Lateralization of Temporal Lobe Epilepsy by Imaging-Based Response-Driven Multinomial Multivariate Models

Mohammad-Reza Nazem-Zadeh, Jason M. Schwalb, Hassan Bagher-Ebadian, Fariborz Mahmoudi, Mohammad-Parsa Hosseini, Kourosh Jafari-Khouzani, Kost V. Elisevich, and Hamid Soltanian-Zadeh, *Senior Member, IEEE*

***Abstract*—We have developed response-driven multinomial models, based on multivariate imaging features, to lateralize the epileptogenicity in temporal lobe epilepsy (TLE) patients. To this end, volumetrics and statistical quantities of FLAIR intensity and normalized ictal–interictal SPECT intensity on left and right hippocampi were extracted from preoperative images of forty-five retrospective TLE patients with surgical outcome of Engel class I. Using multinomial logistic function regression, the parameters of various univariate and multivariate models were estimated. Among univariate response models, the response model with SPECT attributes and response model with mean FLAIR attributes achieved the lowest fit deviance (65.1±0.2 and 65.5±0.3, respectively). They resulted in the highest probability of detection (0.82) and lowest probability of false alarm (0.02) for the epileptogenic side. The multivariate response model with incorporating all volumetrics, mean and standard deviation FLAIR, and SPECT attributes achieved a significantly lower fit deviance than other response models (11.9±0.1, $p < 0.001$). It reached probability of detection of 1 with no false alarms. We were able to correctly lateralize the fifteen TLE patients who had undergone phase II intracranial monitoring. Therefore, the phase II intracranial monitoring might have been avoided for this set of patients. Based on this lateralization response model, the side of epileptogenicity was also detected for all thirty patients who had preceded to resection with only phase I of EEG monitoring. In conclusion, the proposed multinomial multivariate response-driven model for lateralization of epileptogenicity in TLE patients can help in decision-making prior to surgical resection and may reduce the need for implantation of intracranial monitoring electrodes.**

I. INTRODUCTION

Temporal lobe epilepsy (TLE) is the most prevalent type of epilepsy with the most successful surgery outcome [1]. MRI (Magnetic Resonance Imaging) findings such as atrophy on T1-weighted images and hyperintensity on Fluid Attenuated Inversion Recovery (FLAIR), and SPECT (Single Photon Emission Computed Tomography) findings such as hyperintensity in the difference between ictal and interictal phases in the ipsilateral hippocampus, concordant with EEG and neuropsychology help in decision making prior to the resection of mesial temporal structures [2-4]. The current non-quantitative radiological inspections cannot simultaneously incorporate all different and probably discrepant imaging attributes. We hypothesize that the development of quantitative TLE lateralization response models with a definition of a preferred list of MRI and SPECT imaging attributes can optimize selection of surgical candidates and reduce the need for extraoperative implantation of intracranial electrodes.

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Mohammad-Reza Nazem-Zadeh is with the Departments of Research Administration and Radiology, Henry Ford Health System, Detroit, MI, USA (phone: 313-874-4349; e-mail: mohamadn@rad.hfh.edu). Jason M. Schwalb, Hassan Bagher-Ebadian, Fariborz Mahmoudi, Mohammad-Parsa Hosseini, and Hamid Soltanian-Zadeh are with the Departments of Neurosurgery, Neurology, and Radiology, Henry Ford Health System, Detroit, MI, USA (jschwal1@hfhs.org, hbagher1@hfhs.org, fariborzm@rad.hfh.edu, parsah@rad.hfh.edu, hamids@rad.hfh.edu). Kourosh Jafari-Khouzani is with Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (kjafari@nmr.mgh.harvard.edu). Kost V. Elisevich is with the Department of Clinical Neurosciences, Spectrum Health Medical Group, Grand Rapids, MI, USA (kost.elisevich@spectrumhealth.org). Hamid Soltanian-Zadeh is also with the Control and Intelligent Processing Center of Excellence (CIPCE), School of Electrical and Computer, University of Tehran, Tehran, Iran (hszadeh@ut.ac.ir).

II. MATERIALS AND METHODS

A. Patients and treatment

Between June 1993 and June 2009, one hundred and thirteen patients with TLE underwent resection of the mesial temporal structures. In order to catch on the correct lateralization of TLE, we excluded the patients with any outcome rather than Engel class I. Moreover, we excluded the patients for which any of MRI T1-weighted, MRI FLAIR, or SPECT ictal and interictal imaging was not acquired. We further excluded the patients whose acquired images were contaminated by any significant imaging artifact that compromised the accuracy of imaging attributes in or near hippocampi, such as magnetic field inhomogeneity in MRI. After applying these exclusion criteria, forty-five patients (seventeen male with age 42.6±8.5 (mean±std), twenty-eight female with age 35.1±11.4) were included in this study who achieved an Engel class I outcome (41, IA; 2, IB; and 2, ID). For twenty-eight patients the left temporal lobe and for seventeen patients the right temporal lobe was determined to be epileptogenic and resected. Among the patients, fifteen patients had undergone extraoperative electrocorticography (ECoG) to determine the epileptogenic side.

B. MRI and SPECT Data Acquisition

Preoperative MRI images of TLE patients were acquired on a 1.5T or a 3.0T 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. On 1.5T MRI, T1-weighted imaging

parameters were TR/TI/TE=7.6/1.7/500 ms, flip angle=20°, voxel size=0.781×0.781×2.0 mm^3 and FLAIR imaging parameters were TR/TI/TE=10002/2200/119 ms, flip angle=90°, voxel size= 0.781×0.781×3.0mm^3. On 3.0T MRI, T1-weighted imaging parameters were TR/TI/TE=10.4/4.5/300 ms, flip angle=15◦, voxel size=0.39×0.39×2.00 mm^3 and FLAIR imaging parameters were TR/TI/TE= 9002/2250/124 ms, flip angle=90◦, voxel size=0.39×0.39×3.00 mm^3.

TLE 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 hours after the injection of 99mT cethylcysteinate diethylester at a dose of 550 MBq. The energy window was set at 140 keV±7.5%. Interictal SPECT studies were performed when the patient had no documented seizure activity for at least 24 h. For ictal studies, the radiotracer was injected within 56 sec of seizure onset. 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 2.2×2.2×6.1mm^3. Twenty control, nonepileptic subjects underwent the same 3.0T MRI system and T1-weighted and FLAIR images were acquired with the same parameters mentioned above. They also underwent SPECT imaging, six of which with Technetium-99m (99mTc) ethylcisteinate dimer (ECD), and fourteen of which with [99mTc]-labeled hexamethyl-propylene amine oxime (HMPAO).

C. Development of lateralization response models

For sixty-five cases (forty-five TLE patients and twenty control, nonepileptic subjects), the volumetrics of both left and right hippocampi were first extracted 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 [5]).

Four hippocampal imaging attributes including volumetrics [2], mean and standard deviation of FLAIR intensity [2], and mean of normalized ictal–interictal SPECT intensity (the difference between ictal and interictal intensities normalized to the whole brain interictal mean value [3]) were extracted. They were then incorporated into the development of four univariate (Models 1 to 4), and three multivariate (Model 5 to Model 7) response models for lateralization of epileptogenicity. Imaging attributes were considered as independent variables and the decided epileptogenic side (*left* and *right* of TLE patients and *neutral* for control subjects) was considered dependent variable in the development of response models using multinomial logistic function regression [6]:

- Model 1 univariate attributes: Hippocampal volumetrics,
- Model 2 univariate attributes: Mean of FLAIR intensity in left and right hippocampi,
- Model 3 univariate attributes: Standard deviation of FLAIR intensity in left and right hippocampi,
- Model 4 univariate attribute: Mean of normalized "ictal - interictal" SPECT intensity in left and right hippocampi,
- Model 5 bivariate attributes: Mean and standard deviation of FLAIR intensity in left and right hippocampi,
- Model 6 multivariate attributes: Volumetrics, mean and standard deviation of FLAIR intensity in left and right hippocampi,
- Model 7 multivariate attributes: Volumetrics, mean and standard deviation of FLAIR intensity, and mean 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, cross-validation was performed using leave-one-out for sixty-five repetitions considering a single case as validation data, and remaining sixty-four cases as training data [7]. The multinomial logistic models were regressed to training data as follows:

$$\ln\left(\frac{\Pr(Y_i=L|\,M_k)}{\Pr(Y_i=N|\,M_k)}\right) = \beta_L^k \,.\, X_i \,,\, X_i^k \epsilon D \qquad (1)$$

$$\ln\left(\frac{\Pr(Y_i=R|\,M_k)}{\Pr(Y_i=N|\,M_k)}\right) = \beta_R^k \,.\, X_i \,,\, X_i^k \epsilon D \qquad (2)$$

where X_i^k is a vector of i^{th}observation in training dataset D incorporated in Model k. $\Pr(Y_i = L|\,M_k)$, $\Pr(Y_i = R|\,M_k)$, and $\Pr(Y_i = N|\,M_k)$ are the posterior probability of the epileptogenic side Y_i being left (L), right (R), and neutral (N), respectively. β_L^k and β_R^k are the vector of regression coefficients of Model k associated with X_i^k and the posterior probabilities. Since in multinomial logistic regression the epileptogenic side Y_i for each observation in training dataset was assumed to be known, the posterior probabilities $\Pr(Y_i = L|\,M_k)$, $\Pr(Y_i = R|\,M_k)$, and $\Pr(Y_i = N|\,M_k)$ were set to 0 or 1 depending on the decision made on the laterality. By estimation of coefficients β_L^k and β_R^k for Model k, the posterior probability of the epileptogenic side Y_j for j^{th} validation data being left, right, or neutral were calculated, where

$$\Pr(Y_j = L|\,M_k) + \Pr(Y_j = R|\,M_k) + \Pr(Y_j = N|\,M_k) = 1 \qquad (3)$$

The goodness of fit for the response models was assessed by the fit deviance as a generalized residual sum of squares.

For each validation data, by comparing the lateralization result Y_j with the correct decided side $Side_j$, we evaluated the performance of the response models by calculating the probability of detection and false alarm of the epileptogenic side, the probability of detection and false alarm of the left epileptogenic side and the probability of detection and false alarm of the right epileptogenic side for the TLE cases (Pr^D, Pr^{FA}, Pr_L^D, Pr_L^{FA}, Pr_R^D, and Pr_R^{FA}, respectively).

$$Pr^D = \frac{1}{nTLE}\sum_{j\epsilon TLE} 1(Y_j = L|\,Side_j = L) + 1(Y_j = R|\,Side_j = R)$$

$$Pr^{FA} = \frac{1}{nTLE}\sum_{j\epsilon TLE} 1(Y_j = L|\,Side_j = R) + 1(Y_j = R|\,Side_j = L)$$

$$\Pr_{L}^{D} = \sum_{j\epsilon TLE} 1\left(Y_j = L \middle| \text{Side}_j = L\right) / \sum_{j\epsilon TLE} 1(\text{Side}_j = L)$$

$$\Pr_{L}^{FA} = \sum_{j\epsilon TLE} 1\left(Y_j = L \middle| \text{Side}_j = R\right) / \sum_{j\epsilon TLE} 1(\text{Side}_j = R)$$

$$\Pr_{R}^{D} = \sum_{j\epsilon TLE} 1\left(Y_j = R \middle| \text{Side}_j = R\right) / \sum_{j\epsilon TLE} 1(\text{Side}_j = R)$$

$$\Pr_{R}^{FA} = \sum_{j\epsilon TLE} 1\left(Y_j = R \middle| \text{Side}_j = L\right) / \sum_{j\epsilon TLE} 1(\text{Side}_j = L) \quad (4)$$

where nTLE is the total number of TLE patients, and $1(.)$ is a unit function with the value of 1 for true arguments, 0 otherwise.

III. Results

A. Lateralization response models

The parameters of the response Models were estimated and listed in Table 1. Among univariate response Models 1 to 4, the response Model 4 with SPECT attributes and the response Model 2 with mean FLAIR attributes achieved the lowest fit deviance (65.1±0.2 and 65.5±0.3, respectively). They resulted in the highest probability of detection (0.82) and lowest and probability of false alarm (0.02) for the epileptogenic side. However, the response Model 4 with SPECT attributes performed quite poorly by the probability of 0.71 for the detection of the right epileptogenic side in TLE patients (Table 2).

Integrating both mean and standard deviation of FLAIR, the bivariate response Model 5 performed superior to both univariate response Models 2 and 3 (with mean and standard deviation of FLAIR attributes, respectively) by achieving a higher probability of detection (0.96) as well as a lower probability of false alarm (0.02) for epileptogenic sides in TLE patients. The response Model 6 incorporating multivariate attributes of volumetrics, mean and standard deviation of FLAIR performed inferior than the response Models 5 with mean and standard deviation of FLAIR attributes by achieving a slightly lower probability of detection of epileptogenic side (0.93). However, it showed zero false alarm probability and reduced the fit deviance significantly (25.9±0.2; $p<0.001$). Incorporating all multivariate attributes of volumetrics, mean FLAIR, standard deviation FLAIR, and SPECT, the response Model 7 reached a significantly lower fit deviance (11.9±0.1) than any other response Models 1 to 6 ($p < 0.001$). It performed excellent in terms of achieving the probability of detection of 1 with no false alarms in lateralizing the epileptogenicity in TLE patients (Table 2). Moreover, the response Model 7 classified all control cases as *Neutral*. Fig. 1 shows the regressed multinomial logistic function to the data points using response Model 7 with the probability of detected side being *left*, *right,* or *neutral* for each TLE or control case. As can be seen, in this model the regressed multinomial logistic function did not misclassify any multivariate data point.

B. Clinical decision making on the laterality based on response models

By lateralizing the TLE using the multivariate response Model 7, the epileptogenic side was detected for 100% of patients who underwent phase II of intracranial monitoring (for 60% of which there were no discrepancy in lateralization results of the response Models 1 to 7). By decision making based on lateralization response Model 7, the phase II of intracranial monitoring could have been avoided before the patients underwent the surgery.

Based on multivariate response Model 7, the side of epileptogenicity was detected for all thirty patients who underwent only phase I of EEG monitoring with no false alarm for detection of left or right sides, 93% of which were also in agreement with the results of other response models.

TABLE 1. PARAMETERS OF RESPONSE MODELS

Response Models	Parameters	
Model 1:	$\beta_{0L}^{1} = 0.814$	$\beta_{0R}^{1} = -2.52$
	$\beta_{1L}^{1} = -0.006$	$\beta_{1R}^{1} = 0.004$
	$\beta_{2L}^{1} = 0.005$	$\beta_{2R}^{1} = -0.003$
Model 2:	$\beta_{0L}^{2} = 2.65$	$\beta_{0R}^{2} = -10.24$
	$\beta_{1L}^{2} = 0.259$	$\beta_{1R}^{2} = -0.302$
	$\beta_{2L}^{2} = -0.274$	$\beta_{2R}^{2} = 0.337$
Model 3:	$\beta_{0L}^{3} = -5.34$	$\beta_{0R}^{3} = -4.10$
	$\beta_{1L}^{3} = 0.228$	$\beta_{1R}^{3} = 0.014$
	$\beta_{2L}^{3} = -0.048$	$\beta_{2R}^{3} = 0.115$
Model 4:	$\beta_{0L}^{4} = -1.197$	$\beta_{0R}^{4} = -1.537$
	$\beta_{1L}^{4} = 35.17$	$\beta_{1R}^{4} = -26.00$
	$\beta_{2L}^{4} = -27.83$	$\beta_{2R}^{4} = 21.08$
Model 5:	$\beta_{0L}^{5} = 4.435$	$\beta_{0R}^{5} = -17.82$
	$\beta_{1L}^{5} = 0.472$	$\beta_{1R}^{5} = -0.338$
	$\beta_{2L}^{5} = -0.518$	$\beta_{2R}^{5} = 0.368$
	$\beta_{3L}^{5} = 0.553$	$\beta_{3R}^{5} = -0.163$
	$\beta_{4L}^{5} = -0.398$	$\beta_{4R}^{5} = 0.430$
Model 6:	$\beta_{0L}^{6} = 8.85$	$\beta_{0R}^{6} = -18.92$
	$\beta_{1L}^{6} = -0.007$	$\beta_{1R}^{6} = 0.008$
	$\beta_{2L}^{6} = 0.002$	$\beta_{2R}^{6} = -0.006$
	$\beta_{3L}^{6} = 0.380$	$\beta_{3R}^{6} = -0.126$
	$\beta_{4L}^{6} = -0.394$	$\beta_{4R}^{6} = 0.167$
	$\beta_{5L}^{6} = 0.482$	$\beta_{5R}^{6} = -0.070$
	$\beta_{6L}^{6} = -0.326$	$\beta_{6R}^{6} = 0.171$
Model 7:	$\beta_{0L}^{7} = -5.80$	$\beta_{0R}^{7} = -25.38$
	$\beta_{1L}^{7} = -0.011$	$\beta_{1R}^{7} = 0.005$
	$\beta_{2L}^{7} = 0.010$	$\beta_{2R}^{7} = -0.005$
	$\beta_{3L}^{7} = 0.083$	$\beta_{3R}^{7} = -0.321$
	$\beta_{4L}^{7} = -0.088$	$\beta_{4R}^{7} = 0.359$
	$\beta_{5L}^{7} = 0.156$	$\beta_{5R}^{7} = -0.203$
	$\beta_{6L}^{7} = 0.024$	$\beta_{6R}^{7} = 0.590$
	$\beta_{7L}^{7} = 35.91$	$\beta_{7R}^{7} = -21.54$
	$\beta_{8L}^{7} = -12.97$	$\beta_{8R}^{7} = 43.04$

Table note: β_{jL}^{k} and β_{jR}^{k} are the regression coefficients j of Model k associated with X_i^k, i^{th} observation of the training dataset in equations (1) and (2).

IV. Discussion and Conclusion

In this work, univariate and multivariate response-driven lateralization models were proposed based on MRI and SPECT attributes and multinomial logistic regression, to determine the side of epileptogenicity in temporal lobe epilepsy patients. The proposed response models were capable of handling the uncertainty using multinomial regression through which making a neutral decision is possible. Furthermore, the proposed response model can be further generalized by integrating attributes of additional modalities (such as PET- positron emission tomography and DTI- diffusion tensor imaging) into the process.

Lateralizing TLE patients using the proposed response model incorporating multivariate attributes of volumetrics, mean and standard deviation of FLAIR intensity, and mean of normalized SPECT intensity in left and right hippocampi, the phase II of intracranial monitoring could have been avoided for all TLE patients studied in this work. Testing the proposed response model on the patients who had undergone only phase I EEG monitoring, the side of epileptogenicity was also detected for all with no false alarms, which shows the reliability of the proposed model for lateralization of the epileptogenic side of prospective TLE patients.

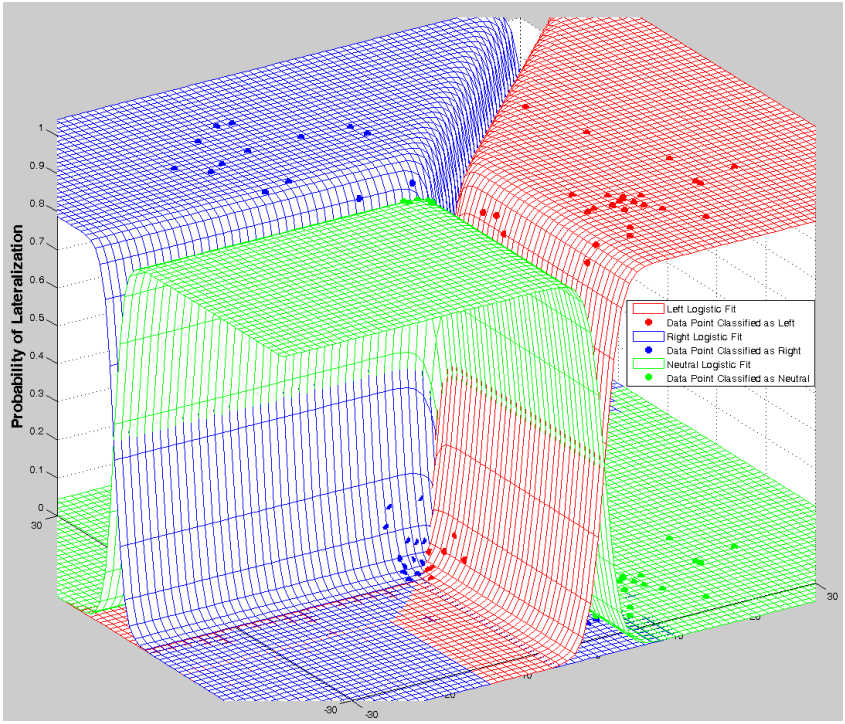

FIG 2. THE REGRESSED MULTINOMIAL LOGISTIC FUNCTION TO THE DATA POINTS USING RESPONSE MODEL 7, ALONG WITH THE PROBABILITY OF DETECTED SIDE BEING LEFT, RIGHT, OR NEUTRAL FOR EACH TLE OR CONTROL CASE. THE HORIZONTAL AXES ARE THE MULTIVARIATE IMAGING FEATURE SPACE AND THE VERTICAL AXIS IS THE PROBABILITY OF LATERALIZATION.

TABLE 3. THE RESULTS OF THE LEAVE-ONE-OUT CROSS-VALIDATION

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
Dev	68.1± 0.2	65.5± 0.3	104.8± 0.4	65.1± 0.2	32.9± 0.2	25.9± 0.2	11.9± 0.1
Pr^{D}	0.78	0.82	0.64	0.82	0.96	0.93	1.00
Pr^{FA}	0.02	0.02	0.18	0.02	0.02	0.00	0.00
Pr_L^{D}	0.86	0.82	0.79	0.89	0.96	0.96	1.00
Pr_L^{FA}	0.06	0.06	0.35	0.00	0.06	0.00	0.00
Pr_R^{D}	0.65	0.82	0.41	0.71	0.94	0.88	1.00
Pr_R^{FA}	0.00	0.00	0.07	0.04	0.00	0.00	0.00

Table note: Dev is the deviance of regression (mean ± standard error). Pr^{D}, Pr^{FA}, Pr_L^{D}, Pr_L^{FA}, Pr_R^{FA}, and Pr_R^{D} are probability of detection and false alarm of the epileptogenic side, probability of detection and false alarm of the left epileptogenic side and probability of detection and false alarm of the right epileptogenic side for the TLE cases, respectively.

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