DYNAMIC MULTI-MODAL RECORDINGS OF NEURONAL ACTIVITY, CEREBRAL BLOOD FLOW, AND fMRI DURING RODENT SPIKE-WAVE SEIZURES

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RATIONALE: Under normal conditions, fMRI signals are related to cerebral blood flow (CBF) metabolism and neuronal activity. Absence seizures are a common form of childhood epilepsy, with brief episodes of staring, accompanied by spike-wave discharges (SWD) on electroencephalography (EEG). Prior neuroimaging studies of absence seizures have been contradictory, with some showing increased CBF or metabolism during SWD, and others showing the opposite. This variability may be caused by limited spatio-temporal resolution, and varying measurement conditions. We therefore sought to directly measure neuronal activity and neuroimaging signals at high spatio-temporal resolution during SWD through multi-modal recordings in WAG/Rij rats, an established animal model of human absence seizures. Understanding spatio-temporal relationships between neuronal activity and neuroimaging signals in SWD has significant practical applications for localizing and treating brain regions responsible for seizure generation.

METHODS: *In vivo* fMRI measurements were performed in a 7T or 9.4T horizontal bore spectrometer in WAG/Rij rats during spontaneous SWDs under fentanyl/haloperidol anesthesia and neuromuscular blockade. EEG was recorded simultaneously with carbon filament electrodes to determine the timing of seizures and artifacts removed. fMRI signals were then analyzed by comparing images acquired during seizures to baseline images, and superimposed on high-resolution anatomical images in the coronal plane. We next measured physiological changes in brain regions identified to show fMRI signal changes during SWD, using a custom-built combination probe. The probe was used to simultaneously record CBF using tissue laser Doppler flow (LDF), and extracellular multiunit activity at high time resolution from the same region during SWD and at baseline.

RESULTS: Comparison of ictal and interictal epochs revealed bilateral increases in fMRI signals in focal cortical and subcortical structures during SWD compared to baseline (Fig 1). In 12 WAG/Rij rats studied, we found that fMRI increases were localized mainly to primary somatosensory cortex and to specific thalamic and brainstem nuclei (Figure 1). The occipital cortex was relatively spared. Electrophysiology mapping studies were performed on 35 WAG/Rij rats, demonstrating strong correspondence between fMRI and electrophysiology for regions involved and spared during SWD. Combined LDF and electrophysiology studies were then performed on 12 WAG/Rij rats, and concentrated on the primary somatosensory (S1BF) and primary visual (V1M) cortex (respectively, involved and spared on fMRI). We found that in S1BF, each SWD produced a transient increase in the rate of neuronal firing (ν), and with a delay of 2-3 seconds, a transient increase in CBF (Fig 2). V1M showed no significant change in ν or CBF during SWD.

CONCLUSIONS: By performing multi-modal high spatio-temporal measurements in the same system we found that fMRI signals, CBF and neuronal firing all increased in regions intensely involved in SWD and did not change in regions spared by seizures. fMRI and CBF changes closely corresponded in space and time to changes in neuronal activity in this system. These findings demonstrate that in this form of epilepsy fMRI can be used to accurately map regional changes in brain function during seizures, which may help the development of improved therapies targeted at these regions.

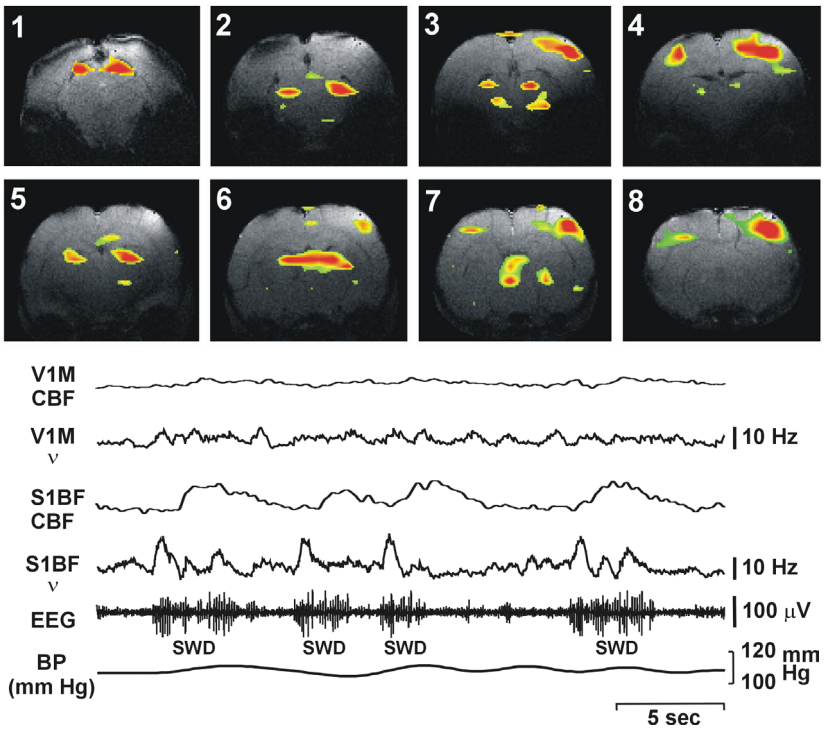

Figure 1 fMRI signal increases during SWD in a WAG/Rij rat under fentanyl–haloperidol anesthesia. Spin echo fMRI data was acquired with simultaneous EEG recordings to determine timing of SWD episodes. t-maps were calculated from images acquired during 23 SWD episodes compared to baseline, and were overlaid onto corresponding high-resolution anatomic images. Eight coronal slices were acquired from back to front (numbered 1–8) at 1-mm intervals, with the first slice at approximately −7.04 and the last slice at +0.40 mm relative to bregma (Paxinos and Watson, 1998). Bilateral and relatively symmetrical increases in BOLD signal were present mostly in frontoparietal (somatosensory) cortex, thalamus, and brainstem nuclei, whereas temporal and occipital regions did not show significant changes.

Figure 2 Dynamic recordings of CBF and neuronal activity during SWD. Changes in CBF and neuronal activity were recorded by combined Doppler flowmetry and extracellular multiunit recordings obtained simultaneously during multiple episodes of SWD, along with EEG and arterial blood pressure (BP) monitoring in a WAG/Rij rat under fentanyl/haloperidol anesthesia. Spontaneous SWD induce parallel increases in CBF and neuronal firing rate (ν), in barrel cortex (S1BF), and no or very small increases in primary visual cortex (V1M). CBF variations are independent of arterial blood pressure fluctuations.