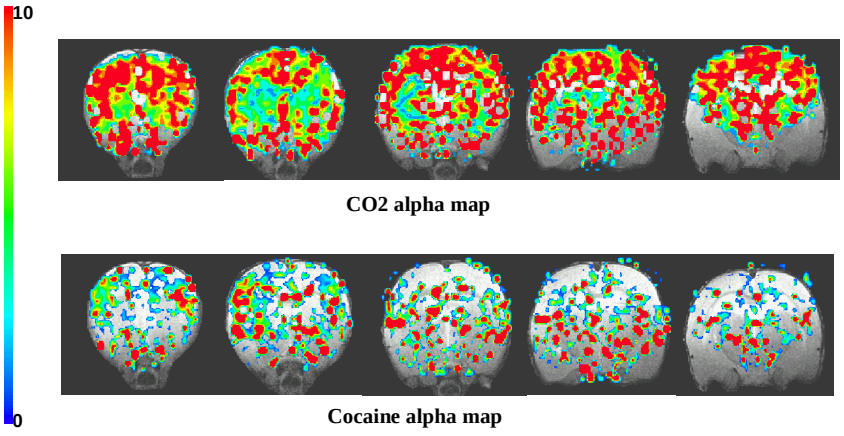
Introduction. fMRI $CMRO_2$ mapping on cognitive functional tasks through the BOLD biophysical model and a hypercapnia calibration procedure has been proposed under a critical assumption that there is no change in $CMRO_2$ under hypercapnia but share the same cerebral vasculature modulation mechanism [1]. Compare to the BOLD signals, $CMRO_2$ is a much simpler and a more straightforward biomarker for changes in brain activity [2]. It's particularly important for pharmacological MRI (eg. drug mechanism studies) where the physiological baseline could be markedly perturbed [3]. Using multi-modal imaging that includes $CMRO_2$ would be a great asset in drug development and research. However, some concerns have been raised regarding the use of hypercapnia for calibrating some of the model-based $CMRO_2$ calculations on neural functions, since vasodilatation induced by hypercapnia appears to differ significantly from that generated by neuronal stimulation with respect to the type and size of the vessels that are dilated [4]. More importantly, it remains unclear whether the $CMRO_2$ fMRI is valid for mapping psychoactive drug effects using hypercapnia caliberations, because psychoactive substances often have complicated effects not only on neuronal function but also on cerebral vasculature, eg. cocaine which elevates dopamine, serotonin and norepinephrine levels. It is known that each of these chemicals can affect cerebral vascular tone. To address whether hypercapnia is a valid calibration procedure for $CMRO_2$ mappings, the present fMRI study was designed to directly measure CBF and CBV under hypercapnia challenge and cocaine infusion in the same animal and assess their relationship. Alpha values in Grubb power law which link CBF and CBV relationship [5] were calculated and compared on a pixel by pixel basis under two different challenges. We tested the hypothesis that hypecapnia and cocaine affect different microcirculatory mechanisms.

Materials and Methods. *Animal Preparation:* Five male Sprague-Dawley rats (250-300 g) were used in the hypercapnia and cocaine challenges. Rats were artificially ventilated with room air under urethane anesthesia (1.2g/kg). Body temperature was maintained at 37 ^{o}C. The right femoral vein was cannulated (PE-50) for MION and cocaine delivery. *Hypercapnia challenge:* all rats underwent hypercapnia challenges with a CO_2 concentration of 5% during CBF and CBV experiments. Each hypercapnia paradigm included two repeated twice 5% CO_2 challenges: with 10 minute break between repeats. *Cocaine challenge*: all rats underwent same cocaine dose (1mg/kg) infusions i.v. in CBF and CBV experiments respectively. Drug was administered 2 min into each 20 min fMRI scan with a inter period of at least 90 min apart from CBF and CBV cocaine studies. *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. 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. *Data analysis:* For each rat, after CBV time courses were calculated based on pre- and post-MION baseline signal intensities, voxel-wise cross-correlation analysis were performed to calculate CO_2 induced signal changes during CBF and CBV experiments using the hypercapnia boxcar reference. A non-linear Beta model was employed to assess cocaine induced CBF and CBV changes. The percentage of CBF and CBV signal changes under both challenges were calculated using AFNI software package. A scatter plot describing the ΔCBF and ΔCBV relationship from ten ROIs under both hypercapnia and cocaine challenges was plotted. Ten ROIs were defined from the five slices (interaural 12.20 mm - 6.2 mm): morter cortex, somatosensory cortex, cingulate gyrus, caudate putamen, nucleus accumbens, hippocampus, corpus callosum, thalamus, hypothalamus and olfactory tubercle. Grubb's formula are shown in equation 1 and its 1st order approximation of the Taylor series expansion in equation 2 which describe a linear relationship between ΔCBF and ΔCBV with the ratio of alpha.

$$\frac{CBF}{CBF_0} = \left(\frac{CBV}{CBV_0}\right)^{\alpha} \quad \text{… Eq.1} \qquad \frac{\Delta CBF}{CBF_0} = \alpha \frac{\Delta CBV}{CBV_0} \quad \text{… Eq.2}$$

Results. A significant difference in the global alpha values were found between CO_2 (α=4.71) and cocaine challenges (α=3.73) (Fig.1). Distribution plots of alpha values linking CBF and CBV are shown in Fig.2.



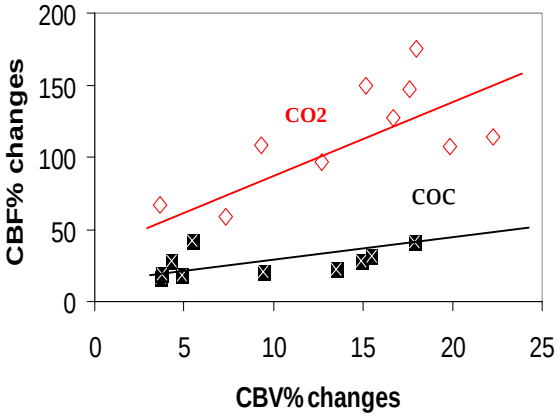


Fig.1 Alpha value maps which link CBF and CBV under hypercapnia and cocaine infusion Fig.2 A scatter plot of CBF v.s. CBV percentage changes from 10 ROIs

Discussion. The issues of validity for drug related $CMRO_2$ mapping using hypercapnia calibration were investigated by comparing CO_2 and cocaine induced hemodynamic changes in the same rat brain. A significantly different distribution of alpha values was found between CO_2 challenge and cocaine infusion (Fig.1). A whole-brain smaller alpha value was found under cocaine challenge. The trend was stronger in frontal and parietal cortexes which might reflects of cerebral vessel constriction under cocaine infusion. Our data suggested that the CBF-CBV relation is different under CO_2 and cocaine challenge. Two different microcirculatory modulation mechanisms might be involved in under hypercapnia and drug stimulus. Although it is not completely clear how CO_2 modulates cerebral vessel, a pH change has long been proposed as one of the most important mechanisms of the hypercapnia induced vessel dilations in addition to its direct action on vessel wall. While CO_2 induced hemodynamic changes are relatively well understood, little is known about cocaine's hemodynamic effects and how these are affecting coupling of blood flow to neuronal activity. It is still unclear whether fMRI detected cocaine induced hemodynamic changes are due primarily to drug's effects on cerebral vessels as well as neuronal or secondary perturbations. Cautions need to be exercised when acquiring fMRI $CMRO_2$ mapping on drug effects through hypercapnia calibration. An alternative calibration method need to be developed which is compatible with drug induced hemodynamic perturbations.

References. [1] Luo F, *et al*. Proc 11th ISMRM 2003; p122. [2] Wu GH, *et al*. MRM 2002; 48 :987-993. [3] Brown GG, *et al*. JCBFM 2003 ; 23 :829-837. [4] Chen W, *et al*. MRM 2001; 45:349-355. [5] Grubb RL, *et al*. Stroke1974; 5:630-639.