Kainic acid induced seizures spread from the cortex to the hippocampus after traumatic brain injury

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Introduction

We have previously shown that kainic acid (KA) induced seizures cause positive BOLD responses under medetomidine sedation in the rat hippocampus [1]. Here we extend this approach to whole brain coverage BOLD fMRI combined to simultaneous hippocampal local field potential (LFP) recordings. We apply this methodology to define the ictogenic region of kainic acid induced seizures at 3 months after traumatic brain injury (TBI), when most of the animals are still undergoing epileptogenesis.

Materials and Methods

Adult male Wistar rats (n=15) were used. Severe TBI was induced in 10 animals using the lateral fluid-percussion injury (FPI) [2]. Five sham-operated rats served as controls. Four rats died after induction of TBI leaving 11 animals (470 ± 39 g) for fMRI studies that were performed 3 months post-TBI. Femoral artery was cannulated for monitoring of blood gases and pH. Femoral vein was cannulated for medetomidine and pancuronium bromide (2 mg/kg/h) administration under isoflurane anesthesia. For simultaneous LFP and fMRI measurements, a tungsten wire electrode was inserted into the contralateral hippocampus (AP 3.6 mm and ML 2.5 mm from bregma, -2.5 mm from the cortical surface). Animals were tracheotomized and artificially ventilated using a mechanical ventilator. After surgery, isoflurane anesthesia was discontinued and a bolus injection of medetomidine was given (bolus 0.05 mg/kg, i.v.) followed by a continuous subcutaneous infusion (0.1 mg/kg/h, i.v.) 5 min later. The LFP signal was measured using a BrainAmp MR plus magnet compatible system and low pass filtered at 1000 Hz (sampling rate 5000 Hz). The MRI experiments were performed in a 9.4 T/31 cm horizontal magnet interfaced with a Varian DirectDrive console. Functional MRI data were acquired using a s single-shot spin-echo echo planar imaging (SE-EPI) (TR 4 s, TE 40 ms, 15 slices, thickness 1.5 mm, image matrix of 64 x 64, and FOV of 2.5 x 2.5 cm^2). Simultaneous LFP and fMRI measurements were performed consisting of 500 images of baseline. Kainic acid was injected in a dose of 8 mg/kg (i.p.) and image acquisition was continued for 1500 images. Anatomical images were collected with fast spin-echo (FSE) sequence (TR = 5.4 s, eff TE = 48 ms, echo spacing = 16 ms, echo train length = 8, FOV = 5 x 5 cm^2, image matrix of 512 × 512, resolution 98 x 98 μm^2, 40 slices, thickness 0.75 mm). All data analyses were conducted using Matlab. The fMRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) along with in-house made Matlab code. LFP signal was analyzed using in-house made Matlab routines.

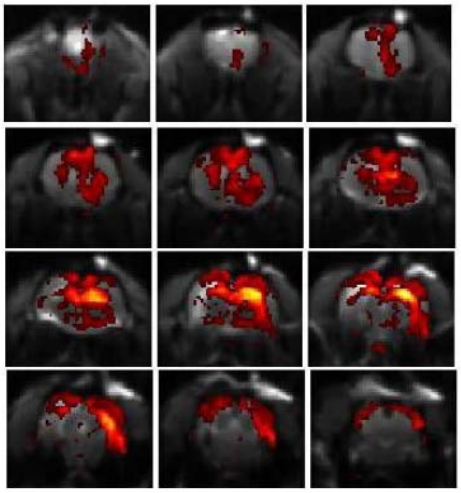

Figure 1. Images from a representative rat demonstrating the distribution of kainic acid induced BOLD activation.

Results

Kainic acid triggered recurrent epileptic seizures in all rats, which could be detected in BOLD fMRI measurements (Figure 1) as well as in hippocampal LFP recordings. In all animals, the first epileptic seizure elicited a BOLD response that was first detected in the cortex and later in the hippocampus (Figure 2). Three of 5 control and 5 of 6 TBI animals developed status epilepticus during the 90 minute follow up period. During a prolonged seizure (status epilepticus) the BOLD response was only slightly elevated in the cortex (Figure 2, from 3200-4000 s).

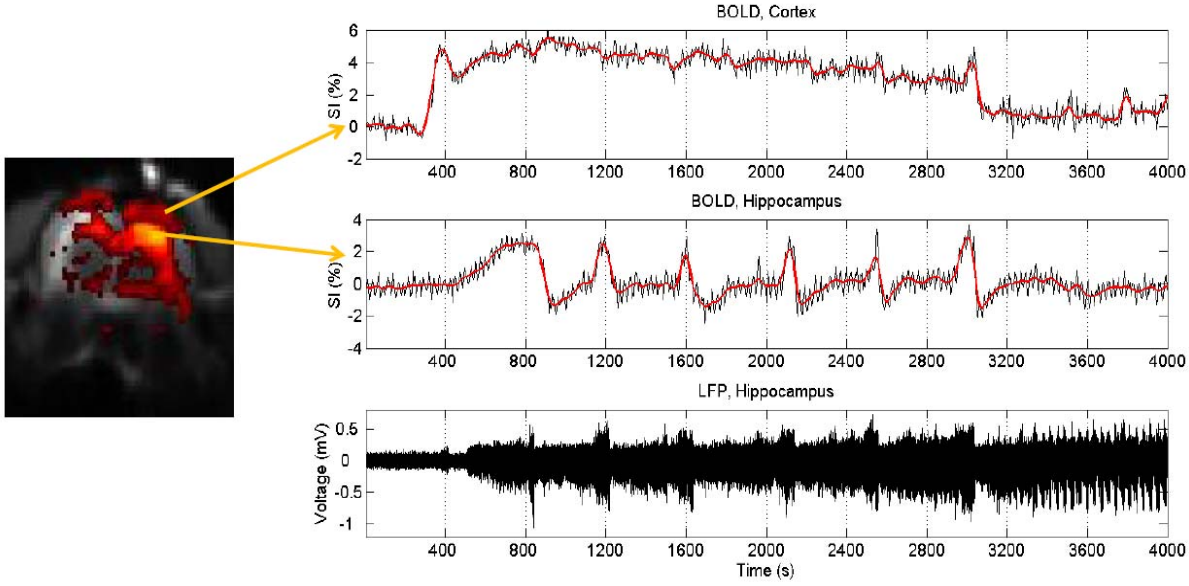

Figure 2. Kainic acid induced BOLD activation map from one slice in one TBI rat. The corresponding BOLD time series form contralateral cortex and hippocampus along with local field potential (LFP) signal from hippocampus. KA was administrated at zero time point.

Discussion

Seizures induced by kainic acid in animals undergoing epileptogenesis after lateral FPI-induced TBI did not originate in the hippocampus as expected but primarily activated the perilesional cortex. Our data indicate that multislice functional imaging with simultaneous electrophysiological recording has a potential to reveal the ictogenic region after TBI. This has great practical implications for guiding, for example, the molecular analysis of ictogenic region in the brain undergoing epileptogenesis after TBI.

References: [1] Airaksinen et al., ISMRM, Stockholm, Sweden, 2010. [2] Kharatishvili et al, Neuroscience, 140(2):685-97,2006.