Using Functional MRI alone for Localization in Focal Epilepsy

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***Abstract*— In the present study, we developed a method for the purpose of localizing epilepsy related hemodynamic foci for patients suffering intractable focal epilepsy using resting state fMRI alone. We studied two groups of subjects: five patients with intractable focal epilepsy, and ten healthy volunteers performing motor tasks. Spatial independent component analysis (ICA) was performed on the fMRI alone data and a set of independent component (IC) selection criteria was developed to identify epilepsy related ICs. The method was then evaluated in the healthy group with motor tasks. In all five surgery patients, there was at least one identified IC concordant with surgical resection. In the motor task study of healthy subjects, our method revealed components with concordant spatial and temporal features as expected from the unilateral motor tasks. These results suggest the lateralization and localization value of fMRI alone in presurgical evaluation for patients with intractable unilateral focal epilepsy. The proposed method is noninvasive in nature and easy to implement. It has the potential to be incorporated in current presurgical workup for the diagnosis of intractable focal epilepsy patients.**

I. INTRODUCTION

Surgical resection is among the well-established methods for seizure control for patients with drug resistant epilepsy. During presurgical planning, if non-invasive methods are not adequate in localizing the epileptic foci, invasive procedures such as electrocorticography (ECoG) and depth electrodes are currently employed to define the seizure onset zone. However these methods are not only invasive in nature, they may also fail to provide additional information needed for surgery due to the relatively limited spatial coverage [1].

Functional MRI (fMRI) is a noninvasive imaging method. It has shown promises in the evaluation of epileptic foci. FMRI is currently used in presurgical assessment to identify eloquent cortex that affect visual, language, motor functions to be spared during surgery [2]. In addition, fMRI may also offer values as a useful tool to localize epileptic foci. It is commonly used in combination with simultaneously collected scalp EEG [3-5] (Liu *et al.*, 2006; Liu & He, 2008; He & Liu, 2008). However, EEG recorded in the scanner is often heavily contaminated with artifacts that are difficult to remove completely. Additionally, recording EEG and fMRI simultaneously requires a complicated setup system that is not easy to use in a clinical setting.

We intended to develop an effective tool to aid surgical planning for surgical candidates. In clinical practice, focal epilepsy is relatively treatable by surgery due to the focality of isolated epileptogenic zone. Therefore, in the present study, we focused on the focal epilepsy population. We then evaluated the results of the proposed method by comparing selected epilepsy-related components to surgical resection in patients; and selected motor-related component to expect motor activation area in healthy subjects respectively.

II. METHODS

A. Data Acquisition

Patients with focal epilepsy:

Five consecutive patients (ages 20-58 years, 35.3±15.9 years, 5 males) with intractable epilepsy who underwent presurgical evaluation at Mayo Clinic (Rochester, MN) were included. Clinical information was listed in Table 1. Resting state functional images were acquired using a General Electric 3T Signa HDx (Waukesha, Wisconsin) scanner. Each set of data was 20 min using a T2*-weighted EPI sequence. TR=3000 ms, flip angle =90, 3 mm isotropic voxel, 30±2 slices. The study was conducted according to a protocol approved by the Institutional Review Boards (IRB) of Mayo Clinic and the University of Minnesota respectively.

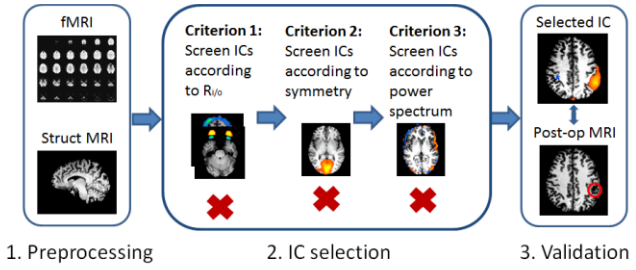

Figure 1. Data analysis procedures

Healthy subjects with motor tasks:

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Ten healthy volunteers (ages 20-36 years, 27.5±5.6 years, 5 males) participated in this study with written consent according to a protocol approved by the Institutional Review Board of the University of Minnesota. The experiment followed a block design where task blocks were interleaved with resting blocks. Each block lasted for 20 s. Within a task block, subjects performed randomized left and right hand movement tasks. The tasks included either finger tapping or hand clenching of a given hand, one hand at a time. Each task block included only one type of task. Each individual anatomical MRI data set consisted of 176 contiguous sagittal slices with 1 mm slice thickness (matrix size: 256 * 256; FOV: 256 mm * 256 mm; TR/TE=20 ms/3.3 ms) on a 3T MRI system (Siemens Skyra, Siemens, Erlangen, Germany).

B. *Data Processing*

Pre-surgical structural MRI was first segmented into two parts: regions within the boundary of the brain volume and those outside of the boundary. FMRI data were then corregistered to the structural MRI. The boundary of the brain from the segmented structural MRI was used as a marker to distinguish voxels corresponded to areas inside *vs.* outside of the brain in a later step after ICA decomposition. All fMRI data were pre-processed for slice scan time correction, 3-D motion correction and temporal filtering using BrainVoyager QX software (Brain Innovation, Maastricht, Netherlands). Independent component analysis (ICA) in the spatial domain was performed using Brain Voyager QX. Detailed methodological principles of ICA decomposition implemented in Brain Voyager QX were previously described [6, 7].

C. *Classification of components*

We proposed a set of data driven criteria to identify epilepsy related independent components (ICs). The criteria and rationales are described as following:

Criterion 1: Biophysical constraints of neurological sources. Neurological activities are known to be generated by neurons residing in the grey matter of the cortex [8]. However the BOLD signal measured is often confounded with other sources caused by physiological activities such as breathing, pulsation, or abrupt motion artifacts [9, 10]. Some of these noisy components tend to have majority of the activity outside of the cortex in areas such as brainstem, eyes or the periphery of the cortex, which is usually due to residual motion artifacts [7, 10]. As described in the pre-processing section, the boundary of the brain obtained from segmenting the structural MRI was used to mark fMRI voxels as inside vs. outside of the brain. To quantify this feature, we used the index $R_{i/o}=N_i/N_o$, where N_i denotes the number of voxels inside the brain, and N_o is the number of voxels outside of the brain. Components with $R_{i/o}$ value below a cut-off value will be excluded from further analysis (Fig. 1, Step 2, Criterion 1). This was to separate cortical components from noisy components with signals concentrated predominantly outside of the brain volume. The default cut-off value was set to be the median of $R_{i/o}$ values of all thirty components. This particular cut-off value was adopted to be inclusive rather exclusive. In this way, half of all the components will remain to be considered based on the next criterion.

Criterion 2: Spatial lateralization of the epilepsy related components in suitable surgical candidates. The concept of lateralization has traditionally been used in EEG to initially lateralize epileptogenic zone and to guide placement of intracranial recording. We now applied a similar concept in fMRI data analysis. As mentioned earlier, the patient population is surgical candidates with focal epilepsy. We assumed the epileptic activity is lateralized to one hemisphere. On the other hand, other common resting state activities in the brain are usually symmetrical. Such components include signals arising from major blood vessels, auditory activities, or default mode network [11-13]. To quantify the symmetricity of the signal distribution of each component, we used the index Corr to denote the correlation of activities among mirroring voxels about the anterior commissure – posterior commissure (ACPC) plane. The correlation value was calculated using Pearson's correlation coefficient. Then the components were ranked according to their Corr values, from the smallest to the largest. Asymmetrical components are thus the ones with low Corr values.

Criterion 3: Temporal features of the components. Components that passed the two aforementioned spatially based criteria were subjected to a third temporally based criterion to remove any additional noise. Components with dominant power outside of the range of 0.01 to 0.1 Hz were excluded. As described by De Martino et al [7], neurophysiologically meaningful components are expected to have certain temporal structure, which often fall within the range of 0.01 to 0.1 Hz [14, 15]. Components with dominant frequency outside of this range are often a reflection of aliasing of cardiac and respiration artifacts (>0.1 Hz) or scanner susceptibility artifacts (<0.01 Hz).

Evaluation

Patients with focal epilepsy

In the patient study, the spatial patterns of identified components were compared to the co-registered postoperative MRI. If the area of activity in the identified component falls within or well overlaps with the resected area, the component was considered as concordant. The surgical outcome was also used as a reference.

Healthy subjects with motor tasks

In the motor task experiment, the accuracy of identified components was evaluated both temporally and spatially. In the temporal aspect, the time course of identified components was then compared with the expected time course to compute the correlation coefficient. The expected time course of motor response was obtained by convolving the block design time and the canonical hemodynamic response function (HRF). Spatially, a general linear model was used with expected time course as a regressor to obtain the activation maps corresponds to the motor tasks. The activation maps were compared to maps of identified components.

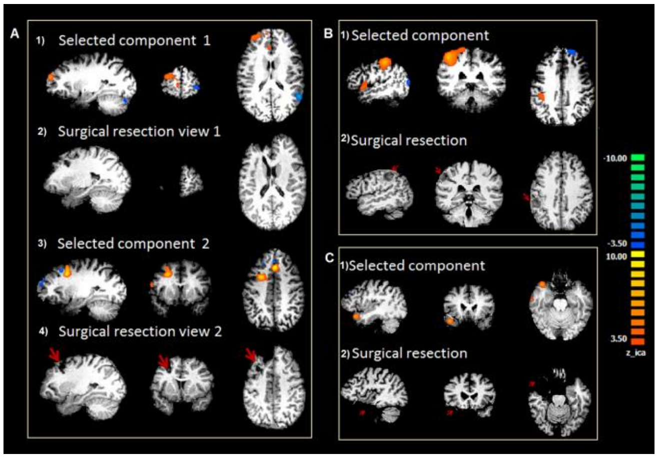

Figure 2. Results from Patient 1-3. A: Results from Patient #1. 1) and 3) are the components selected by the proposed algorithm. 2) and 4) are post-operation MRI, showing two different surgical locations corresponding to the two identified components. B: Results from patient #2. B1 shows the only component selected by the algorithm and accepted by visual inspection. B2 shows surgical resection in left parietal lobe, indicated by red arrows. C: Results from Patient #3. C1 shows the only component selected by the algorithm and accepted by visual inspection. C2 shows surgical resection in left temporal lobe.

III. RESULTS

Patient 1 was diagnosed with frontal lobe epilepsy and underwent left frontal craniotomy. In our component selection algorithm, the cut-off value of $R_{i/o}$ used in Criterion 1 is 0.9 and the cut-off value of Corr used in Criterion 2 is 0.16. Three out of fifteen components passed Criterion 2.The first component (Fig. 2-A1, $R_{i/o}$=2.62, Corr = 0.12) shows activity in left frontopolar cortex, which falls within the surgical resected zone as indicated by the red arrow in postoperative MRI (Fig. 2-A2). Component 2 ($R_{i/o}$=0.90, Corr = 0.16) has two areas of activities (Fig. 2-A3). One is located in the midline along the longitudinal fissure, and another near to the left middle frontal gyrus, which coincides with another region of resection as shown in Fig. 2-A4.

Patient 2 had left parietal epilepsy. Presurgical EEG showed frequent epileptogenic abnormalities over the left central region, which was consistent with a partial seizure disorder. In this patient, the cut-off value of $R_{i/o}$ in Criterion 1 is 1.2 and the mean of $R_{i/o}$ and cut-off value of Corr used in Criterion 2 is 0.29. Two out of the fifteen components passed Criterion 3 and were examined by visual inspection. One first component (Fig. 2-B1, $R_{i/o}$= 2.2, Corr=0.27) localized in the close vicinity of the surgical resected parietal cortex (Fig. 2-B2). This patient received intra-cranial recording and left parietal cortical resection. The largest cluster with the highest z-sore of the selected component falls in the right parietal cortex, which is in concordance with the resected region.

Information and results of all patients were summarized in Table 1. All five patients received surgery. Epilepsy related components found in all five patients were highly concordant with surgical resection.

TABLE I. RESULT SUMMARY

Pt ID	***Age***	***Sex***	***Clinical Diagnosis***	***Resection***	***No. of ICs****	***Surgical Outcome***
1	27	M	Left frontal	Left frontal focal resection	2 (3)	--
2	25	F	Left parietal	Left frontoparietal focal resection	1 (2)	ILAE-1
3	58	F	Left temporal	Left temporal lobectomy	1 (1)	ILAE-4
4	20	M	Left temporal	Left temporal lobectomy	2 (2)	ILAE-1
5	58	M	Right temporal	Optic laser ablation of hippocampus	1 (3)	ILAE-1

* # ICs concordant: the number of components that are in concordant with surgical resection area. The total number of components selected by the algorithm is indicated in the parenthesis. Clinical follow-up for Pt#1 is not available.

Healthy subjects with motor tasks

Results from healthy subjects performing motor tasks served as an evaluation of the sensitivity of the proposed algorithm. The method detected lateralized motor-task-related components from ICA with minimal supervision and high accuracy across all subjects. We examined the spatial and temporal features of the selected components to the timing of the task design. The time course of the selected component was correlated with the expected time course based on the known stimulus onset convolved with canonical HRF. The identified components have BOLD activities in the sensorimotor areas correspond to the left or right hand. Fig. 3A shows the averaged map obtained from maps of identified motor task related ICs. Fig. 3B shows the averaged map obtained from GLM using expected time course derived from experiment design as the main regressor. Temporally, the Pearson's correlation coefficient between the identified IC time course and the expected time course specified by the experiment is 0.72 ±0.08.

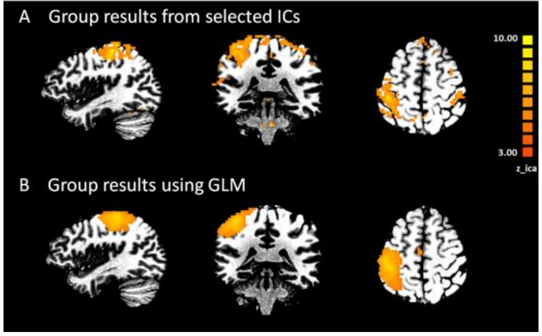

Figure 3. Group results in healthy subjects performing right hand motor tasks. A) Averaged map of selected independent components(IC) from all subjects. B) Group averaged activation map obtained from GLM analysis.

IV. DISCUSSION

For the purpose of localizing hemodynamic foci in focal epilepsy patients, we proposed an automated algorithm that detects epilepsy related components from ICA with minimal supervision and high accuracy. Our algorithm was evaluated by comparing the identified components to surgical resection. In the current patient group we were able to lateralize and localize hemodynamic foci using proposed method reasonably well. We also tested the algorithm in healthy subjects with motor tasks and the results showed reasonable sensitivity and specificity of the method.

A. *Model Applications*

This proposed method can be readily incorporated in the current presurgical workup to provide additional information for guiding the surgical resection. The benefits are two folds. Firstly of all, the data currently used were collected as part of clinical routine for mapping of eloquent brain to preserve during the surgery. Therefore, to implement this method, no additional scans need to be prescribed. Secondly, the algorithm is automated and does not require subjective input or excessive training from the clinicians. However, at this stage, it is not meant to replace any aspect of the presurgical planning process, but rather to further inform each step of presurgical planning.

B. *Model Assumptions*

In this study, we aimed to identify epilepsy related components from components produced by spatial ICA of resting state fMRI by applying three basic assumptions. The first assumption is that neurological activity dominant components should locate mainly inside the brain volume. This was assessed by calculating the ratio between the numbers of voxels with activity inside *vs.* outside of the brain volume. Secondly, we focused on focal epilepsy patients and assumed that this group of patients have unilateral, epilepsy related BOLD foci. With this condition, we could easily separate epilepsy related components from other neurophysiological components associated with auditory or occipital activation. The third assumption is that BOLD fluctuations due to neurological activity have a frequency range near to 0.01 to 0.1 Hz. Some noisy components may fall within the perimeter of the brain and have asymmetrical distribution, but these components often have dominant frequency fall below 0.01 Hz or above 0.1 Hz due to artifacts from aliasing of cardiac and respiration activity or scanner susceptibility.

C. *Method Limitations*

Although the proposed method worked reasonably well in the current patient group, where patients only had unilateral focal epilepsy, this method was not intended to be an all-encompassing approach that will detect all epilepsy foci in all focal epilepsy cases. If the epileptic activities originate bilaterally, the method will not provide additional insight. This method is also not perfect in rejecting all non-epilepsy components. As seen in both patient and healthy subject results, there are a small number of non-epilepsy related components selected by the algorithm. A further improvement in the algorithm could potentially exclude such components.

V. CONCLUSION

In the present study we proposed an ICA-based automated method to lateralize and localize hemodynamic foci in focal epilepsy patients for presurgical evaluation. Focal activities identified by our method were in concordant with surgical resection in majority cases studied. Our findings suggest the possibility of noninvasively and accurately localizing hemodynamic epileptic foci using fMRI alone in presurgical planning. Overall, this is a feasibility study to demonstrate the value of the proposed method. A larger patient population needs to be studied to test the broad applicability of this method. This proposed method can be easily implemented in the current presurgical workup to provide additional information for guiding the surgical resection.

REFERENCES

[1] Rodionov R, De Martino F, Laufs H, Carmichael DW, Formisano E, Walker M, et al. “Independent component analysis of interictal fMRI in focal epilepsy: comparison with general linear model-based EEG-correlated fMRI”. Neuroimage 2007; 38:488–500.

[2] Thornton R, Powell R, Lemieux L. fMRI in Epilepsy. In Filippi M, editors. fMRI Techniques and protocols, Neuromethods, 41, Springer, 2009: 681-735.

[3] Liu Z, Kecman F, He B. Effects of fMRI-EEG mismatches in cortical current density estimation integrating fMRI and EEG Noninvasive cortical imaging of epileptiform activities from interictal spikes in pediatric patients: a simulation study. Clin Neurophysiol 2006; 117:1610–22

[4] Liu Z, He B. fMRI-EEG integrated cortical source imaging by use of time-variant spatial constraints. Neuroimage 2008; 39(3):1198–214.

[5] He B, Liu Z. *Multimodal functional neuroimaging: integrating functional MRI and EEG/MEG*. IEEE Rev Biomed Eng 2008; 1:23–40.

[6] Formisano E, Esposito F, Di Salle F, Goebel R. Cortex-based independent component analysis of fMRI time-series. Magn Reson Imaging 2004; 22:1493–1504.

[7] De Martino F, Gentile F, Esposito F, Balsi M, Di Salle F, Goebel R, et al. Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers. NeuroImage 2007; 34:177–194.

[8] Arthurs OJ and Boniface S. How well do we understand the neural origins of the fMRI BOLD signal? Trends Neurosci 2002; 25:27–31.

[9] McKeown MJ, Jung T-P, Makeig S, Brown GG, Kindermann SS, Lee T-W, et al. Spatially independent activity patterns in functional magnetic resonance imaging data during the Stroop color-naming task. Proc Natl Acad Sci U S A 1998; 95:803–810.

[10] Mitra PP, Ogawa S, Hu X, Ugurbil K. The nature of spatiotemporal changes in cerebral hemodynamics as manifested in functional magnetic resonance imaging. Magn Reson Med 1997; 37:511–518

[11] Raichle ME, MacLeod AM, Snyder AZ, PowersWJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001*;* 98:676–682.

[12] Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005; 102:9673–9678.

[13] Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 2009; 19:72-78.

[14] Cordes D, Haughton VM, Arfanakis K, Carew JD, Turski PA, Moritz CH, et al. Frequencies contributing to functional connectivity in the cerebral cortex in “resting state” data. Am. J. Neuroradiol 2001; 22:1326–1333.

[15] Negishi M, Martuzzi R, Novotny E, Spencer DD, Constable RT. Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. Epilepsia 2011; 52:1733-1740.