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New approaches to structural and functional imaging in focal epilepsy

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The purpose of this brief communication is to describe two novel imaging approaches to the study of epilepsy, being undertaken at the UCLA Seizure Disorder Center. One involves structural anatomic surface modeling utilizing statistical parametric mapping (SPM) to identify epilepsy-related magnetic resonance imaging (MRI) abnormalities of hippocampus and neocortex. The other utilizes functionalized magnetonanoparticles (MNPs) conjugated to bioactive ligands in order to image specific local cerebral function using MRI, rather than positron emission tomography (PET).

Structural Statistical Parametric Mapping

Hippocampal maps were obtained from patients with mesial temporal lobe epilepsy (MTLE), as shown in Fig. 1, and similar maps of neocortical thickness were also obtained. Studies were carried out on patients with a clinical and MRI diagnosis of MTLE with hippocampal sclerosis (HS), pathologic confirmation of this diagnosis, and a seizure-free

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Disclosure

Drs. Engel and Akhtari are founders of Epinano, Inc., which has licensed the magnetonanoparticle technology reported here from UCLA. The remaining authors have no conflicts of interest.

postoperative course. SPM was used to compare hippocampi of the study population with those of patients with MTLE-HS who were not seizure-free postoperatively (Lin et al., 2005). Non-seizure-free patients had more diffuse hippocampal atrophy ipsilaterally and more region-specific atrophy contralaterally. SPM analysis of neocortex demonstrated bilateral decreases in cortical thickness in frontal, temporal, and occipital regions regardless of the side of HS; however, cortical thickness of superior frontal and parahippocampal gyrus ipsilateral to HS was related to the duration of epilepsy (Lin et al., 2007). The strategy of this approach is to develop a disease-specific anatomic atlas of MTLE with HS in order to determine whether structural deviation from this pattern in individual patients predicts poor surgical outcome, as well as behavioral disturbances.

More recently, the same approach to hippocampal mapping was used to correlate patterns of regional atrophy with electrophysiologic findings in patients with MTLE and HS. One study found clear differences between patients with depth electrode-recorded hypersynchronous ictal onsets and those with low-voltage fast ictal onsets (Ogren et al., 2009a). Whereas the former showed a classical pattern of ipsilateral hippocampal atrophy with CA2 sparing, the latter had more diffuse ipsilateral atrophy involving CA2, as well as more pronounced contralateral atrophy (Fig. 2). These data suggest the existence of two distinctly different forms of MTLE with HS. SPM of the hippocampus has also demonstrated a spatial correlation between the location of regional atrophy and the location of depth microelectrode-recorded fast-ripple oscillations, but not ripple oscillations (Ogren et al., 2009b).

Magnetanoparticles for Functional MRI

Functionalized MNPs consisting of a paramagnetic iron oxide core surrounded by a dextran coating were developed and conjugated with alpha-methyl-tryptophan (AMT), a putative surrogate marker of epileptogenic tissue (Akhtari et al., 2008). These particles were given intravenously to rats injected intrahippocampally with kainic acid, immediately after status epilepticus, and weeks to months later. In the acute condition, MRI showed that plain MNPs without ligand crossed the blood-brain barrier and localized to the injected hippocampus, presumably reflecting inflammatory processes. MNPs conjugated with AMT (AMT-MNP) were concentrated in hippocampi bilaterally, suggesting a relationship to epileptogenicity distant from areas of inflammatory changes. Weeks to months later, MRIs after AMT-MNP injection showed bilateral hippocampal uptake in rats later shown by electrophysiologic analysis to have bilateral ictal onsets, uptake in only one hippocampus in rats shown to have unilateral ictal onsets, and no localized AMT-MNP uptake was seen in one rat with no spontaneous seizures recorded behaviorally or electrophysiologically (Fig. 3). This work suggests that MRI with MNPs is potentially applicable for use with other bioactive molecules as ligands for imaging normal and abnormal localized cerebral function, similar to studies currently performed with PET, without the limitations of a short half-life, radioactivity, and requirements for specialized imaging equipment. Functionalized MNP studies are also underway utilizing other bioactive ligands potentially useful for the study of epilepsy.

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Figure 1.

Three-dimensional (3D) magnetic resonance imaging (MRI) reconstruction of the hippocampus begins with (A) manual tracing of hippocampus on serial coronal MRI scans, (B, C) then using anatomic modeling software to generate a 3D parametric surface model. (D) Surfaces from patients are averaged to produce a mean hippocampal surface model, (E) and a medial curve, which derives from the center of mass of each successive slice in the hippocampus, is used to measure the distance between the medial curve and each surface point. (F) Distances represent radial size or thickness throughout the hippocampus. From Thompson et al. (2004).

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Figure 2.

Three-dimensional (3D) surface maps of hippocampal atrophy in patients with unilateral hypersynchronous (HYP) ictal electroencephalography (EEG) onsets or low-voltage fast (LVF) ictal onsets. Areas of statistically significant atrophy (i.e., $p < 0.05$) in patients relative to controls are colored white and red, whereas areas with no difference are colored blue. (A) Ipsilateral to seizure onset, patients with HYP onsets had a pattern of atrophy that resembled hippocampal sclerosis with CA2 sparing, whereas patients with LVF onsets had more diffuse atrophy that included CA2 (lateral aspect on superior surface). (B) Atrophy was also found in the contralateral hippocampus of both patient groups, but to a greater extent in patients with LVF onsets compared to the HYP onset group, particularly in lateral hippocampal areas. Orientation axis (upper left) denotes lateral (L) and anterior (A). From Ogren et al. (2009a).

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Figure 3.

Magnetic resonance (MR) images of rats #3, 4, 5, 6, and 7 (top to bottom) are shown before (left column) and after (middle column) tail vein injection of magnetonanoparticles conjugated with alpha-methyl-tryptophan (AMT-MNPs) (15 mg/kg). Rats #3 and 4 showed bilateral uptake of particles (white circles in the right column); rats #5 and 6 showed unilateral uptake, and rat #7 did not show any particle uptake. Arrows in the left column show the areas of hippocampal atrophy due to kainic acid (KA) injection. Rats #3–6 had spontaneous behavioral seizures; rat #7 did not show any behavioral seizure activity. The location of areas with AMT-MNP uptake is shown in the right column on sections from Paxinos (1997). Images were taken 6 h after AMT-MNP injection for rats #3, 4, and 7; 2 h after injection for rat #5; and 4 h after injection for rat #6. From Akhtari et al. (2008).

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