Application of GluCEST MRI in Detection of Epileptogenic Foci in Temporal Lobe Epilepsy

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Introduction: Epilepsy is a common neurologic disorder that affects ~65 million people worldwide of whom roughly one third are refractory to anti-seizure medications[1]. For the ~1/3 of localization related epilepsy (LRE) patients with no lesion identified on MRI[2], rates of seizure freedom after surgery are lower with a 2-3 times greater chance of good surgical outcome if a MRI or histopathological lesion is present[3]. Glutamate is the most common excitatory neurotransmitter in the central nervous system[4], and animal and human data support a role of glutamate in seizures with increases in both intracellular and extracellular glutamate at the seizure focus[5]. Prior human studies have measured glutamate via microdialysis and in postmortem tissue with increased glutamate in the seizure focus[6] . Impaired glutamate-glutamine cycling with downregulation of glutamine synthetase in astrocytes resulting in slowed glutamate clearance most marked in CA1 and CA3 of the hippocampus is a proposed underlying mechanism[7]. The *rationale* for this work is that glutamate is widely thought to be central to epileptogenesis, and Glutamate Chemical Exchange Saturation Transfer (GluCEST) will enable high-resolution imaging of this crucial neurotransmitter in epileptogenesis. The *objective of this work* is to apply a novel noninvasive functional imaging technique, GluCEST to map epileptic networks[8,9] in patients with established epilepsy in comparison to healthy control subjects. The use of 7.0T GluCEST MRI to map glutamate may yield improved identification of seizure networks and improved outcomes after surgical or other epilepsy treatments.

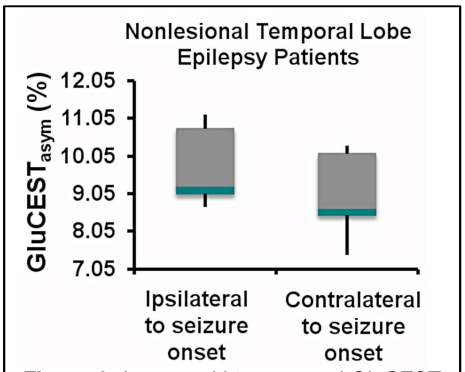

Figure 1: Increased hippocampal GluCEST ipsilateral to seizure onset (p=0.004). All 5 patients lateralized to hippocampus of seizure onset.

Methods: All of the human studies were conducted under an approved Institutional Review Board protocol of the University of Pennsylvania. GluCEST MRI was acquired on 7.0T Siemens scanner with a 32-channel phased-array head coil from 11 healthy controls (HC) and 5 individuals suffering from temporal lobe epilepsy (TLE)[8,11-12]. The study protocol consisted of the following steps: a localizer, T1-weighted anatomical 3D magnetization prepared rapid gradient echo (MPRAGE) images of whole brain (176 axial slices, TR = 2800 ms, TE = 4.4 ms, TI = 1500 ms, α = 7°, 0.8x0.8x0.8 mm^3 resolution), T_2-weighted imaging (224 coronal slices, TR = 3000 ms, TE = 388 ms, 0.4x0.4x1.0 mm^3 resolution) followed by the acquisition of GluCEST. For T_2-weighted imaging, the 3D MPRAGE images were reformatted in sagittal view and slice orientation was set perpendicular to hippocampus. For GluCEST, anatomical images acquired from T_2-weighted imaging were used to select the axial hippocampal slice. The GluCEST imaging parameters were: slice thickness = 5 mm, field of view read = 200 mm, field of view phase = 162.5 mm, matrix size = 208 × 256, GRE read out TR = 6.2 ms, TE = 3 ms, number of averages = 2, shot TR = 10000 ms, shots per slice = 2, with one saturation pulse at a $\mathbf{B}_{1rms}$ of 3.06 μT with 800 ms duration. Raw CEST images were acquired at varying saturation offset frequencies from ±1.8 to ±4.2 ppm (relative to water resonance) with a step size of ±0.3 ppm. GRE images at two echo times (TE1 = 4.24 ms; TE2 = 5.26 ms) were collected to compute $\mathbf{B}_0$ map. $\mathbf{B}_1$ map was generated from the two images obtained using square preparation pulses with flip angles 30° and 60°. Overall, acquisition time of CEST images, $\mathbf{B}_1$ and $\mathbf{B}_0$ field maps is approximately 20 minutes. In brief, CEST images obtained from ±1.8 to ±4.2 ppm were interpolated using the cubic spline method to generate images with a fine step size of 0.01 ppm. $\mathbf{B}_0$ corrected CEST images at ±3 ppm were generated from the interpolated CEST images by picking signals according to the frequency shift in the $\mathbf{B}_0$ map. The $\mathbf{B}_0$ corrected ± 3.0 ppm images were then used for computing the percentage GluCEST contrast, which is equal to 100 x (M_{-3ppm}–M_{+3ppm})/M_{-3ppm}, where M_{-3ppm} and M_{+3ppm} are $\mathbf{B}_0$ corrected images saturated at -3ppm and +3ppm respectively with respect to water[16]. $\mathbf{B}_1$ inhomogeneity artifacts in GluCEST maps were removed using $\mathbf{B}_1$ calibration curves as previously reported. The $\mathbf{B}_0$ and $\mathbf{B}_1$ corrected GluCEST contrasts were then averaged within expertly drawn regions-of-interest (ROIs) in the bilateral hippocampi. Paired 2 sample t-test for means was performed on the control and epilepsy subjects (2 tailed).

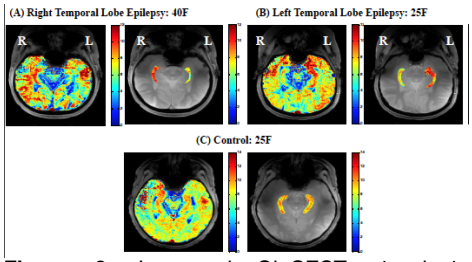

Figure 2: Increased GluCEST signal in hippocampus ipsilateral to seizure onset in subjects with TLE: (A) Subject with MRI negative right TLE with visible increase in GluCEST signal in right hippocampus. (B) Subject with MRI negative left TLE with visible increase in GluCEST signal in left hippocampus most marked in CA1 region. (C) Control subject with symmetric hippocampal GluCEST signal.

Results: In all 5 patients the GluCEST values were increased in the epileptogenic hippocampus (p=0.007) with controls showing no significant asymmetry from left to right hippocampus (p=0.268) (figure 1). Figure 2 shows the visible increases in GluCEST values. Of interest, one subject recently underwent intracranial EEG evaluation because based upon scalp EEG and standard imaging data, it was uncertain if seizures were right or left temporal onset. Intracranial EEG results were concordant with GluCEST findings.

Conclusions: GluCEST shows promise in localizing epileptic networks in nonlesional epilepsy patients. We plan further study with increased sample size. In addition, preliminary evidence indicates that analysis of hippocampal subfields will yield additional localizing information.

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