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Cross-modal Consistency of Epileptogenic Network in SEEG and Resting-state fMRI

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Abstract—**Electrophysiological recording and metabolic imaging are two complimentary techniques in preoperative evaluation of epilepsy surgery. High frequency electrical brain activity has been increasingly used in localizing seizure onset zone (SOZ) owing to the development of stereo-EEG (SEEG) technique. However, SEEG recording has no capacity of whole brain coverage as functional MRI. In this study, we performed cross-modal validation of epileptogenic network defined by SEEG and that by resting-state fMRI on individual brain of epilepsy patients. Epileptogenicity index (EI) based on abnormal high frequency SEEG signals was employed to define the epileptogenic network in electrophysiology. Meanwhile, taking the SEEG sites with highest EI as the seed, resting-state functional MRI and connectivity analysis were used to define the epileptogenic network in hemodynamics. The spatial consistency of these two networks was measured by ROC, and the average AUC reached 0.87, which proved a good consistency between electrophysiological and hemodynamic networks in epileptic brain. The difference part in resting-state fMRI network may supplement the SEEG electrode coverage, to reveal more information about epileptic network.**

I. Introduction

The monitoring and analysis of electrophysiological changes in epileptic brain are crucial for the diagnosis and the surgical planning of resection. In recent years, intracranial EEG has received increasing attention, allowing high-resolution mapping of biomarkers of epileptogenicity. Quantification approaches using spectral or time-frequency analysis include epileptogenicity index (EI) and epileptogenicity map (EM) [1-3]. Those areas with early onset and high energy of high frequency activity usually have high EI values, and are more likely to be seizure onset zones (SOZs). The idea that focal epilepsies involve networks of varying scales has become progressively accepted. The network concept, being a key factor in identifying the anatomic distribution of epileptogenic process, is important in the context of epilepsy surgery [1]. However, the electrical neural signals measured with SEEG electrodes has a sparse spatial coverage, and may miss critical sites in epileptogenic network.

Functional imaging, including functional MRI and PET, provides whole-brain connectivity and metabolic information. fMRI detects the blood oxygenation level dependent (BOLD) signals and resting-state fMRI (rsfMRI) reflects a relatively long-term stable functional network in the brain. In the epileptic brain, rsfMRI can be used to find whether there is an abnormality in network connectivity [4-5]. PET provides abnormal metabolic information, which is often related to the seizure onset zones (SOZs). Some explorations have been made to reveal the strong correlation between PET imaging and SEEG-based epileptogenicity map [6], while the relationship between rsfMRI network and SEEG-based epileptogenic network has not yet been explored. With this link established, rsfMRI can be used to provide information of those areas in the epileptogenic network but not covered by SEEG electrodes.

In this study, we projected epileptogenic network defined by SEEG and that by resting-state fMRI onto individual brain atlas of epilepsy patients, to perform cross-modal validation. Using noninvasive multimodal neuroimaging techniques, the Brainnetome atlas provides a connectivity-based parcellation framework [7]. In this study, the Brainnetome atlas was projected onto the individual brain of epilepsy patients to obtain the anatomical location of each SEEG electrodes. A good spatial consistency was found between SEEG and resting fMRI based networks, with an average AUC of 0.87, which suggested a close link between electrophysiological and hemodynamic networks in epileptic brain.

II. Methods

A. Patients' Information and Data Acquisition

Six patients with refractory epilepsy at the Yuquan Hospital, Tsinghua University were recruited for this study and informed consent were obtained from all patients. The current study focused on the patients with SOZs located in the gray matter only. The patients required video-EEG monitoring, MRI scan, high-resolution CT scan with implanted electrodes, and SEEG as part of their presurgical evaluation. A resting-state fMRI scan of 16 minutes was collected for each patient before electrode implantation. Clinical information about these patients are provided in Table I. The SEEG signals were acquired by EEG-1200C electroencephalograph (NIHON KOHDEN, Japan), with a sampling rate of 2000 Hz. Each patient has 8-16 electrodes implanted according to clinical needs, with 8-16 electrode contacts on each electrode. MRI and resting-state fMRI scans were acquired by Achieva 3.0T TX scanner (Phillips, USA). The SEEG data and fMRI data were processed using FreeSurfer [8] and MATLAB.

B. High Frequency Epileptogenicity Index (HFEI)

Epileptogenicity index (EI) was first proposed by Bartolomei et al., which was a quantitative measure to identify the epileptogenic zones based on both spectral and temporal properties of intracranial EEG signals [1-2]. Four

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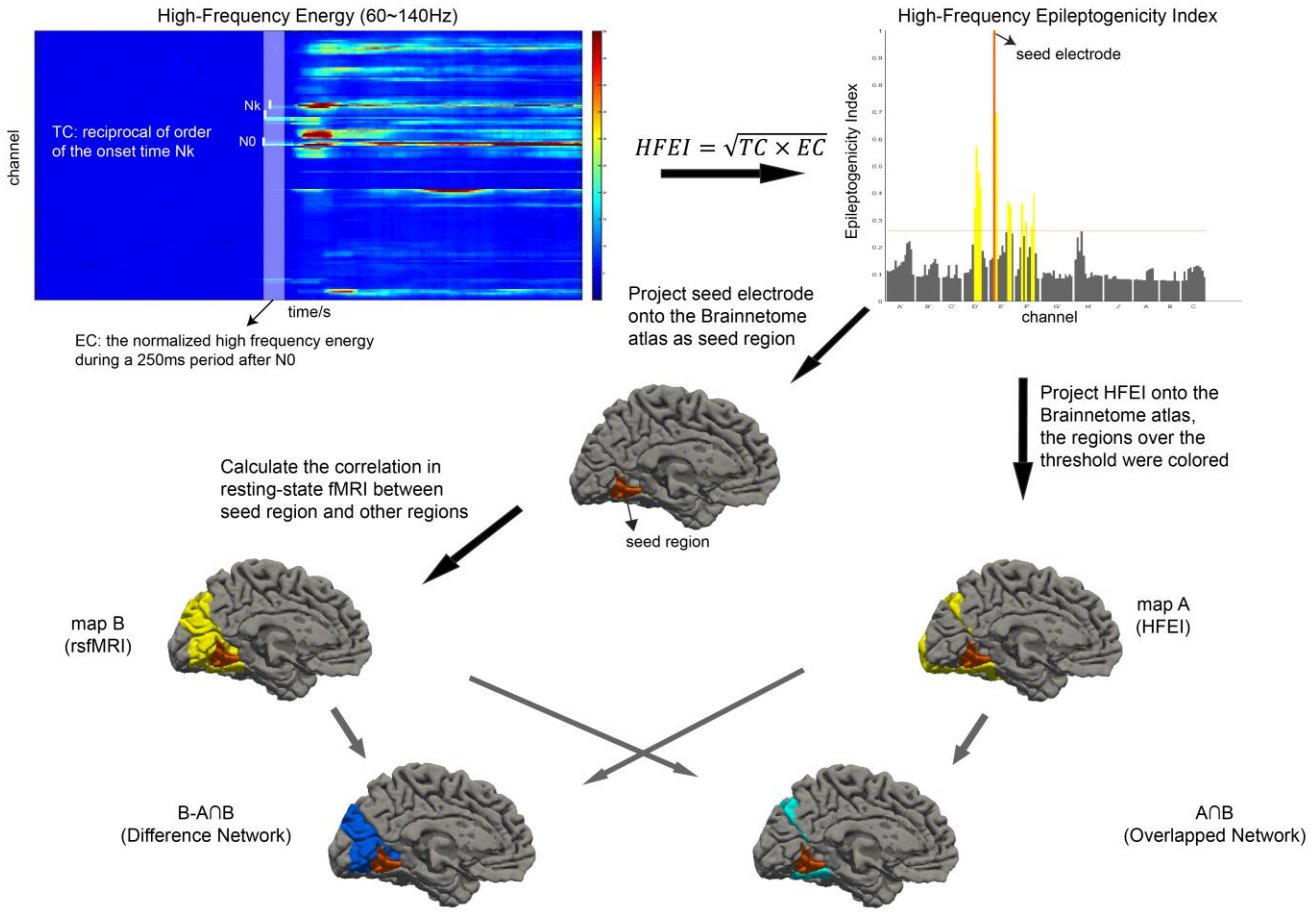

Fig. 1. Flow chart of HFEI calculation and the definition of epileptogenic network in SEEG and rsfMRI (S2).

frequency bands (theta, alpha, beta and gamma) were considered for measuring EI, which hinders the easy application. Here in this study, a simplified version of EI was proposed. Firstly, we obtained high frequency signals in the gamma and high-gamma (60-140Hz, power noise at 50Hz), using FIR filter (fourth-order Chebyshev). Secondly, the band-passed SEEG signal of each electrode was transformed into the high-frequency energy by amplitude squaring and window smoothing. The high frequency energy signals were normalized by dividing the average value of high-frequency energy of the baseline (BL), void of any epileptic activity and of any artifact. The normalized high frequency energy signals were rearranged as a matrix (channel x timepoints) for visualization (Fig.1, upper panel). Thirdly, time coefficient (TC) and energy coefficient (EC) were calculated according to the normalized high frequency energy (NHFE). For each channel, the onset time N_k of high frequency activity was defined as the time when NHFE reaches the threshold, which was determined as below:

$$threshold_{onset\ time} = max(NHFE_{BL}) + 10\sigma(NHFE_{BL})$$

TC of each electrode was defined as the reciprocal of order of the onset time N_k, taking the seizure onset time N_0 as the first N_k. EC was defined as the normalized high frequency energy during a 250ms period after N_0. Finally, HFEI of each electrode was calculated using the formula:

$$HFEI = \sqrt{TC \times EC}$$

A HFEI threshold was set based on the HFEI values of all channels:

$$HFEI\_threshold = mean(HFEI) + std(HFEI)$$

The channels with HFEI value above the threshold were included in the SEEG network.

Taking the candidate SOZ electrodes selected by clinicians as the reference, we quantified the performance of the HFEI method using sensitivity and specificity.

TABLE I. PATIENTS' INFORMATION

Patient	Age	Sex	Number of Electrodes	SOZ (clinical diagnosis)
S1	19	M	8L(102)	L posterior paracentral lobule
S2	43	M	9L+3R(150)	L Basal temporal occipital lobe
S3	13	F	10R(126)	R posterior inferior temporal sulcus
S4	19	F	11R(140)	L posterior central gyrus
S5	22	F	11R+1L(150)	R operculum temporal lobe
S6	35	F	11R(134)	L posterior superior frontal gyrus

C. Definition of epileptogenic SEEG/rsfMRI network

The SEEG/rsfMRI epileptogenic network and the consistency analysis were performed on individual Brainnetome atlas [7], which contains 211 cortical sub-regions. Individual cortical topomap was obtained by projecting the Brainnetome atlas onto individual brain.

We obtained the location of the each electrode based on the co-registration of MRI and CT images, and projected the electrodes onto the cortex volume of individual Brainnetome atlas [7]. The HFEI value for each Brainnetome region was defined as the maximum of the EI values of all electrodes within the region. The HFEI value for the region without electrode was set to zero. The brain regions exceeding the threshold (map A in Fig.1) were included in the SEEG-based epileptogenic network.

We assumed that the region with the highest EI value was most likely to be in the epileptogenic network. Therefore, the region with the highest EI value was set as the seed region for subsequent seed-based rsfMRI connectivity analysis. We obtained the correlation efficient between the seed region and all other cortical regions. The top 10% regions with the highest correlation values were selected to be included in the rsfMRI based epileptogenic network (map B in Fig.1). An example of rsfMRI correlation efficient distribution across voxels from patient S1 are shown in Fig. 2b, with top 10% boundary marked in red.

After obtaining the SEEG and rsfMRI based epileptogenic network (map A and B respectively, Fig.1), we further derived the overlapped network and the difference network. The overlapped network is the coincident part of epileptogenic networks defined by SEEG and rsfMRI ($A \cap B$). The difference network corresponds to the regions only in rsfMRI but not in SEEG network ($B - A \cap B$).

III. Results

A. SEEG network defined by HFEI

TABLE II. SENSITIVITY AND SPECIFICITY OF HFEI

Patient	By Electrodes		By Regions	
	Sensitivity	*Specificity*	*Sensitivity*	*Specificity*
S1	43.75%	97.67%	80.00%	99.51%
S2	47.37%	96.18%	100.00%	95.63%
S3	62.50%	95.76%	75.00%	99.03%
S4	71.43%	96.99%	100.00%	95.65%
S5	56.25%	97.76%	100.00%	96.60%
S6	44.44%	95.20%	100.00%	96.65%
Average	54.29%	96.59%	92.50 %	97.18%

The SEEG network was first identified by using high frequency EI and validated with the clinical diagnosis. The sensitivity and specificity were first calculated by electrodes. The results of 6 patients are shown in Table II. The average sensitivity was 54.29% and the average specificity reached 96.59%. The high specificity and relative low sensitivity reflected the conservative nature of HFEI, which may avoid excessive and unnecessary resection of brain tissue. We also did the calculation by Brainnetome regions [7] and obtained significant improvement of sensitivity (92.50 %, Table II).

B. Consistency evaluation

In seed-based rsfMRI correlation analysis, Brainnetome regions with the top 10% of the correlation values were considered to be in the epileptogenic network (Fig.2b). The seed region is colored in orange and other regions with correlation values above threshold are colored in yellow. The overlapping portion of the regions are rendered in cyan. In the example patient S1 showed in Fig. 2, the region with the highest EI value was the paracentral lobule in the frontal lobe, which was considered as SOZ. The overlapped network, which may be thought as the propagation network, includes superior parietal lobule, precuneus in parietal lobe and cingulate gyrus in limbic lobe. In addition, the difference network included precentral gyrus in frontal lobe, inferior temporal gyrus in temporal lobe and postcentral gyrus in parietal lobe. The overlapped network and difference network were obtained for all 6 patients (Fig. 3). There are substantial regions in overlapped network, which indicates a good consistency between the epileptogenic networks in SEEG and rsfMRI. The massive regions in difference network may provide additional network information from rsfMRI analysis.

When evaluating the cross-modal consistency, the network defined by SEEG was treated as the reference and the threshold in rsfMRI analysis was adjusted to obtain the receiver operating characteristic (ROC) curve. The area under curve (AUC) can be used to evaluate the consistency between the spatial patterns of these two networks. Higher AUC

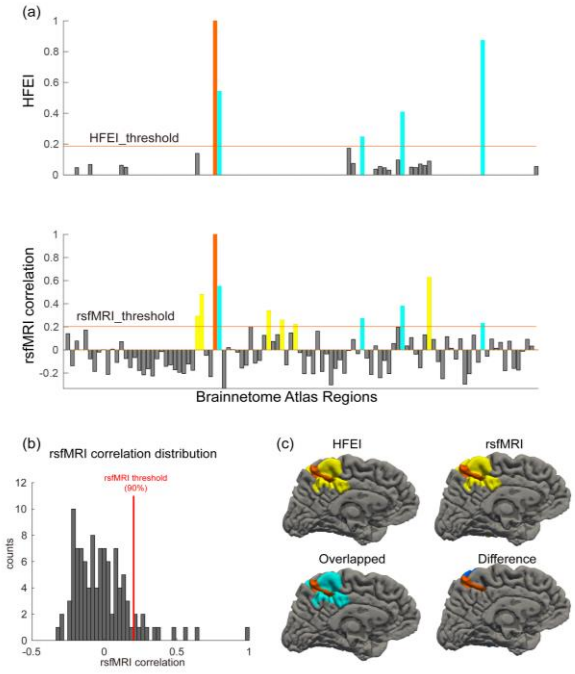

Fig. 2. The epileptogenic networks of patient S1. (a) EI value (upper panel) and rsfMRI correlation value (lower panel) of each Brainnetome atlas regions. (b) The distribution of rsfMRI seed correlation values. (c) Brainnetome regions with value above threshold. Red: seed region; yellow: regions with value above threshold in EI or rsfMRI analysis; orange: regions above threshold in both EI and rsfMRI.

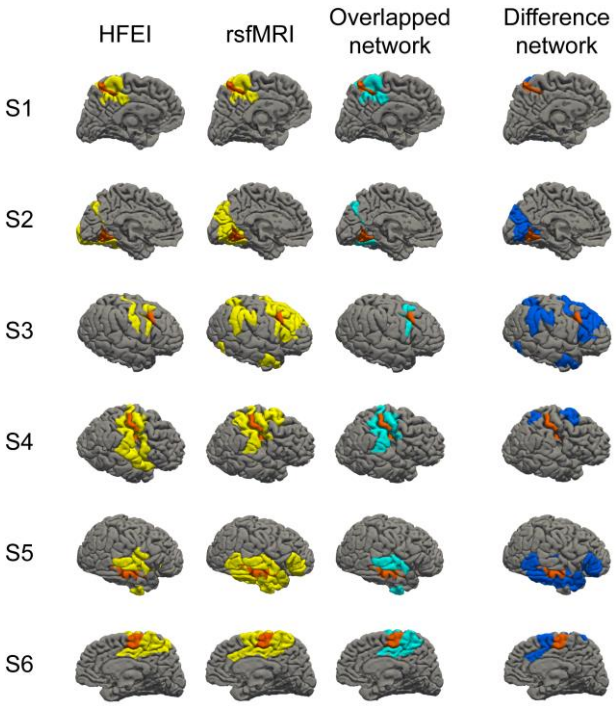

Fig. 3. The overlapped and difference networks of 6 patients.

indicates a higher consistency. The ROC curves and average AUC are shown in Fig. 4. The average AUC of 6 patients is 0.87, which reflects the network defined by hemodynamic signals can cover the network defined by electrophysiological well.

IV. Discussions

This study compared the cortical presence of abnormal discharges at SOZ, recorded by SEEG, with the interictal spatial correlation patterns of spontaneous BOLD fluctuations. The consistency between these two modalities was proved by a high AUC in ROC curve. Some studies have considered the epileptic network in electrophysiology and hemodynamics and obtained similar results. Stufflebeam et al. found that the epileptogenic areas identified by ECoG were overlapped by the foci identified by fMRI connectivity [9]. In the study of Otarula et al., more high frequency oscillations were found inside than outside the region with maximum hemodynamic response in patients with unifocal epilepsy [10]. In this study, we linked SEEG and rsfMRI network with the SEEG electrode having the highest EI value, and explicitly defined the epileptogenic network in both modalities.

Our approach also obtained the difference network between modalities, which corresponds to the network regions only in rsfMRI analysis. The difference between two networks can be explained by the limited spatial coverage of SEEG electrodes. One case in the study of Vulliemoz et al. showed an epileptic network found in fMRI, including regions that could not be sampled by intracranial EEG, but in agreement with findings from magnetoencephalography [11]. In addition to the issue of electrode coverage, the difference between the two modalities may also because of the distinction of sources of information. Benar et al. observed a high proportion of energy in the low frequency band of SEEG in regions with increased fMRI

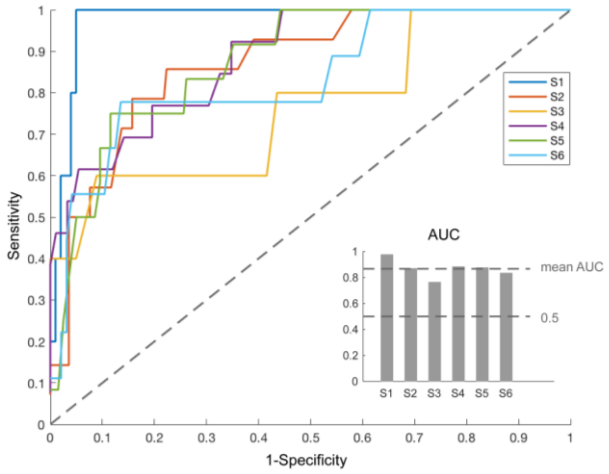

Fig. 4. The ROC curves and AUC of 6 patients.

signal, which suggested that the fMRI response might also correlate with the low frequency content of the SEEG epileptic transients (slow waves) [12]. Thus, we postulate that interictal rsfMRI analysis can provide additional information about the SOZ, which helps the evaluation during preoperative diagnosis. The next step of our study is to validate this postulation with more patients.

References

[1] F. Bartolomei, S. Lagarde, F. Wendling, et al. “Defining epileptogenic networks: Contriburion of SEEG and signal analysis”. *Epilepsia*, vol. 58, no. 7, pp. 1131-1147, 2017.

[2] F. Bartolomei, P. Chauvel, F. Wendling. “Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG”. *Brain*, vol. 131, vol. 7, pp. 1818-1830, 2008.

[3] O. David, T. Blauwblomme, A. S. Job, et al. “Imaging the seizure onset zone with stereo-electroencephalography”. *Brain*, vol. 134, no. 10, pp. 2898-2911, 2011.

[4] M. D. Fox, M. E. Raichle. “Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging”. *Nature Reviews Neuroscience*, vol. 8, no. 10, pp. 700-71, 2007.

[5] MH Lee, CD Smyser, JS Shimony, et al. “Resting-State fMRI: a review of methods and clinical applications”. *American Journal of neuroradiology*, vol. 34, no. 10, pp. 1866-1872, 2013.

[6] F. Lamarche, A. S. Job, P. Deman, et al. “Correlation of FDG-PET hypometabolism and SEEG epileptogenicity mapping in patients with drug-resistant focal epilepsy”. *Epilepsia*, vol. 57, no. 12, pp. 2045-2055, 2016.

[7] L. Fan, H. Li, J. Zhuo, et al. “The human brainnetome atlas: a new brain atlas based on connectional architecture”. *Cerebral Cortex*, vol. 26, no. 8, pp. 3508-3526, 2016.

[8] B. Fischl, DH. Salat, E. Busa, et al. “Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain”. *Neuron*, vol. 33, no. 3, pp. 341-355, 2002.

[9] SM. Stufflebeam, HS. Liu, J. Sepulcre, et al. “Localization of focal epileptic discharges using functional connectivity magnetic resonance imaging”. *Journal of Neurosurgery*, vol. 114, no. 6, pp. 1693-1697, 2011.

[10] Karina A. Gonzalez. Otarula, Hui Ming Khoo, Nicolas von Ellenrieder et al. “Spike-related haemodynamic responses overlap with high frequency oscillations in patients with focal epilepsy”. *Brain*, vol. 141, pp. 731-743, part 3, 2018.

[11] S. Vulliemoz, D. W. Carmichael, K. Rosenkranz, et al. “Simultaneous intracranial EEG and fMRI of interictal epileptic discharges in humans”. *Neuroimage*, vol. 54, Issue. 1, pp. 182-190, 2011.

[12] CG. Benar, C. Grova, E. Kobayashi, et al. “EEG–fMRI of epileptic spikes: Concordance with EEG source localization and intracranial EEG”. *Neuroimage*, Vol. 30, Issue. 4, pp. 1161-1170, 2006.