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Lateralization of temporal lobe epilepsy by multimodal multinomial hippocampal response-driven models

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ABSTRACT

Purpose: Multiple modalities are used in determining laterality in mesial temporal lobe epilepsy (mTLE). It is unclear how much different imaging modalities should be weighted in decision-making. The purpose of this study is to develop response-driven multimodal multinomial models for lateralization of epileptogenicity in mTLE patients based upon imaging features in order to maximize the accuracy of noninvasive studies.
Methods and materials: The volumes, means and standard deviations of FLAIR intensity and means of normalized ictal–interictal SPECT intensity of the left and right hippocampi were extracted from preoperative images of a retrospective cohort of 45 mTLE patients with Engel class I surgical outcomes, as well as images of a cohort of 20 control, nonepileptic subjects. Using multinomial logistic function regression, the parameters of various univariate and multivariate models were estimated. Based on the Bayesian model averaging (BMA) theorem, response models were developed as compositions of independent univariate models.
Results: A BMA model composed of posterior probabilities of univariate response models of hippocampal volumes, means and standard deviations of FLAIR intensity, and means of SPECT intensity with the estimated weighting coefficients of 0.28, 0.32, 0.09, and 0.31, respectively, as well as a multivariate response model incorporating all mentioned attributes, demonstrated complete reliability by achieving a probability of detection of one with no false alarms to establish proper laterality in all mTLE patients.
Conclusion: The proposed multinomial multivariate response-driven model provides a reliable lateralization of mesial temporal epileptogenicity including those patients who require phase II assessment.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is the most prevalent type of epilepsy considered for surgery [1]. Reliable lateralization by noninvasive means would expedite surgical intervention, reduce the surgical risk of invasive monitoring and lessen the expense of investigation. Conventional noninvasive presurgical evaluation has often consisted of scalp electroencephalography (EEG), magnetic resonance imaging (MRI) and both ictal single photon emission computer tomography (SPECT) interictal SPECT to identify seizure onset in mTLE prior to a resection. In the imaging realm, quantitative methods have been applied to both MRI and SPECT with promising results to establish laterality in mTLE. Automated and manual hippocampal segmentation approaches for volume assessment have yielded 74% and 78% lateralization accuracy [2,3] whereas, fluid-attenuated inversion recovery (FLAIR) MRI signal analysis yielded a 98% accuracy in a single study [4]. Compartmentalized hippocampal SPECT analysis correctly lateralized mTLE in 91% of cases [5].

Where confident lateralization is not possible by qualitative assessment of these imaging modalities and individual quantitative measures of each do not provide effective differentiation, patients must undergo implantation of intracranial electrodes to clarify the situation [6] and must, in turn, bear the risk of such intervention [7]. An approach that would further capitalize on the benefits of the quantitative imaging approach [8] could serve to achieve the goals of improving patient safety and lessening cost.

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A multimodal lateralization framework would ostensibly increase sensitivity and confidence in the lateralization of mTLE, if agreement was confirmed among individual imaging modalities. These modalities differ in their reliabilities and may, to some degree, show discrepancies in predicting laterality. The approach uniformly taken in these circumstances involves an assignment of a score of zero or one as a measure of this reliability in lateralizing a mTLE [9,10]. A weighted integration scheme, in which a probability is assigned to individual modalities as a measure of their reliability, may provide a more accurate reflection of laterality, particularly in those cases that ultimately require invasive monitoring. Multimodal postprocessing is defined as a simultaneous rendering of various modalities which are spatially coregistered [11]. It can incorporate all anomalous information of multiple modalities simultaneously without having to assign a posterior probability to the lateralization result of any individual modality.

Any variability in quantitative imaging indices can be attributed to natural physiological occurrences or pathology underlying the epileptogenicity. In order to distinguish these features, imaging indices of a cohort of control, nonepileptic subjects must be ascertained to account for the variability seen in natural circumstances. A multinomial response model that takes into account such natural variability would overcome the limitations of a binomial response model that does not.

We hypothesize that a quantitative multimodal multinomial response model, using a preferred list of MRI and SPECT attributes, will optimize lateralization of mTLE and the selection of surgical candidates while reducing the need for extraoperative electrocorticography (ECoG).

2. Methods

2.1. Patients and treatment

The current research study at Henry Ford Health System is federally regulated and approved by the Henry Ford Health System Institutional Review Board (IRB). Between June 1993 and June 2009, 113 patients with mTLE underwent resection of the mesial temporal structure. Only those cases with Engel class I outcomes were selected from this initial cohort. Subsequently, those patients were excluded for whom any of their T1-weighted and FLAIR MRI or SPECT ictal imaging and interictal imaging had not been acquired. Others, whose acquired images were contaminated by imaging artifact that compromised the quality of imaging attributes in or near the hippocampi, such as magnetic field inhomogeneity were also removed from consideration. Forty-five patients remained (17 males aged 42.6 ± 8.5 (mean ± std); 28 females aged 35.1 ± 11.4). The majority of cases achieved an Engel class Ia outcome (41 Ia, 2 Ib, 2 Id). Resections were performed on the left side in 28 patients and on the right in 17. Fifteen patients required ECoG as part of their investigation. Twenty control, nonepileptic subjects were also included in this study.

2.2. MRI and SPECT data acquisition

Preoperative MRI was acquired on a 1.5 T or a 3.0 T MRI system (Signa, GE, Milwaukee, USA) including coronal T1-weighted (using inversion recovery spoiled gradient echo, IRSPGR protocol) and coronal T2-weighted (using fluid attenuated inversion recovery, FLAIR protocol) images. For the 1.5 T MRI, T1-weighted imaging parameters were TR/TI/TE = 7.6/1.7/500 ms, flip angle = 20°, voxel size = $0.781 \times 0.781 \times 2.0$ mm^3 and FLAIR imaging parameters were TR/TI/TE = 10002/2200/119 ms, flip angle = 90°, voxel size = $0.781 \times 0.781 \times 3.0$ mm^3. For the 3.0 T MRI, T1-weighted imaging parameters were TR/TI/TE = 10.4/4.5/300 ms, flip angle = 15°, voxel size = $0.39 \times 0.39 \times 2.00$ mm^3 and FLAIR imaging parameters were TR/TI/TE = 9002/2250/124 ms, flip angle = 90°, voxel size = $0.39 \times 0.39 \times 3.00$ mm^3.

Patients underwent preoperative SPECT imaging with a triple-head Picker gamma camera 3000XP imaging system with high-resolution fan-beam collimators (Picker International, Inc., Cleveland Heights, OH) within 2 − 3 h after the injection of 99mT ethylcysteinate diethylester at a dose of 550 MBq. The energy window was set at 140 keV ± 7.5%. For ictal studies, the radiotracer was injected within 56 s of seizure onset. Interictal SPECT studies were performed when the patient had no documented seizure activity for at least 24 h. Total acquisition time was about 30 min. The images were reconstructed by filtered backprojection and then filtered with a Wiener filter into a 128 × 128 image matrix with a voxel size of $2.2 \times 2.2 \times 6.1$ mm^3.

Control subjects underwent the same 3.0 T MRI system and T1-weighted and FLAIR images were acquired with the same parameters mentioned above. They also underwent SPECT imaging, with six receivingTechnetium-99 m (99mTc) ethylcisteinate dimer (ECD), and 14 receiving [99mTc]-labeled hexamethyl-propylene amine oxime (HMPAO).

2.3. MRI and SPECT image co-registration and feature extraction

For each of the 65 cases (45 mTLE patients and 20 control subjects), both left and right hippocampi were first segmented from manually drawn ROIs on T1-weighted images. The manually segmented hippocampi were then co-registered to both FLAIR and ictal and interictal SPECT images using a rigid registration technique (FLIRT; [12]; Fig. 1).

The four hippocampal imaging attributes used for this study were volume [4], mean and standard deviation of FLAIR intensity [4], and mean of normalized ictal–interictal SPECT intensity (the difference between ictal and interictal intensities normalized to the whole brain interictal mean value) [5].

2.4. Development of single lateralization response models

The extracted imaging features were incorporated into the development of four univariate (Models 1 to 4) and three multivariate (Models 5 to 7) single response models for lateralization of epileptogenicity. Imaging attributes were considered as independent variables whereas laterality (i.e., left and right in the case of mTLE patients and neutral for control subjects) was considered the dependent variable in the development of response models using multinomial logistic function regression [13]:

- Model 1 univariate attributes: hippocampal volumes
- Model 2 univariate attributes: means of FLAIR intensity in left and right hippocampi
- Model 3 univariate attributes: standard deviations of FLAIR intensity in left and right hippocampi
- Model 4 univariate attribute: means of normalized “ictal interictal” SPECT intensity in left and right hippocampi
- Model 5 bivariate attributes: means and standard deviations of FLAIR intensity in left and right hippocampi
- Model 6 multivariate attributes: volumes, means and standard deviations of FLAIR intensity in left and right hippocampi
- Model 7 multivariate attributes: volumes, means and standard deviations of FLAIR intensity and means of normalized “ictal − interictal” SPECT intensity in left and right hippocampi

In order to assess how the multinomial logistic function generalized to an independent data set and how accurately this response model performed in practice, a cross-validation was performed using leave-one-out for sixty-five repetitions considering a single case as validation