Sustained Negative BOLD, CBF, CBV, and CMRO2 fMRI responses to the noxious stimuli in the rat striatum at 11.7T

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INTRODUCTION The striatum receives numerous afferent inputs from other brain structures and involves in various aspects of pain processing [1]. We recently reported that noxious forepaw electrical stimulation increases neuronal spike activity but, surprisingly, decreases CBV fMRI in the striatum [2]. The goal of the present study was to investigate this apparent discrepancy by using BOLD, CBF, CBV, and $CMRO_2$ fMRI on the same animals at 11.7T. BOLD fMRI was used to provide a combined hemodynamic and metabolic index, whereas continuous arterial spin-labeling (CASL) and MION were used to measure CBF and CBV, respectively. Davis's biophysical BOLD model was used to estimate $CMRO_2$ [3]. Multparametric fMRI is expected to shed light on the neurovascular coupling or uncoupling among these hemodynamic/metabolic parameters in the striatum.

METHODS Three rats were anesthetized with α-chloralose (60 mg/kg first dose, 25 mg/kg/hr, i.v.), mechanically ventilated, paralyzed with pancuronium bromide (3 mg/kg first dose, 1 mg/kg/hr, i.v.). Hypercapnic challenges were used for $CMRO_2$ calculation. Forepaw stimulation was applied unilaterally using 10-mA electrical stimulation (3-Hz, 10-ms pulse) [2]. Stimulation paradigm was OFF-ON-OFF-ON-OFF where OFF = 2 mins and ON = 1 min. Two to ten repeated trials were made on each animal. MRI studies were performed on a Bruker 11.7-Tesla/16-cm scanner and a 77G/cm B-GA9S gradient. Rats were placed in a head holder consisting of ear and tooth bars. A custom-made surface coil was placed on the rat head. BOLD and CBF were measured using the CASL technique. After that, MION was administered (30 mg/kg, i.v.) for CBV-weighted fMRI. Images were acquired using single-shot gradient echo EPI. The CASL MRI parameters were: TR = 3000 ms, TE = 10.5 ms, labeling duration = 2.9 sec, matrix size = 64x64 (zero-filled to 128x128), FOV = 2.24x2.24 cm, slice thickness = 1.5 mm, and bandwidth = 300 kHz. The parameters were essentially identical for MION-CBV MRI, except TR = 1500 ms. The nominal in-plane resolution was 175×175×1500 μm. BOLD, CBF, CBV, and $CMRO_2$ fMRI analysis was performed using Matlab and custom-built image processing interface [2,4]. Stimulus-evoked % changes of the BOLD, CBF, CBV, and $CMRO_2$ were tabulated for the cortex and striatum in both hemispheres. Error bars were SEM.

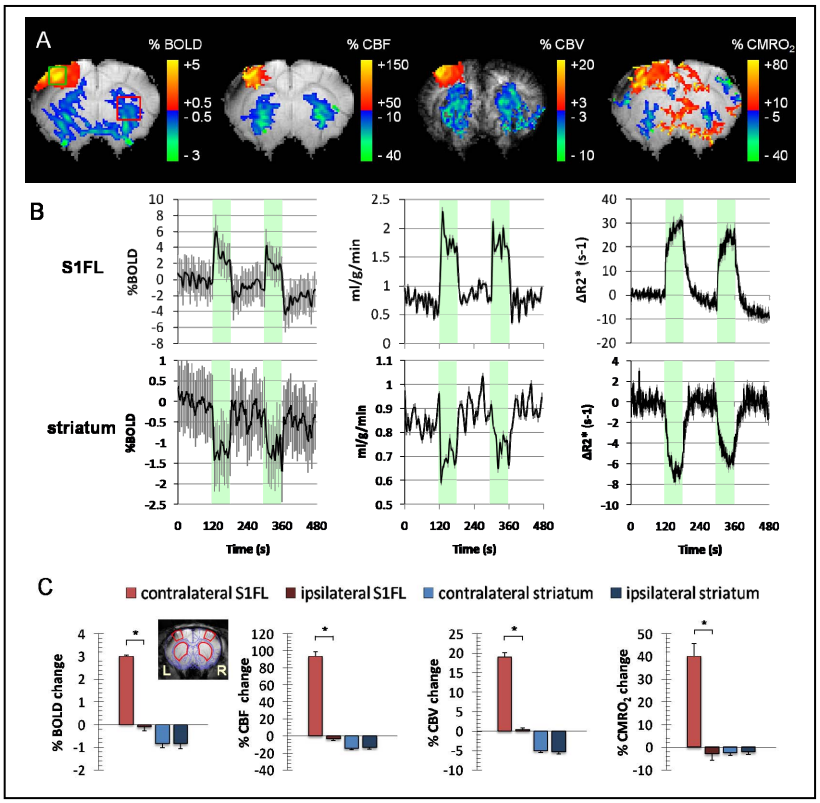
RESULTS Increases of BOLD, CBF, CBV, and $CMRO_2$ were predominantly localized in the contralateral primary somatosensory cortex of the forelimb (S1FL), whereas decreases of all four fMRI signals were found in bilateral striatum (**Fig A**, one animal). **Fig B** shows the signal time courses of the contralateral S1FL and ipsilateral striatum from the ROIs shown in Fig A. The color-shaded regions indicate stimulus ON epochs. In the S1FL, an initial overshoot after stimulus onset was observed in BOLD and CBF, but not in CBV, while poststimulus undershoot was observed in BOLD and CBV, but not in CBF. Compared with S1FL, no apparent onset overshoot or poststimulus undershoot was observed in the striatum. **Fig C** shows the group-averaged BOLD, CBF, CBV, and $CMRO_2$ changes in the S1FL and the striatum of both hemispheres. The ROIs (inset) were defined via the anatomy to avoid bias to a particular activation map (L: contralateral, R: ipsilateral). Significant ipsilateral and contralateral difference was found in the S1FL (P<0.05), but not in the striatum in all four fMRI modalities.

The S1FL:stratium ratios appeared similar for BOLD, CBF, and CBV fMRI signal changes. Although CMRO2 estimates were noisy in general due to propagation of errors, the magnitude S1FL:stratium ratio appeared to be larger for $CMRO_2$ change than the other fMRI signal changes (Fig. C).

DISCUSSION Peripheral noxious stimulus evoked sustained negative BOLD, CBF, CBV, and $CMRO_2$ responses in the striatum bilaterally but positive responses in the S1FL contralaterally to the noxious forepaw stimulation.

Noxious forepaw stimulation has been reported to increase spike activity in the striatum, together with vasoconstriction [2]. Moreover, the magnitude of stimulus-evoked striatal CBV responses can be reduced by intravenous injection of a dopamine D_2/D_3 receptor antagonist [2] or lesion of dopamine neuron in the substantia nigra [5]. However, the present study showed a small decrease (but not increase) in striatal oxygen consumption during noxious forepaw stimulation. There are at least two possible explanations for the uncoupling between spike activity and $CMRO_2$: 1) the biophysical BOLD model [3] might be invalid in this particular case, and 2) spike activity and $CMRO_2$ measured different aspects of neuronal responses and thus increased spike activity without significant changes in $CMRO_2$, as observed, is possible. Further studies are needed to clarify this apparent discrepancy.

In conclusion, this study established an animal model with robust cortical and subcortical responses for multimodal fMRI studies. This protocol may prove useful to study neurovascular uncoupling and dysfunctions of the striatum in neurological disorders, such as Parkinson's, Huntington's disease, and stroke.



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