Simultaneous fMRI/CBV and EEG during spike-wave seizures in WAG/Rij rats

A. M. Mishra[1], D. J. Ellens[2], U. Schridde[1,3], J. E. Motelow[1], M. J. Purcaro[1], F. Hyder[4], and H. Blumenfeld[1,5]

[1]Neurology, Yale University School of Medicine, New Haven, CT, United States, [2]Neurology, Yale University School of Medicine, [3]Physiology of Cognitive Processes, YMPI for Biological Cybernetics, Tübingen, Tübingen, Germany, [4]Diagnostic Radiology, Yale University School of Medicine, New Haven, CT, United States, [5]Neurobiology, Yale University School of Medicine, New Haven, CT, United States

INTRODUCTION: In absence and other generalized seizure disorders, an abnormal electrical activity termed as spike-wave discharges (SWD) is observed by electroencephalograph (EEG). fMRI during SWD in humans and animal absence epilepsy models show both increases and decreases in blood oxygenation level dependent (BOLD) signals **[1-3]**. However the fundamental mechanisms of these changes are poorly understood, and paradoxical effects, such as decreased BOLD with increased neuronal activity can occur in seizures **[4]**. An animal model can provide a detailed understanding of the relationship between fMRI signals and changes in neuronal energy metabolism through multi-modal studies of BOLD and cerebral blood volume (CBV) fMRI. Wistar albino Glaxo rats of Rijswijk (WAG/Rij), an established model of human absence epilepsy, were used to characterize brain regions involved during SWD using multi-modal fMRI and EEG.

METHODS: All experiments were conducted in female WAG/Rij rats (n = 12) at 9.4T. Anesthesia was induced using 1.5% halothane and then switched to fentanyl (40 mg/Kg, IV) and haloperidol (1 mg/Kg, IP). Animals were tracheotomized and artificially ventilated. A femoral artery was cannulated for continuous arterial blood pressure monitoring and blood sampling. Blood gases (pCO_2, pO_2) and pH were monitored periodically and maintained within physiological range by adjusting ventilation and depth of anesthesia if necessary. D-tubocurarine (3 mg/kg, IV) was administered to prevent movement. For CBV fMRI, rats were injected with AMI-227 (12 mg/kg; IV). BOLD and CBV data were obtained using spin-echo EPI with the following parameters: TR = 1000 ms, TE = 25 ms, FOV = 2.5×2.5 cm, slice thickness = 1 mm, image matrix = 64×64. Epochs of 11 images/sec interleaved with 5 sec of EEG recordings were obtained for 15-30 minutes continuously. EEG was acquired simultaneously during fMRI using carbon wires placed laterally on one side of the head between the scalp and the outside surface of the skull. Signals were amplified and filtered (1-100 Hz; 60 Hz notch filter) and digitized at 1 kHz. Digital filtering reduced scanner noise from EEG data. Pairs of baseline ($\mathbf{B_i}$) and SWD activated ($\mathbf{A_i}$) images were selected and analyzed using paired t tests for each slice (Fig. 1).

RESULTS: All activation maps in Figs. 2 and 3 were thresholded at the same statistical value. Increased BOLD signal was found primarily in sensorimotor areas (n = 21), thalamus, and brainstem (n = 18) during SWD (Fig. 2). However there were also BOLD signal decreases in the caudate putamen (n = 19; Fig. 2A) and hippocampus (n = 20; Fig. 2B) during SWD (Fig. 2A). The CBV data corresponded well with BOLD data for signal increases (Fig. 3). Large areas of BOLD signal decreases (e.g., hippocampus and caudate-putamen) were in partial agreement with the CBV decreases, where the areas were slightly smaller.

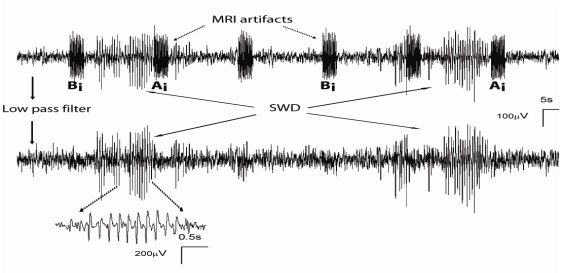

Fig. 1 Baseline ($\mathbf{B_i}$) and SWD activated ($\mathbf{A_i}$) images identified from artifact free EEG data (bottom trace).

DISCUSSION: Regional BOLD increases and decreases during SWD were generally accompanied by CBV increases and decreases in the same areas. Unlike prior work in tonic-clonic seizures, showing decreased BOLD with *increased* CBV, we observed that during spike-wave seizures decreased BOLD signals were associated with *decreased* CBV **[4]**. This may suggest a difference in physiological mechanisms of fMRI decreases in the different seizure types. Further work will be needed to determine if regions of BOLD decreases during SWD represent vascular steal, a primary neuronal mechanism, or a defect in neurovascular coupling. These findings will be important for the interpretation of various fMRI signals in human absence epilepsy.

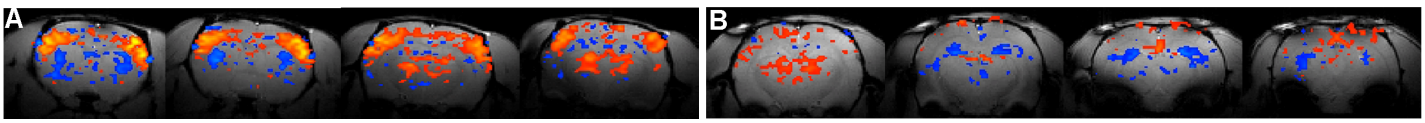

Fig. 2 BOLD signal increases (red) and decreases (blue) during SWD in anterior (A) and posterior (B) regions of the brain.

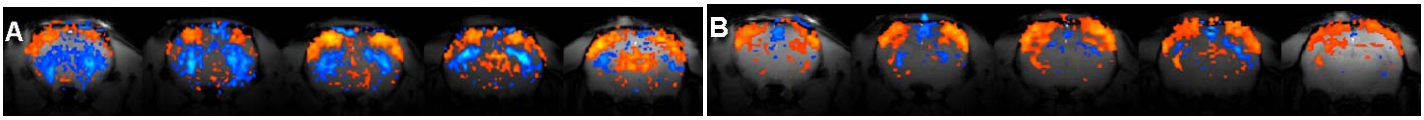

Fig. 3 BOLD (A) and CBV (B) increases (red) and decreases (blue) during SWD. Same slices are shown in A and B (from the same rat).

REFERENCES: **[1]** Berman et. al., (2005) Epilepsia AES abstracts. **[2]** Nersesyan et. al., (2004) J Cereb Blood Flow Metab. 24:589-99. **[3]** Nersesyan et. al., (2004) J Cereb Blood Flow Metab. 24:1057-68. **[4]** Schridde et al., (2007) Cerebral Cortex. (in press).

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