# Biomarkers of epileptogenesis in temporal lobe epilepsy: Quantitative MRI and EEG

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## Introduction:

Temporal lobe epilepsy (TLE) is the most common medically intractable focal epilepsy. Following an initial brain injury, dynamic changes in brain structure, function and metabolism are thought lead to the development of spontaneous recurrent seizures, a process known as epileptogenesis. A better understanding of mechanisms of epileptogenesis and their biomarkers, their evolution and correlation with electrophysiological characteristics is key to the development of treatment strategies to prevent the development of epilepsy. This study combined quantitative ultra high-field multi-echo T2 and diffusion weighted MR with electroencephalography (EEG) to characterize epileptogenesis-related changes in TLE mouse model.

## Methods:

We studied Swiss CD-1 mice with status epilepticus (SE, n=16) following injection of pilocarpine and control animals (CN, n=10). Mice were randomized into two groups with different time points of MR imaging. Group I was imaged at 3h, 7, 28, 49 days and group II was imaged at 1, 2, 14, 35 days after injection. MR data were acquired on Bruker 16.4T widebore vertical NMR scanner (Karlsruhe, Germany). The 2D spin echo T2 images (in plane 0.06 × 0.06 mm, slice thickness 1mm without gap) were acquired with multi echoes of 14, 28, 42, 56, 70, and 84 ms. The diffusion weighted images (in plane 0.12 × 0.12 mm, slice thickness 1 mm without gap) were acquired in one diffusion direction with four gradient values of 0, 400, 800, and 1200 s/mm$^2$. EEG data were acquired with a Compumedics 32-channel E series & ProFusion system. Nine to ten weeks post-SE, 2 epidural electrodes were implanted over parietal cortex bilaterally in 7 animals. Continuous 24/7 video-EEG monitoring was performed for 3 weeks to detect and quantify ictal (seizures) and interictal (spikes) events. Spike frequency was calculated for a 96-hour interval at 12 weeks post-SE. The T2 time and apparent diffusion coefficient (ADC) were calculated. Skull stripping for these images was performed using a knowledge-guided active contour method. T1 images were then registered to an averaged mouse brain template using normalized mutual information and nonlinear B-spline registrations. The resultant transformation matrices were used to normalize the T2 and ADC. Registered images were smoothed with a 1mm FWHM Gaussian kernel. Statistical parametric mapping with SPM8 was used to compare ADC and T2 maps between the SE and control groups. The relative T2 and ADC changes of SE to CN animals were correlated voxel-wise with EEG results using SPM8 and spike frequency as the regressor. Because of the small number of animals, a threshold of P<0.001 uncorrected for multiple comparisons was used.

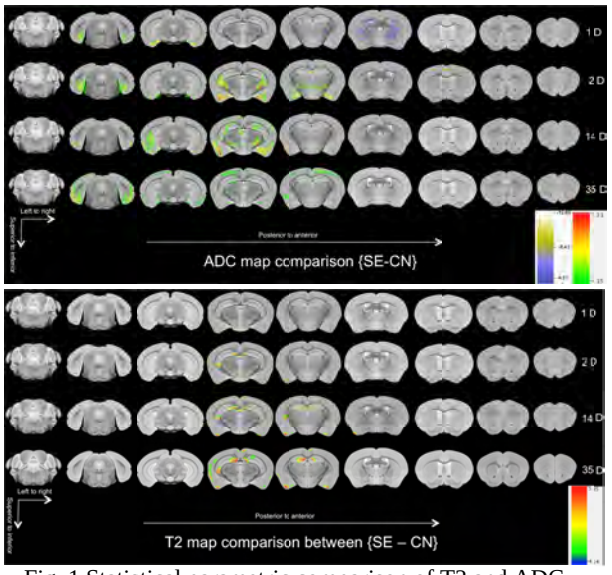


Fig. 1 Statistical parametric comparison of T2 and ADC

## Results:

In the SE group, ADC was reduced in the hippocampus (HC) and thalamus at day 1 and subsequently recovered. Both ADC and T2 (Fig.1) were elevated in the parahippocampal cortex (PHC) at later time points and in the HC and amygdala (AMG) at both early and late time points (FWE corrected $\alpha < 0.05$). Significant correlation between ADC changes and EEG spike frequency was found in HC and thalamus at day 7 (unadjusted $P < 0.001$).

## Discussion:

Dynamic changes were observed in HC, AMG, and PHC following SE at different times post-SE. This temporal pattern most likely reflects the evolution of pathological changes underlying the development of TLE from neuronal swelling and cytotoxic edema to gliosis. The MR changes in HC and thalamus at day 7 was significantly correlated with spike frequency on EEG. This finding suggests a critical time point during the latent period of epilepsy development, a finding that requires replication in a larger cohort of animals.

## Conclusion:

Specific progressive structural changes were observed in mice that exhibited spontaneous chronic seizures following SE. This is the first study showing a critical time point during the latent period of epilepsy development.

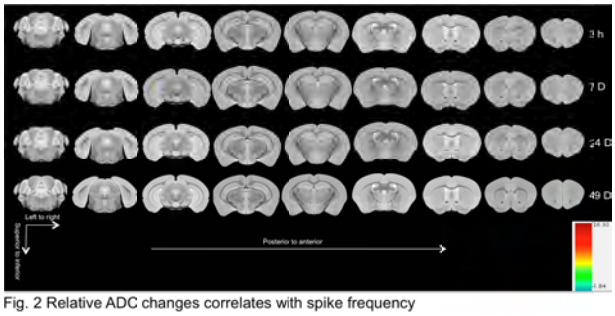


Fig. 2 Relative ADC changes correlates with spike frequency