Resting state fMRI of acute focal ischemic rat brain

Y-Y. I. Shih[1], H-Y. Wey[1], F. Du[1], S. Huang[1], Q. Shen[1], K. M. Karkar[1], and T. Q. Duong[1]
[1]Research Imaging Institute, University of Texas Health Science Center at San Antonio, San Antonio, TX, United States

INTRODUCTION Spontaneous low frequency BOLD fluctuations (0.01-0.08 Hz) at rest reveal functional connection of the brain without external stimuli [1-3]. This phenomenon, termed resting state fMRI (rsfMRI), persists across species and preserves in unconscious states [2,3]. Perturbed rsfMRI activities have been reported in schizophrenia, depression, Alzheimer's disease, and chronic stroke in humans [4]. rsfMRI overcomes some difficulties associated with evoking stimulation responses from anesthetized animals. With a few exceptions [5] rsfMRI in animal stroke models remains largely unexplored and, to our knowledge, has not been applied to study acute stroke in animal models. It is likely that there are marked differences in rsfMRI signals among different ischemic tissue types during the acute phase that can be used to advantages. The present study aimed to depict rsfMRI time course pattern in acute focal ischemic rat brain. Surprisingly, intermittent BOLD fluctuation (over 10%) was observed specifically in the perfusion-diffusion mismatch area, which may associate with peri-infarct spreading depolarization (PID).

METHODS Four adult male Sprague Dawley rats were anesthetized with 1.0−1.2% isoflurane. Permanent focal brain ischemia of the right hemisphere was induced by intraluminal middle cerebral artery occlusion (MCAO). MRI was performed on a Bruker 7T Biospec with a surface coil (ID~2 cm). rsfMRI was performed by single-shot GE EPI for 15 mins using spectral width = 300 kHz, TR/TE = 3000/25 ms, FOV = 2.56x2.56 cm, slice thickness = 1.5 mm, matrix = 96x96 (zero-filled to 128x128). Continuous arterial spin labeling technique with a separate neck coil for spin labeling was used for CBF measurement, whereas DWI was obtained in 30 directions with 1200 s/mm^2 using spin-echo EPI (TR/TE = 3000/37 ms, Δ = 17.53 ms, δ = 5.6 ms). rsfMRI data were acquired in time series, and corrected for potential drift before additional analysis. Data were processed using Matlab and custom-built image analyzing interface [6]. The seed selection for the rsfMRI data was base on the rat brain atlas. Correlation coefficient maps were computed after band-pass filtering (0.01 – 0.08 Hz).

RESULT & DISCUSSION Bilateral rsfMRI connectivity of the somatosensory cortex is apparent in normal rat (data not shown), but was markedly reduced or abolished in regions with ischemic injury (**Fig.1A**). The rsfMRI temporal patterns of perfusion-diffusion mismatch are distinctly different from that of the ischemic core, both are also distinctly different from normal tissue, indicating rsfMRI is useful to classify tissue states during acute stroke without external stimuli.

rsfMRI detected multiple spontaneous waves in the mismatch region (**Fig. 1B**). During blocks of 15-min acquisition, 2 or 3 waves of 12% BOLD changes were detected with each wave lasting 2-3 mins. They started in the cortex, spread laterally and downward, grew in size, and ended in the striatum (**Fig. 2**). These observations were reproducible in 3 stroke rats although the timing, duration and frequency differed slightly. These waves are consistent with that of spontaneous spreading depolarization in stroke. The duration of the rsfMRI BOLD waves are also in good accordance with those reported in rodents using laser speckle imaging of the PID in cortical surface [7].

PID has been shown to closely correlate with the stroke progression. Previous study has demonstrated a linear relationship between infarct size and number of spontaneous PIDs [8] and it was later shown, critically, that number of PIDs is the determining variable in this relationship [9]. Accumulative evidence has suggested that spreading depolarization (induced by potassium chloride) are associated with marked increases in BOLD and CBF in rats [10,11] and the pattern of PIDs can be used to approach ischemic penumbra [7].

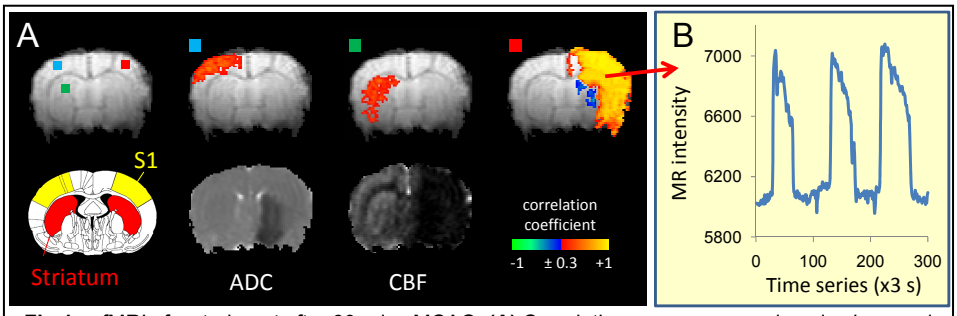

Fig 1. rsfMRI of a stroke rat after 60-mins MCAO. **(A)** Correlation maps were analyzed using seed method, showing abolished bilateral functional connectivity in the cortex and the striatum. Perfusion-diffusion mismatch area showed consistent pattern with high correlation. **(B)** During 15 mins acquisition, there were 3 similar epochs of BOLD waves. Each wave showed above 10% BOLD increases. Although the duration varied slightly, it was on the order of 2-3 mins.

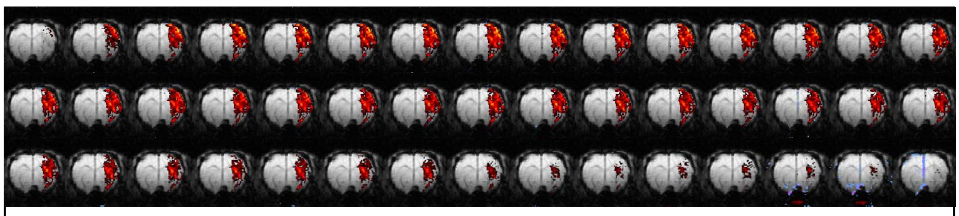

Fig 2. Spatiotemporal progression of an rsfMRI BOLD wave from an animal after 60-mins MCAO. Dynamic subtracted time-series images start from the top left to the bottom right, which started in the cortex, spread downward, grew in size, and ended in the striatum.

CONCLUSION The present study applied a novel rsfMRI approach to depict spontaneous BOLD waves in acute stroke rat for the first time. This method provides new and clinically relevant data on tissue at risk, which may have long-term clinical applications. rsfMRI of PID offers unique advantages over optically based imaging techniques because it is not limited to cortical surface and covers the entire brain. Future studies will investigate different MCAO durations, employ CBF-based rsfMRI and simultaneous rsfMRI and electrophysiology to evaluate the source of spontaneous BOLD waves.

REFERENCE [1] Biswal et al., *MRM* 1995, 34:537. [2] Zhao et al., *Neuroimage* 2008, 39:248. [3] Pawela et al., *MRM* 2008, 59:1021. [4] Greicius, *Curr Opin Neurol* 2008, 21:424. [5] van Meer et al., JCBFM 2010, 30:1707. [6] Shih et al., *J Neurosci Res* 2008, 86:1801. [7] Shin et al., *JCBFM* 2006, 26:1018. [8] Mies et al., Neuroreport 1993, 4:709. [9] Back et al., *JCBFM* 1996, 16:202. [10] Gardner-Medwin et al., *JCBFM* 1994, 14:7. [11] Ayata et al., *JCBFM* 2004, 24:1172.