Striatal fMRI of Focal Ischemic Rat Brain

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INTRODUCTION Stroke is fourth leading cause of death and long-term disability [1]. Damages to the striatum – which is involved in sensory discrimination, initiation of motor reaction, among others – are known to have severe behavioral impairment [2-4]. fMRI in animal models of stroke provides great opportunities to probe tissue functional integrity, predict tissue outcome, and evaluate novel treatments. Unfortunately, in vivo imaging of striatal functional impairment after stroke in animal models remains to be a major challenge due to the lack of non-invasive imaging methodologies. We recently demonstrated that striatal vasoconstriction occurred under noxious forepaw electrical stimulation [5,6]. This unique feature has potential to serve as a novel imaging marker for striatal functional integrity. The present study aimed to longitudinally investigate the striatum function in two groups of stroke rats (20-min middle cerebral artery occlusion (MCAO) and 45-min MCAO) up to 28 days following stroke.

METHODS Adult male Sprague Dawley rats (n = 10, 250–300 g) were used in this study. Ischemia was induced by **MCAO** for **20-min** (n = 5) or **45-min** (n = 5) followed by reperfusion [8]. CBV fMRI was performed under 1.1-1.2% isoflurane anesthesia and mechanical ventilation using MION (30 mg Fe/kg, i.v.). Images were acquired longitudinally on 3 days before stoke surgery (***Control***), and on ***Day 1*** (immediately after surgery), ***Day 7***, and ***Day 28*** on a Bruker 7T Biospec scanner with a surface coil (ID~2cm). fMRI data were acquired with single-shot GE EPI, with spectral width = 300 kHz, TR/TE = 1000/13.8 ms, FOV = 2.56x2.56 cm, slice thickness = 1.5 mm, and matrix = 96x96. Striatal and cortical responses were evoked by bilateral forepaw electrical stimuli at 10 mA to generate striatal vasoconstriction [5,6], 12 Hz to provide better hemodynamic response under isoflurane anesthesia [7], and 3 ms pulse duration which has been optimized in our pilot studies [8]. Stimulation paradigm was 60s OFF, 30s ON, and 60s OFF. Five to ten repeated trials were made and averaged on each fMRI measurement. Data analysis was performed using a custom-built image processing interface [9]. Statistical analysis employed ANOVA followed by Fisher's post-hoc test to compare the responses over time and paired t-test to compare the responses between two hemispheres. Significant level was set at P<0.05. Error bars are SEM.

RESULT & DISCUSSION This study demonstrated a novel fMRI application to investigate the striatal functional integrity after 20 or 45 min transient focal ischemia. Striatal dysfunction was successfully depicted after stroke. 20-min MCAO showed better functional recovery compared with 45-min MCAO as expected. In the 20-min MCAO group, the striatal and cortical responses at the lesioned hemisphere were suppressed on Day 1 and showed apparent recovery on Day7 (**Fig. 1 & Fig. 3A**). Interestingly, the lesioned striatum showed hypersensitivity on Day 7. In the 45-min MCAO group, the striatal and cortical responses at the lesioned hemisphere were completely diminished on Day 1. The lesioned cortex showed partial recovery on Day 28, whereas the lesioned striatum remained silence (**Fig. 2 & Fig. 3B**). The striatum involves in various aspects of brain signaling. Stroke in the striatum has been implicated in many subsequent neurological disorders, such as Alzheimer's disease [2] and Parkinson's disease [3]. Patients and animals with striatal ischemia are also known to have late-onset cognitive and behavioral impairment [4]. Prior to our studies, there was lack of animal fMRI protocol to evoke the striatal response in stroke rats. Our findings complement the existing MRI procedures in animal models of stroke [10-12] and making it possible to investigate the functional reorganization and treatment efficacy in the striatum of the same animal over time.

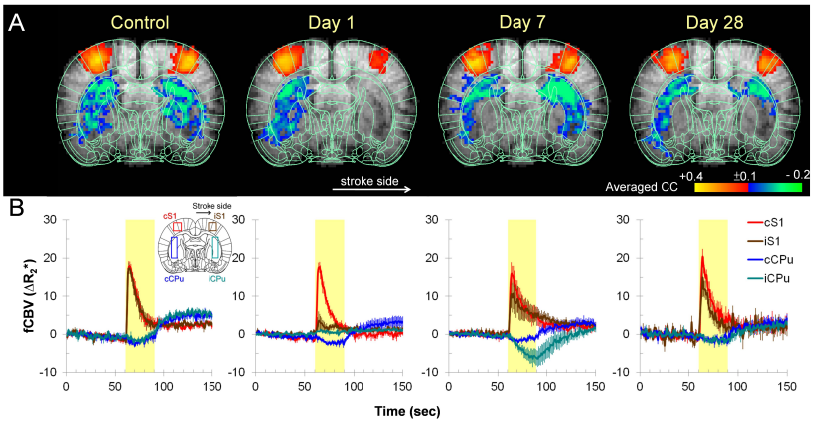

Fig 1. CBV fMRI of **20-min MCAO** (n = 5). **(A)** Averaged CBV fMRI correlation coefficient (CC) maps after co-registration. **(B)** Corresponding averaged CBV fMRI time courses (fCBV unit: s^{-1}). Yellow-shaded area indicates stimulus epoch.

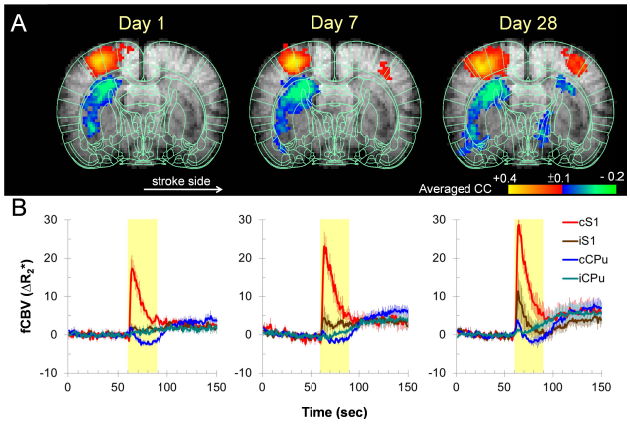

Fig 2. CBV fMRI of **45-min MCAO** (n = 5). **(A)** Averaged CBV fMRI correlation coefficient (CC) maps. **(B)** Corresponding averaged CBV fMRI time courses.

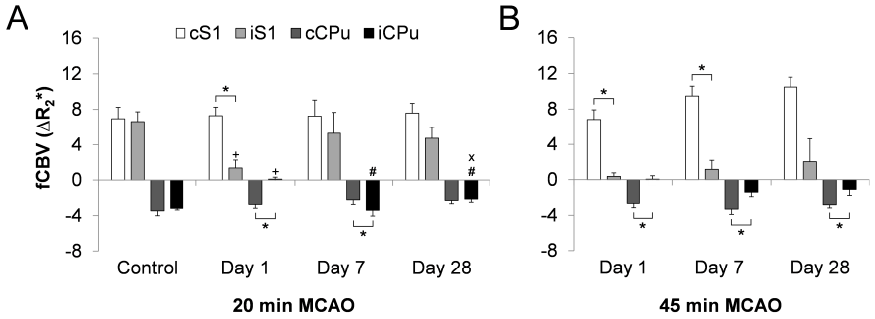

Fig 3. CBV fMRI on Day 1, 7, and 28. **(A)** 20-min MCAO. **(B)** 45-min MCAO. $^{+}$different from Control, $^{\#}$different from Day 1, ^{X}different from Day 7, and *different from contralateral side.

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