Clinical Usefulness of Simultaneous Electroencephalography and Functional Magnetic Resonance Imaging in Children With Focal Epilepsy

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Background and Purpose The current study analyzed the interictal epileptiform discharge (IED)-related hemodynamic response and aimed to determine the clinical usefulness of simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI) in defining the epileptogenic zone (EZ) in children with focal epilepsy.

Methods Patients with focal epilepsy showing IEDs on conventional EEG were evaluated using EEG-fMRI. Statistical analyses were performed using the times of spike as events modeled with multiple hemodynamic response functions. The area showing the most significant t-value for blood-oxygen-level-dependent (BOLD) changes was compared with the presumed EZ. Moreover, BOLD responses between -9 and +9 s around the spike times were analyzed to track the hemodynamic response patterns over time.

Results Half (n=13) of 26 EEG-fMRI investigations of 19 patients were successful. Two patients showed 2 different types of spikes, resulting in 15 analyses. The maximum BOLD response was concordant with the EZ in 11 (73.3%) of the 15 analyses. In 10 (66.7%) analyses, the BOLD response localized the EZs more specifically. Focal BOLD responses in the EZs occurred before IEDs in 11 analyses and were often widespread after IEDs. Hemodynamic response patterns were consistent in the same epilepsy syndrome or when repeating the investigation in the same patients.

Conclusions EEG-fMRI can provide additional information for localizing the EZ in children with focal epilepsy, and also reveal the pathogenesis of pediatric epilepsy by evaluating the patterns in the hemodynamic response across time windows of IEDs.

Keywords electroencephalography; functional magnetic resonance imaging; child; focal epilepsy.

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INTRODUCTION

Patients with drug-resistant epilepsy (DRE) experience a considerable burden when their condition is being treated. Despite the introduction of over 20 new antiepileptic drugs over the past several decades, 30%–40% of patients with epilepsy are refractory to pharmacotherapy.[1] The surgical removal of brain regions responsible for the epileptogenic onset may represent the only option that will result in patients with DRE becoming seizure-free, especially for those with focal onset. The accurate localization of the epileptogenic zone (EZ) can not only improve seizure outcomes but also reduce postoperative complications in the functional areas of the brain. Multimodal approaches combining multiple functional imaging methods such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) can clarify the mechanism underlying the epileptic process and

help improve the accuracy of localizing the EZ. However, it is often difficult to apply these nuclear medical techniques to evaluate seizures in young children due to the need for the separate assessment and administration of the radiocontrast agent. Furthermore, even with extensive presurgical evaluation, adequate localization of the EZ is challenging, specifically in patients without noticeable lesions on brain magnetic resonance imaging (MRI).[2]

Simultaneous electroencephalography and functional magnetic resonance imaging (EEG-fMRI) is a noninvasive functional imaging technique used to detect hemodynamic changes associated with interictal epileptiform discharges (IEDs) observed on scalp EEG.[3,4] By combining time information of the EEG markers of epilepsy with blood-oxygenation-level-dependent (BOLD) signal changes on fMRI, EEG-fMRI can visualize changes in neuronal activity across the whole brain with a high spatial resolution during epileptic activity. IEDs arise from the so-called irritative zone, which is usually more extensive than the EZ.[5] However, previous studies of EEG-fMRI have suggested that IED-related BOLD changes, especially those with the highest t-value, are highly concordant with the presumed EZ.[6-10] Moreover, such studies have contributed to a better understanding of the epileptogenic network predominant in children, such as in Lennox−Gastaut syndrome, childhood absence epilepsy, and childhood epilepsy with centrotemporal spikes (CECTS).[11-13]

One challenge when applying the EEG-fMRI procedure in clinical settings is poor patient cooperation, especially among children with intellectual disabilities. This means that most children need to be sedated to reduce anxiety, which might affect the EEG-fMRI results.[10,14] Furthermore, age, sleep status, and antiepileptic medication can affect IED-related BOLD changes, which may increase differences in the detection rates of the EZ.[14,15]

The current study aimed to determine the clinical usefulness of EEG-fMRI for the localization of the EZ in children with focal epilepsy. We measured the success rate of EEG-fMRI investigations in pediatric epilepsy and identified how the measured hemodynamic response associated with IEDs contributes to the localization of EZ. Additionally, we evaluated BOLD changes across pre-, peri-, and postspike periods in order to obtain more information about epileptic networks.

METHODS

Patients

We recruited patients with focal epilepsy who were diagnosed and treated at Kyungpook National University Hospital between March 2019 and March 2021. A detailed clinical evaluation, conventional MRI, and routine EEG were performed in each patient prior to EEG-fMRI. EEG-fMRI data were acquired in patients who fulfilled the following inclusion criteria: presence of frequent focal IEDs on routine EEG (>10 within 20 min), aged between 8 and 18 years, and able to undergo MRI without sedation. This research was approved by the Research Ethics Committee of Kyungpook National University Hospital (approval number: 2018-11-028-001). All patients and their parents provided written informed consent prior to study participation.

EEG-fMRI data acquisition

Before acquiring the EEG-fMRI data, EEG data were recorded for 10 min with the patient outside the fMRI scanner to differentiate the morphology and type of IEDs. Patients were then transferred to the MRI scanner table and instructed to remain motionless with their eyes closed. We encouraged participants to sleep during the study. No sedating medication was administered. All patients underwent two or three 10-min fMRI sessions and T1-weighted whole-brain structural imaging. fMRI data were obtained using a 3-T MRI system (MAGNETOM Skyra; Siemens Healthcare, Erlangen, Germany). The gradient-echo echo-planar imaging parameters for fMRI were as follows: repetition time (TR)/time to echo (TE)=2,000 ms/30 ms, field of view (FOV)=192×192 mm², thickness=3 mm, flip angle (FA)= 80°, matrix size=64×64, 31 slices, in-plane acceleration factor=2, and number of reference lines=24. For anatomical imaging, the parameters for 3D T1-weighted imaging sequence were as follows: TR/TE= 2,530 ms/1.67 ms, FOV=256×256 mm², thickness=1 mm, FA=7°, matrix size=256×256, and 176 slices.

EEG data were acquired using a 64-electrode MRI-compatible EEG cap (GES 300; EGI, Eugene, OR, USA). EEG data were bandpass filtered at cutoff frequencies of 0.7 and 55 Hz, and the sampling rate was 500 Hz. MRI gradient and pulse-related artifacts were removed by template subtraction and optimal basis set methods using the Net Station software of the EEG system, respectively.[16] Two experienced epileptologists (Y.J.L and S.H.K.) reviewed and manually marked IEDs in the filtered EEG recordings according to their spatial distribution and morphology for each patient. Each EEG recording was reviewed in both bipolar and referential montages to accurately identify IEDs. IEDs with different spatial distributions and morphology were considered as different types of IEDs and therefore analyzed separately.

EEG-fMRI data analysis

fMRI data were preprocessed and analyzed using Statistical Parametric Mapping software (version 12, https://www.fil.ion. ucl.ac.uk). The following preprocessing process was applied to the data sets acquired in each recording session: realign-

ment, coregistration, normalization, and smoothing (Gaussian kernel with full width at half maximum of 8 mm). EEG data obtained in scans with motion artifacts were excluded. We used general linear modeling with each IED type using its own regressor. The times of IEDs were convolved with four single gamma functions peaking at 3, 5, 7, and 9 s after the event.[17] The highest absolute value among the four t-value maps was used to generate a combined map of t-values. The BOLD response was considered significant for a criterion of $t>3.1$ corresponding to $p<0.01$, corrected for multiple comparisons (family-wise error rate), and a cluster size voxel with a minimum of five continuous voxels.[18] Both significant activation and deactivation BOLD responses were considered equally, based on previous observations of both in the EZ.[10,19] Patients for whom at least three IEDs were not recorded inside the scanner or whose EEG or MRI data were of unsatisfactory technical quality were excluded from the final analysis.

To evaluate hemodynamic changes may reflect the epileptic network, they were evaluated by performing separate analyses using hemodynamic response functions (HRFs) consisting of a single gamma function peaking at -9, -7, -5, -3, -1, +1, +3, +5, +7, and +9 s relative to the event. Three combined maps were created to fuse several peak timings by taking the highest absolute values for each voxel among a group of t-value maps. The pre-, peri-, and postspike maps combined the t statistics of the HRFs peaking from -9 to -5 s, from -3 to +1 s, and from +3 to +9 s, respectively. BOLD signals were considered significant for $t>3.1$ and a cluster size with a minimum of 12 continuous voxels to obtain a p-value of 0.05, corrected for multiple comparisons.[20] We defined the cluster having the maximum t-value from each map and compared the highest t-value and the extent of the cluster between the maps. The extent of the response was quantified by measuring the number of activated voxels within a cluster. If a BOLD response in the spike field or presumed EZ was found in several maps, we compared the extent of the response between the maps. The presumed EZ was defined for each patient on the basis of clinical information available from routine EEG, ictal semiology, and conventional MRI.

BOLD-response assessments

Deactivation BOLD responses in the default-mode network—including the posterior cingulate cortex, precuneus, bilateral inferior parietal lobule, and ventral medial prefrontal cortex—were not considered significant BOLD responses due to the absence of a localizing value.[21,22] Responses outside the brain parenchyma were also excluded from the analysis. Concordance was confirmed when the cluster with the maximum t-value was consistent with the presumed EZ; otherwise dis-

cordance was confirmed. EEG-fMRI results were considered contributory when more information was obtained from the BOLD responses than from routine EEG, such as when they enabled a more-accurate localization of the cortical regions responsible for the generation of a spike within a lobe or showed a maximum t-value in deep brain structures likely to be part of the EZ. A successful EEG-fMRI investigation was defined as that with good quality fMRI and EEG data and an active EEG recording showing frequent IEDs.

RESULTS

A total of 19 patients (9 females) underwent 26 EEG-fMRI investigations (Fig. 1), which were repeated in 7 patients. The age at evaluation was 10.7 ± 2.3 years (mean$\pm$SD, range 8−15.9 years). Overall, 13 (50%) of the 26 EEG-fMRI investigations performed in 11 patients were successful, with the remainder having fewer than 3 IEDs ($n=7$, 26.9%), failure of data acquisition due to patient discomfort ($n=3$, 11.5%), or serious artifacts ($n=3$, 11.5%). We did not succeed in obtaining the data from five of the seven patients who underwent a second EEG-fMRI investigation due to the absence of IEDs during recordings. Two patients experienced two distinct IED types during EEG-fMRI. Finally, 15 analyses were performed to evaluate the hemodynamic response to IEDs.

The clinical data of the 11 patients included in the final analyses are presented in Supplementary Table 1 (in the online-only Data Supplement). Four patients showed structural abnormalities on MRI. Four patients were diagnosed with epilepsy syndrome, namely CECTS ($n=3$) and Panayiotopoulos syndrome (PS, $n=1$). Among the 29 sessions included in the final analysis, 15 (51.7%) sessions were obtained during
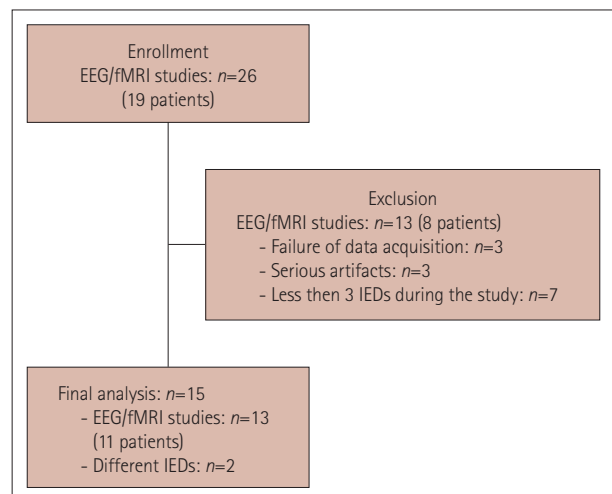

Fig. 1. Flowchart of the study population. EEG, electroencephalography; fMRI, functional magnetic resonance imaging; IED, interictal epileptiform discharge.

the waking period. Nine patients were taking antiepileptic drugs at the time of data acquisition.

Concordance between BOLD responses and the EZ

Both significant activation and deactivation BOLD responses were observed during all 15 analyses. The cluster with the highest t-value was observed at the activation and deactivation responses in 11 and 4 analyses, respectively. The cluster with the highest t-value was concordant with the EZ in 11 (73.3%) of the 15 analyses, among which 8 and 3 were in activation and deactivation BOLD responses, respectively (Table 1). Two patients who underwent a second EEG-fMRI investigation showed the same lesion as the cluster with the highest t-value in each study, which was concordant with the presumed EZ. One patient with malformation of cortical development (MCD) on the right temporal lobe (Patient 10) exhibited the same lesion as in the area with the highest t-value, but it appeared once as activation and once as deactivation.

Contribution of BOLD responses to localizing the EZ

The clusters with the highest t-values contributed to the more-precise localization of the EZ in 10 (66.7%) of the 15 analyses, among which 6 and 4 cases had non-lesional and lesional epilepsy, respectively (Table 1). In nine analyses, the BOLD response was better than EEG alone at determining the cortical region generating the spike within a lobe (Fig. 2A). One patient (Patient 10) exhibited maximum BOLD responses in the deep brain structure (fusiform gyrus) likely belonging to the EZ. However, in one analysis (Patient 7), the cluster with the maximum t-value response was concordant with the spike field, but it did not contribute to determining the focal region due to the broad extent of the cluster (Fig. 2B).

Patterns of the hemodynamic response over time

To evaluate the hemodynamic response before and after IEDs, separate analyses were conducted using HRFs consisting of a single gamma function peaking from -9 to +9 s. After comparing clusters with the maximum t-value in different maps and the presumed EZs, we found that clusters with the maximum t-value in 1 of the 3 maps were concordant with the presumed EZs in all 15 analyses. The detailed responses for each map are summarized in Table 2. The pattern of responses did not differ systemically between patients with and without structural abnormalities. Focal BOLD responses within the presumed EZ area were observed in the early maps (prespike map, $n=6$; perispike map, $n=9$) in 11 analyses (Table 3). These focal BOLD responses extended to larger clusters or several small clusters within the presumed EZ in the postspike map. Four analyses revealed significant BOLD responses in the EZ area appearing as activation in the early maps (pre- or perispike) followed by deactivation response in the later maps (postspike) (Investigations 3, 12, 13, and 14) (Table 3). In contrast, three analyses revealed significant deactivation BOLD responses in the early maps that were followed by activation

Table 1. Comparisons between the maximum BOLD response and the presumed EZ

Investigation	Pt	ES	IED types during EEG–fMRI	Number of IEDs	EZ	BOLD response with maximum t–value[†]	Concordance	Contribution
1	1	CECTS	R CT	347/20 min	R CT	R primary sensory	Y	Y
2	1	CECTS	R CT	38/20 min	R CT	R primary sensory	Y	Y
3	2	CECTS	L CT	727/30 min	L CT	L primary sensory	Y	Y
4	3	CECTS	L C	59/20 min	L C	L insular	Y	Y
5	4	PS	L PO	332/20 min	L O	L visual association*	Y	Y
6	5	-	R F	63/30 min	R F	L orbitofrontal	N	N
7	6	-	L CT	44/20 min	L CT	R primary sensory*	N	N
8	6	-	R CT	26/20 min	R CT	R temporopolar*	Y	Y
9	7	-	L FCP	96/30 min	L FCP	R sensory association	N	N
10	7	-	R FP	134/30 min	R FP	R primary sensory	Y	N
11	8	-	R F	135/20 min	R F	R premotor	Y	Y
12	9	-	L F	255/20 min	L F	L frontal eye field	Y	Y
13	10	-	R TP	510/20 min	R TP	R fusiform	Y	Y
14	10	-	R TP	133/20 min	R TP	R fusiform*	Y	Y
15	11	-	R FCT	942/20 min	R F	L secondary visual	N	N

*Deactivation BOLD response; [†]BOLD response with maximum t-value from the four t maps created with the four hemodynamic response functions peaking at 3, 5, 7, and 9 s after the event.
BOLD, blood-oxygenation-level-dependent; C, central; CECTS, childhood epilepsy with centrotemporal spikes; CT, centrotemporal; EEG, electroencephalography; ES, epilepsy syndrome; EZ, epileptogenic zone; F, frontal; FCP, fronto-centro-parietal; FCT, fronto-centro-temporal; fMRI, functional magnetic resonance imaging; FP, frontoparietal; IED, interictal epileptiform discharge; L, left; N, no; O, occipital; PO, parietooccipital; PS, Panayiotopoulos syndrome; Pt, patient; R, right; TP, temporoparietal; Y, yes.
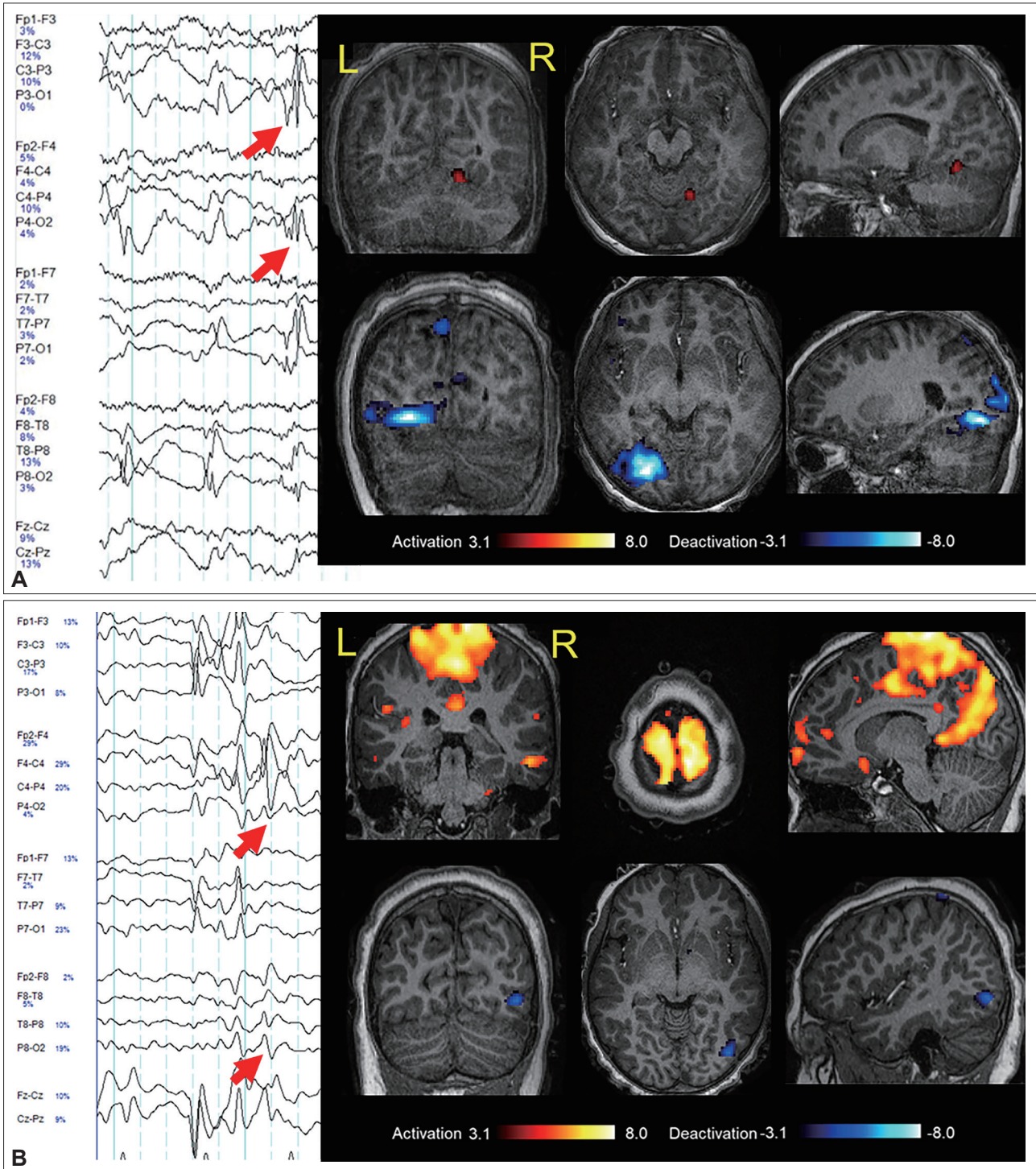
Fig. 2. Examples of blood-oxygenation-level-dependent (BOLD) responses. A: An 8-year-old patient with Panayiotopoulos syndrome (Patient 4). The interictal epileptiform discharges (IEDs) were spike discharges in the bilateral occipital area, predominantly on the left side (red arrows). The cluster with the maximum t-value was deactivation in the left visual association cortex (t=8.09). This is an example of a BOLD response that was considered concordant and contributory. B: An 8-year-old patient with multiple IEDs on scalp electroencephalography (EEG) (Patient 7). There were two different types of spike discharges on scalp EEG. This map was analyzed with the spike in the right fronto-centro-temporal area (red arrows). The cluster with the highest t-value was an activation BOLD response in the right primary sensory cortex, which was concordant with the spike field but did not contribute to the determination of the focal region due to the broad extent of the cluster.

responses in the later maps (Investigations 1, 8, and 15) (Table 3).

We then evaluated the patterns of response according to epilepsy syndrome. One patient with PS exhibited a significant deactivation BOLD response in the occipital lobe in all three maps, which was consistent with the area of the pre-

Table 2. Areas with BOLD responses having the maximum *t*-values in the three maps

Investigation	Pt	ES	IED types during EEG–fMRI	EZ	Prespike map (–9 to –5 s)	Perispike map (–3 to +1 s)	Postspike map (+3 to +9 s)	Concordance
1	1	CECTS	R CT	R CT	R primary motor*	R primary sensory†	L thalamus	Y
2	1	CECTS	R CT	R CT	R primary motor	R primary motor	R primary motor†	Y
3	2	CECTS	L CT	L CT	R posterior superior temporal	L primary sensory†	L primary sensory*	Y
4	3	CECTS	L C	L C	R SMA*	L insular†	L dorsolateral prefrontal cortex	Y
5	4	PS	L PO	L O	L orbitofrontal*	L visual association*†	L visual association*	Y
6	5	–	R F	R F	R primary sensory	R orbitofrontal	L orbitofrontal†	Y
7	6	–	L CT	L CT	R occipital	R premotor*†	L premotor	Y
8	6	–	R CT	R CT	L primary motor*	R temporal pole*†	R premotor	Y
9	7	–	L F	L FCT	L primary sensory	R parietal†	R parietal	Y
10	7	–	R FP	R CTP	R primary sensory	R primary sensory	R primary sensory†	Y
11	8	–	R F	R F	L premotor	R SMA	L anterior prefrontal†	Y
12	9	–	L F	L F	R fusiform	L frontal eye field	L frontal eye field*†	Y
13	10	–	R TP	R TP	R angular	R fusiform†	R fusiform*	Y
14	10	–	R TP	R TP	R supramarginal	R visual association	R fusiform*†	Y
15	11	–	R FCT	R F	R frontal eye field*†	R frontal eye field*	L pars triangularis	Y

*Deactivation BOLD response; †BOLD response with the maximum *t* value among in the three maps (pre-, peri-, and postspike maps).
BOLD, blood-oxygenation-level-dependent; C, central; CECTS, childhood epilepsy with centrotemporal spikes; CT, centrotemporal; CTP, centro-temporo-ro-parietal; EEG, electroencephalography; ES, epilepsy syndrome; EZ, epileptogenic zone; F, frontal; FCT, fronto-centro-temporal; fMRI, functional magnetic resonance imaging; FP, frontoparietal; IED, interictal epileptiform discharge; L, left; N, no; O, occipital; PO, parietooccipital; PS, Panayiotopoulos syndrome; Pt, patient; R, right; SMA, supplementary motor area; TP, temporoparietal; Y, yes.

Table 3. Extent of significant BOLD response in the presumed EZ

Investigation	Pt	ES	IED types during EEG–fMRI	EZ	Prespike map (–9 to –5 s)	Perispike map (–3 to +1 s)	Postspike map (+3 to +9 s)
1	1	CECTS	R CT	R CT	Diffuse* and contralateral*	Focal† and contralateral	Diffuse
2	1	CECTS	R CT	R CT	Focal	Diffuse and contralateral	Diffuse†
3	2	CECTS	L CT	L CT	Contralateral and distant	Focal and distant†	Focal*
4	3	CECTS	L C	L C	Contralateral	Focal†	Distant
5	4	PS	L PO	L O	Focal*	Diffuse*†	Diffuse*
6	5	–	R F	R F	Distant	Focal	Contralateral†
7	6	–	L CT	L CT	Contralateral	Contralateral* and focal†	Focal
8	6	–	R CT	R CT	Contralateral*	Focal*†	Focal and distant
9	7	–	L F	L FCT	Focal	Diffuse† and distant	Focal and contralateral
10	7	–	R FP	R CTP	Focal	Diffuse† and distant	Focal and contralateral
11	8	–	R F	R F	Contralateral	Focal	Diffuse† and contralateral
12	9	–	L F	L F	Contralateral	Focal	Focal*†
13	10	–	R TP	R TP	Focal	Diffuse†	Diffuse*
14	10	–	R TP	R TP	Focal	Diffuse	Diffuse*†
15	11	–	R FCT	R F	Diffuse*†	Focal	Diffuse

*Deactivation BOLD response; †BOLD response with the maximum *t*-value among in the three maps (pre-, peri-, and postspike maps).
BOLD, blood-oxygenation-level-dependent; C, central; CECTS, childhood epilepsy with centrotemporal spikes; CT, centrotemporal; CTP, centro-temporo-ro-parietal; EEG, electroencephalography; ES, epilepsy syndrome; EZ, epileptogenic zone; F, frontal; FCT, fronto-centro-temporal; fMRI, functional magnetic resonance imaging; FP, frontoparietal; IED, interictal epileptiform discharge; L, left; O, occipital; PO, parietooccipital; PS, Panayiotopoulos syndrome; Pt, patient; R, right; TP, temporoparietal.

sumed EZ. Four investigations of three patients with CECTS revealed a significant positive BOLD response in the contralateral centrotemporal area in the early map followed by in the ipsilateral centrotemporal area in the later map (Table 3, Fig. 3).

Two patients (Patients 1 and 10) who underwent a second EEG-fMRI investigation showed the same BOLD response patterns as in their first investigation (Table 3). The patient with MCD (Patient 10) showed a focal positive BOLD response followed by a negative response in the fusiform area,

which is likely to be part of the EZ (Investigations 13 and 14) (Fig. 4). One patient with CECTS (Patient 1) showed consistent patterns in two investigations, where a focal positive BOLD response in the primary motor cortex in the early map spread diffusely in the later map (Investigations 1 and 2).

DISCUSSION

Success of EEG-fMRI in children
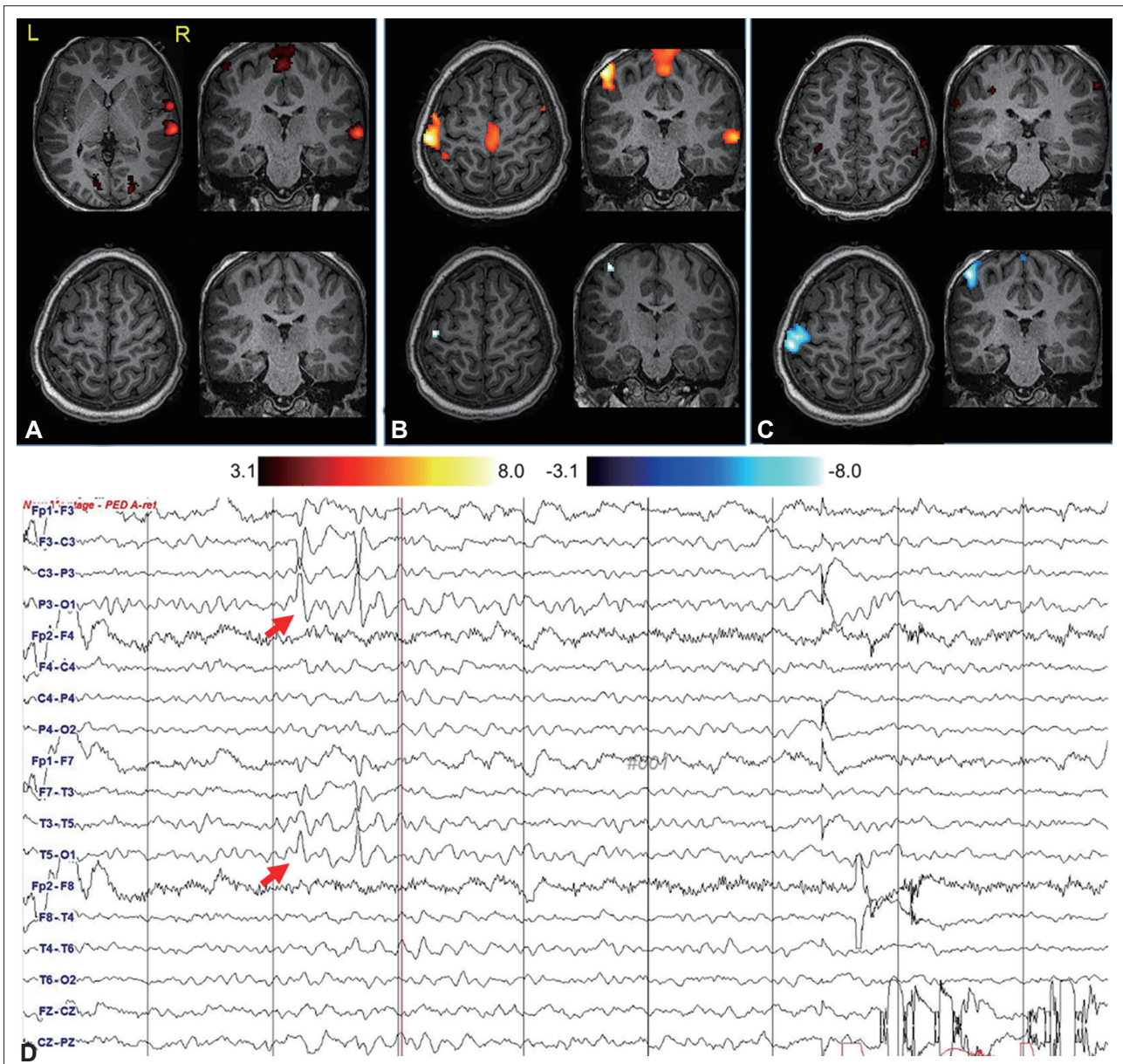This study evaluated the clinical usefulness of EEG-fMRI in

Fig. 3. Hemodynamic response patterns in a patient with childhood epilepsy with centrotemporal spikes (Patient 2). A: Prespike map. B: Perispike map. C: Postspike map. Spikes from the left centrotemporal area can be seen on scalp electroencephalography (D, red arrows). The prespike map showed a focal activation response in the right posterior superior temporal area (t=5.67). This was followed by activation in the left primary sensory cortex in the perispike map (t=7.97), which changed to deactivation in the postspike map (t=-6.62).

delineating the EZ in children with epilepsy. Half of the EEG-fMRI investigations were successful in children with epilepsy aged 8−18 years without sedation. Performing EEG-fMRI in the pediatric population is challenging due to a lack of co-operation, especially among young children and those with mental disabilities, which can often be the case with patients suffering from epilepsy. In the current study, parents stayed in the MRI room during data acquisition instead of being sedat-ed, which is often applied when children feel anxious. Chloral hydrate is widely administered for EEG recordings, and has shown minimal effects on IEDs and on the sensitivity of EEG-fMRI for mapping the epileptogenic regions.[10,23] However, the effects of sedation on epileptic activity and hemodynamic changes remain poorly understood.[23,24] Given the complex-ity of sedation, one group studied the impact of presenting a child-friendly natural stimulus (i.e., a movie) inside a scan-
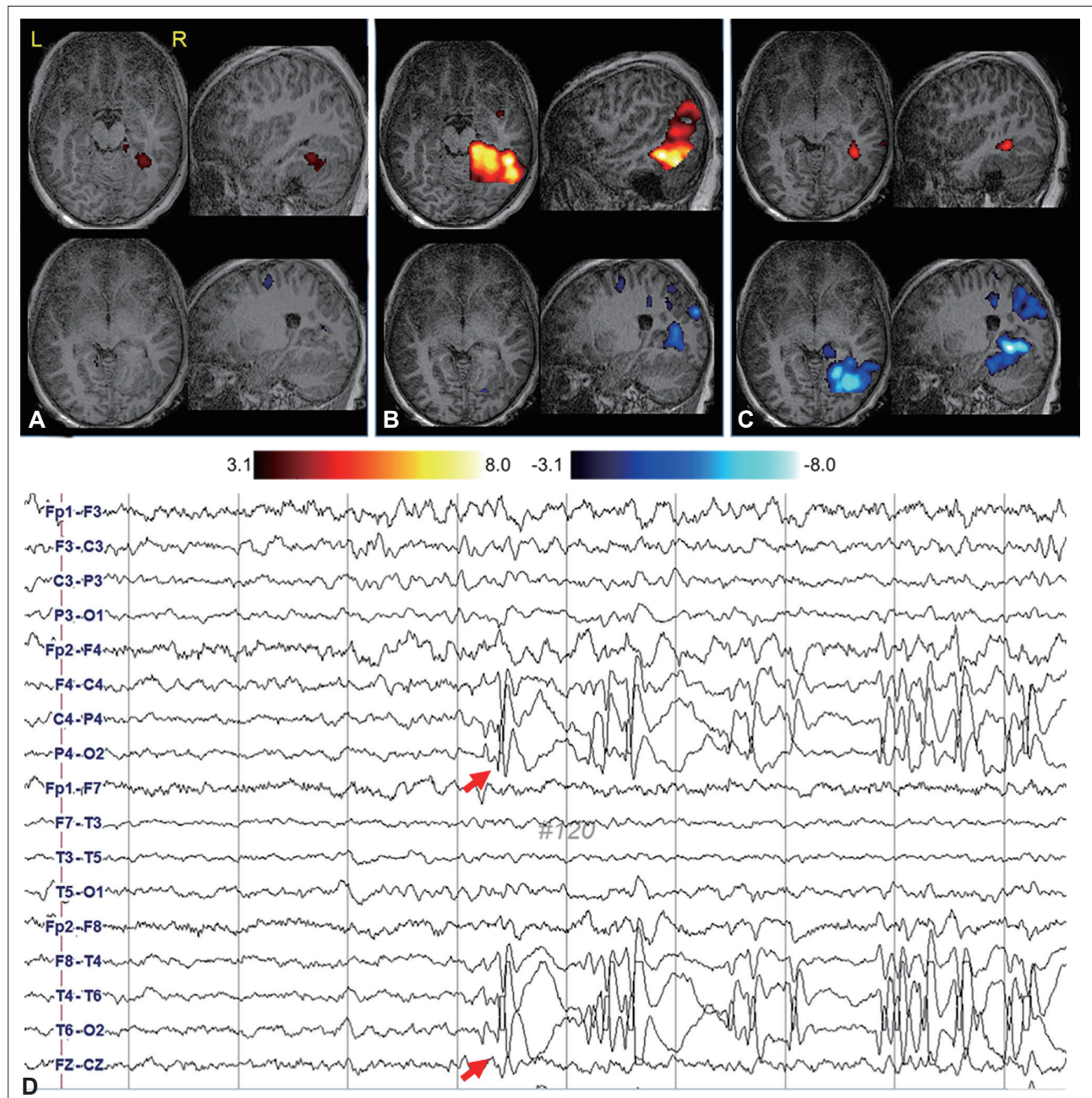

Fig. 4. Hemodynamic response patterns in a patient with malformation of cortical development (Patient 10). A: Prespike map. B: Perispike map. C: Postspike map. Spikes from the right temporoparietal area can be seen on scalp electroencephalography (D, red arrows). A focal activation response in the right fusiform area was found in the prespike map (t=4.08) and perispike map (t=12.43), which was followed by a deactivation response in the same region in the postspike map (t=-8.83).

ner on the tolerability and results of EEG-fMRI in children.[25] It was notable that this type of stimulus was found to improve the tolerability of EEG-fMRI without affecting the occurrence of IEDs or the quality of the obtained EEG-fMRI maps.

Another challenge for successful EEG-fMRI is the absence of IEDs during recordings. During seven (26.9%) of the recordings obtained herein, the patients did not exhibit an adequate number of IEDs in EEG. This result may be due to different vigilance states during the sleep−awake cycle, the use of antiepileptic drugs, and follow-up recordings after long-term treatment.[26] Furthermore, given that patients were recruited based on previous short-term EEG recordings, we could not predict how active the IEDs would be on the day of EEG-fMRI.[27] Other methods involving independent component analysis, EEG-derived scalp topography-based methods, and local connectivity analysis may be useful when IEDs are not detected.[28-30] Further studies are nonetheless needed to improve the success rate of EEG-fMRI investigations in pediatric epilepsy.[24]

Usefulness of EEG-fMRI in localizing the presumed EZ

Despite the difficulty of successfully acquiring EEG-fMRI data in children, our results suggest that EEG-fMRI can be used to accurately localize the epileptogenic foci even in epilepsy with or without extensive or multifocal structural abnormities. The BOLD response was concordant with the presumed EZ in 11 (73.3%) of 15 analyses. Moreover, focal BOLD responses were able to accurately localize the cortical regions responsible for the generation of a spike in 10 (66.7%) of 15 analyses, among which 6 and 4 involved non-lesional and lesional epilepsy, respectively. Although the relationship between irrigative-zone-generating IEDs and the EZ is still a matter of debate, previous studies have demonstrated that IEDs related to BOLD responses had more-specific localization and were generally in good agreement with the EZs, which was similar to the present findings.[6,7,10,25,27] One group reported that the areas exhibiting the most-significant hemodynamic response to IEDs were concordant with the stereoencephalography (SEEG)-defined seizure onset zone in 30 (68%) of 44 recordings in patients with difficult-to-localize focal epilepsy.[7] Another study involving a pediatric population found that BOLD responses were correlated with either the spike field or the lesion in 84% of the analyses.[10] These results indicate that IEDs may propagate from the same group of neurons or local neuronal networks from where seizures start, resulting in an appearance of a widespread irritative zone.

Previous studies have found that the sensitivity of ictal SPECT varied from 81% to 90% and that of PET varied from 30% to 80%, depending on the lobes and subject age.[31-33] Although the current study could not directly compare the utility of EEG-fMRI with PET or SPECT in localizing the EZ, our results suggest that these three techniques have comparable abilities in EZ localization. EEG-fMRI can clinically impact surgical decisions, including about whether to proceed with surgery or modifying the surgical plan, resulting in better surgical outcomes.[27] Therefore, a multimodal approach combining PET and/or SPECT with EEG-fMRI can be useful in providing additional information for localizing the EZ and guiding electrode placement in difficult-to-localize cases of focal DRE.[27,34]

Several factors could influence the sensitivity of EEG-fMRI, such as the magnetic field strength of the scanner, the analysis method (i.e., using the canonical HRF or multiple HRFs), and the number of IEDs.[35] There is evidence that the actual HRF following epileptic discharges varies between brain regions, individuals, and recording times, and is assumed to differ from the standard HRF that peaks after 5.4 s.[36] Furthermore, the poor understanding of how age and brain maturation impact the HRF might make modeling spike-related BOLD signal changes in children even more difficult. Jacobs et al.[15] demonstrated that the HRF peaked later in younger children (0−2 years) than in older children and adults. Another study suggested that significant activations already occur several seconds before IEDs in some children.[37] Therefore, patient-specific HRFs or multiple HRFs should be considered when analyzing the hemodynamic response to IEDs in pediatric epilepsy.[17,38]

One of our patients (Patient 11) who presented a higher spiking rate (942 spikes/20 min) during recordings showed a BOLD response discordant with the EZ. An interspike interval shorter than the HRF can lead to linear superimposition of the amplitudes of the overlapping responses, resulting in the general linear model no longer being a good representation of the BOLD signal.[15] Therefore, the use of alternative analysis techniques such as independent component analysis may be more appropriate when the spiking rates are high.[28]

Deactivation BOLD responses in the presumed EZs

This study found that 4 of 15 maximum BOLD responses were deactivations, among which 3 were concordant with the EZ. This indicated that similar to activation, deactivation had a strong localization value. One study demonstrated that deactivations in the EZ are more frequent in children with focal epilepsy than in adults.[10] However, the response patterns found in IEDs in the present study indicated that deactivation may be preceded or followed by a more-focal activation response. Deactivation and activation responses could originate from the same neuronal population but a different mech-

anism as a result of changes in baseline neuronal activity or inhibition.[35] One of the patients consistently showed a de-activation BOLD response without an activation BOLD response (Investigation 5). This result may reflect differences in hemodynamic changes with the individual type and duration of epileptic activity.[39] Moreover, the time window observed herein might not cover the full timelines of the BOLD response to IEDs.

Patterns of the hemodynamic response to IEDs

Evaluating the hemodynamic response across the pre-, peri-, and postspike periods revealed that a focal BOLD response occurred early in the EZs and was often widespread after IEDs, although the BOLD response with the maximum *t*-value occurred in the later map. This is consistent with previous studies demonstrating that HRFs to epileptic discharges peaked up to several seconds prior to the spike.[37,40] It can be suggested that the preceding BOLD response represents synchronized neuronal activity that would be detectable with a depth electrode but is invisible on scalp EEG.[41] In some cases, the early BOLD response reflects a metabolic phenomenon but did not consist of synchronized neuronal activity.[41]

We did not observe systemic differences in the pattern of the hemodynamic response between patients with and without structural abnormalities. However, there was a specific pattern in CECTS, namely a significant BOLD response in the sensorimotor cortex, which was similar to previous EEG-fMRI findings.[42,43] In addition, BOLD responses also occurred in the contralateral sensory motor cortex in the early map of CECTS. This result could be correlated with EEG of patients with CECTS often showing bilateral or contralateral centrotemporal spikes in repeated investigations. Similar to our results, a previous study suggested that functional connectivity is present between the rolandic operculum and the superior frontal, middle temporal, and triangular parts of the inferior frontal gyrus in the contralateral hemisphere.[44] In patient with PS, negative BOLD responses in the occipital area occurred consistently throughout the three maps. A previous study noted that activation responses were present in the occipital area in PS.[45] Furthermore, two patients who underwent a second EEG-fMRI investigation showed the same response patterns as in their first investigation. These findings suggest that EEG-fMRI can reveal the pathogenesis of pediatric epilepsy by evaluating the changes in the hemodynamic response across time windows of IEDs.[46] Furthermore, EEG-fMRI can reveal the mechanism of comorbidity in pediatric epilepsy by analyzing the real-time effects of IEDs on language, behavior, or cognitive functions.[44,47]

Limitations

The current study has some limitations that are worth noting. First, only a small number of subjects were included. Second, we recruited subjects who did not need sedation for EEG-fMRI. This could have introduced bias given that patients in whom the EZ is well characterized may not be fully representative of the population with pediatric epilepsy, especially since DRE is commonly combined with intellectual disability. However, we measured epileptic activity more accurately by performing EEG-fMRI without sedation. Third, given that we did not perform epilepsy surgery, we could not confirm the spatial accuracy of the obtained EEG-fMRI data. Nevertheless, our results confirmed the localizing value of EEG-fMRI for better targeted implantation before performing more-invasive monitoring for surgical resection. Further studies are needed to compare the accuracy of this test with other presurgical evaluation tools such as SPECT, PET, SEEG, and intracranial EEG monitoring.

Conclusions

This study has shown that EEG-fMRI is a useful neuroimaging technique that can provide additional information regarding the EZ in children with focal epilepsy. BOLD responses with the highest *t*-value or those with more-focal lesions in the early map may be useful for localizing the EZ. EEG-fMRI revealed common hemodynamic response patterns in the same types of epilepsy syndrome or in the same individual, which might be associated with the epileptic network. The present findings strongly support the need for a larger evaluation of the usefulness of EEG-fMRI in improving the targeting of epilepsy surgery and for investigating the pathogenic mechanisms of different forms of pediatric epilepsy.

Supplementary Materials

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