Subsecond EEG-fMRI analysis for presurgical evaluation in focal epilepsy

Yuji Ito, MD, PhD,^{1–3} Satoshi Maesawa, MD, PhD,^{1,4} Epifanio Bagarinao, PhD,¹ Yu Okai, MD,^{1,2} Daisuke Nakatsubo, MD,^{1,4} Hiroyuki Yamamoto, MD, PhD,^{1,2} Hiroyuki Kidokoro, MD, PhD,^{1,2} Naotaka Usui, MD, PhD,⁵ Jun Natsume, MD, PhD,^{1,2,6} Minoru Hoshiyama, MD, PhD,¹ Toshihiko Wakabayashi, MD, PhD,⁴ Gen Sobue, MD, PhD,^{1,7} and Norio Ozaki, MD, PhD^{1,8}

¹Brain & Mind Research Center, Nagoya University, Nagoya, Aichi; Departments of ²Pediatrics, ⁴Neurosurgery, ⁶Developmental Disability Medicine, ⁷Neurology, and ⁸Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Aichi; ³Department of Pediatrics, Aichi Prefecture Mikawa Aoi Medical and Rehabilitation Center for Developmental Disabilities, Okazaki, Aichi; and ⁵Department of Neurosurgery, National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

OBJECTIVE The authors recently reported a novel subsecond analysis method of analyzing EEG–functional MRI (fMRI) to improve the detection rate of epileptic focus. This study aims to validate the utility of this method for presurgical evaluation in pharmacoresistant focal epilepsy.

METHODS Among 13 patients with focal epilepsy undergoing presurgical examinations including simultaneous EEG–fMRI at 3T, 11 patients had interictal epileptiform discharges (IEDs) during fMRI. The authors used the sequence of topographic maps during the IEDs as a reference to obtain subsecond fMRI activation maps with the same temporal resolution as the EEG data, and constructed “spike-and-slow-wave-activation-summary” (SSWAS) maps that showed the activation frequency of voxels during IEDs. Clusters were defined by thresholding the SSWAS maps (voxel value > 10), and those containing voxels with the top 3 highest activation frequencies were considered significant. Significant hemodynamic responses using conventional event-related (ER) analysis and SSWAS maps were compared with the resection areas and surgical outcomes at 1 year after surgery.

RESULTS Using ER analysis, 4 (36%) of 11 patients had significant hemodynamic responses. One of 4 patients had significant hemodynamic responses in the resection area and good surgical outcome. Using SSWAS maps, 10 (91%) of 11 patients had significant hemodynamic responses. Six of 10 patients had significant hemodynamic responses in the resection area, and 5 of the 6 patients achieved good surgical outcomes. The remaining 4 patients had significant hemodynamic responses distant from the resection area, and only 1 of the 4 patients achieved good surgical outcomes. The sensitivity, specificity, positive predictive value, and negative predictive value of SSWAS maps were 83.3%, 75.0%, 83.3%, and 75.0%, respectively.

CONCLUSIONS This study demonstrated the clinical utility of SSWAS maps for presurgical evaluation of pharmacoresistant focal epilepsy. The findings indicated that subsecond EEG–fMRI analysis may help surgeons choose the resection areas that could lead to good surgical outcomes.

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KEYWORDS electroencephalography; epilepsy; functional magnetic resonance imaging; preoperative evaluation; simultaneous EEG–fMRI

PHARMACORESISTANT epilepsy accounts for approximately 30% of epilepsy cases.^{27,32} This causes various comorbidities and diminishes quality of life in patients. In patients with intractable focal epilepsy, accu-

rate identification of the epileptogenic network and eloquent cortices is essential for curative surgery.^{9,24} Although intracranial EEG (icEEG) recordings are usually required for presurgical evaluation, icEEG is invasive and can only

ABBREVIATIONS AED = antiepileptic drug; BOLD = blood oxygen level–dependent; ER = event-related; fMRI = functional MRI; FOV = field of view; FWEc = family-wise error cluster level correction; FWEp = family-wise error peak level correction; GLM = general linear model; HRF = hemodynamic response function; icEEG = intracranial EEG; IED = interictal epileptiform discharge; ILAE = International League Against Epilepsy; MNI = Montreal Neurological Institute; SOZ = seizure onset zone; SSWAS = spike-and-slow-wave-activation-summary; TLE = temporal lobe epilepsy.

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cover a limited space.¹⁵ Noninvasive multimodal evaluation prior to the placement of icEEG electrodes is needed for good surgical outcomes.

Recently, new noninvasive neurophysiological modalities have been advanced to detect the epileptic foci before implantation of icEEG electrodes. Simultaneous EEG–functional MRI (EEG–fMRI) is one of these modalities, and can identify brain regions associated with interictal epileptiform discharges (IEDs) by measurement of hemodynamic changes in blood oxygen level–dependent (BOLD) signals.^{11,12,22} Several studies have shown the clinical utility of EEG–fMRI for presurgical evaluation and demonstrated its high sensitivity and specificity using surgical outcomes as the reference standard.^{28,29} However, detecting IEDs on EEG recordings during fMRI is difficult in some patients due to the influence of the strong magnetic field inside the MRI machine.¹¹ In other patients, detecting significant spike-related BOLD changes is challenging despite proper detection of IEDs.^{1,25}

In our recent work, we proposed a new method of analyzing EEG–fMRI using the sequence of topographic maps during IEDs as a reference to detect subsecond fMRI activation changes. The obtained sequence of activation maps was then used to construct a “spike-and-slow-wave-activation-summary” (SSWAS) map, which represented the number of times (frequency) a given voxel became active during the sequence.⁵ Although we have demonstrated the efficacy of using SSWAS maps to detect epileptic foci, we have not yet validated their usefulness for preoperative workup.

This study aimed to evaluate the utility of using SSWAS maps for presurgical evaluation, paying particular attention to the associations among the localization of spike-related BOLD changes observed in SSWAS maps, resection areas, and postoperative outcomes.

Methods

Study Population

Between January 2016 and June 2018, a total of 19 patients with pharmacoresistant focal epilepsy underwent radical resective surgery with at least 12 months of follow-up at Nagoya University Hospital. Among these 19 patients, 13 consented to participate in this prospective study and underwent EEG–fMRI recordings before surgery. Of the 13 patients, 11 displayed identifiable IEDs during simultaneous EEG–fMRI and were eligible for subsequent analysis. The position of icEEG placement and areas of resection were determined based on clinical data, scalp EEG findings, and neuroimaging modalities other than EEG–fMRI, with the EEG–fMRI results only used for method validation at this time.

This study was approved by the research ethics board of Nagoya University Graduate School of Medicine. Written informed consent was obtained from all patients or their parents before participation in this study.

Acquisition of EEG–fMRI

MR images were acquired using a Magnetom Verio 3-T scanner (Siemens) with a 32-channel head coil at the Brain and Mind Research Center of Nagoya University.

High-resolution T1-weighted images were acquired using a 3D magnetization prepared rapid acquisition gradient echo acquisition sequence: TR 2.5 seconds, TE 2.48 msec, 192 sagittal slices with a distance factor of 50% and 1-mm thickness, in-plane voxel resolution 1 mm × 1 mm, field of view (FOV) 256 mm × 256 mm, and matrix size 256 × 256. All fMRI was recorded in a single continuous 15-minute session with a T2-weighted gradient echo planar imaging sequence: TR 2.5 seconds, TE 30 msec, FOV 192 mm, matrix size 64 × 64, 39 transverse slices with a 0.5-mm interslice interval and 3-mm thickness, flip angle 80°, and a total of 360 volumes.

EEG and electrocardiogram data were simultaneously recorded inside the MRI scanner using a 32-channel MRI-compatible system (Electrical Geodesics Inc.). An EEG cap connected to a combined digitizer-amplifier system was worn by the patient throughout the scan and data from the amplifier sampled at 1 kHz were continuously retrieved using NetStation software (version 5.0, Electrical Geodesics Inc.).²⁰ Adult patients were instructed to keep their eyes closed and remain relaxed during the scan. Pediatric patients were sedated in a drug-induced sleep condition using triclofos sodium at 80 mg/kg body weight.

Preprocessing for fMRI and EEG

Data for fMRI were preprocessed using SPM software (version 12, Wellcome Trust Centre for Neuroimaging) running on MATLAB (MathWorks). The first 5 images were discarded to remove inhomogeneity at the beginning of the scan. The remaining images were corrected for temporal differences in slice acquisition and head motion, spatially normalized to the Montreal Neurological Institute (MNI) space, and smoothed with a Gaussian kernel of 8 mm full-width at half-maximum.

EEG data were preprocessed using NetStation software (version 5.0). The gradient artifact was removed using the template subtraction method, and the ballistocardiogram artifact was removed using principal component analysis.^{3,21} Two experienced epileptologists (Y.I. and S.M.) marked the onset of IEDs (t_{ons}), which are similar to those recorded outside the MRI scanner (MRI preparation room) using the same instruments for 15 minutes just before the scan.

Conventional Event-Related Analysis

EEG–fMRI data were analyzed using SPM statistical software (version 12). Identified IED onsets were used to generate a series of spikes, which were then convolved with the canonical hemodynamic response function (HRF) and used in the statistical analysis of the preprocessed fMRI data using a general linear model (GLM) approach.² For each individual, 1-tailed t-tests were applied to test IED-related regional BOLD signal changes. The significance level was set at $p < 0.05$ corrected for multiple comparisons using family-wise error cluster level correction (FWEc) with a cluster-forming threshold of $p = 0.001$. When cluster size was more than 10,000 voxels, the significance level was reset to a more stringent threshold at $p < 0.05$ corrected for multiple comparisons using family-wise error peak level correction (FWEp) to further

FIG. 1. Constructing SSWAS maps. The EEG topographic map at the time of onset of IEDs (t_{ons}) was used as the reference map, and the similarity between the reference map and topographic map at any time t was measured. The value of the similarity measure ranges from 0 to 1, with 0 indicating no similarity and 1 being the same map. The time series of these similarity values were then convolved with the canonical HRF, and statistical analysis was performed using the GLM. The significance level was set at $p < 0.05$ corrected for multiple comparisons using an FWEc. This process was repeated every 4 msec (ms) in the sequence of topographic maps during the IEDs (from $t_{\text{ons}} - 56$ msec to $t_{\text{ons}} + 340$ msec) to obtain subsecond fMRI activation maps with the same temporal resolution as the EEG data. From the sequence of activation maps, the SSWAS map, which showed the activation frequency (values ranging from 0 to 100) of voxels during the IEDs, was constructed. Figure is available in color online only.

identify significant peak locations within the cluster. We defined clusters containing voxels with the top 3 highest t -values as relevant to the epileptic foci. Activation maps were superimposed onto individual coregistered T1-weighted images.

Subsecond Analysis and Constructing SSWAS Maps

The method used to analyze EEG-fMRI data to generate subsecond fMRI activation maps and to construct SSWAS maps was previously reported in more detail.⁵ This analysis was performed using an in-house MATLAB script and SPM software.

Basically, our approach advanced the method proposed by Grouiller and colleagues.¹³ Unlike conventional event-related (ER) analysis, this new method required whole-scalp EEG topographic maps from simultaneously recorded scalp EEG data. The EEG topographic map at the time of t_{ons} was used as the reference map, and the similarity between the reference map and the topographic map at

any time t was measured. The value of the similarity measure ranges from 0 to 1, with 0 indicating no similarity and 1 being the same map. The time series of these similarity values were then convolved with the canonical HRF and used in the statistical analysis of the preprocessed fMRI data using the GLM approach. For each individual, 1-tailed t -tests were applied to test IED-related regional BOLD signal changes. The significance level of the obtained activation maps was set at FWEc $p < 0.05$.

This process was then repeated every 4 msec in the sequence of topographic maps during the IEDs (from $t_{\text{ons}} - 56$ msec to $t_{\text{ons}} + 340$ msec) to obtain subsecond fMRI activation maps with the same temporal resolution as the EEG data. Next, the obtained sequence of activation maps was used to construct the SSWAS map, which showed the activation frequency (values ranging from 0 to 100) of voxels during the IEDs (Fig. 1). Clusters containing voxels with the top 3 highest activation frequency values and with voxel values greater than 10 were considered sig-

nificant. SSWAS maps were superimposed onto the individual coregistered T1-weighted images.

Comparison of BOLD Responses With Resection Areas and Surgical Outcomes

Areas identified with IED-related hemodynamic responses using conventional ER analysis and the SSWAS map were compared using the resection areas and surgical outcomes at 1 year after surgery.

We judged agreement between the identified and resection areas as follows: 1) “concordant,” when voxels having the first- to the third-highest t-values (for conventional ER analysis) or activation frequencies (for SSWAS maps) were inside the resection areas; 2) “borderline,” when voxels were outside the resection areas, but ≤ 2 cm from the resection margin; and 3) “discordant,” when voxels were distant from resection areas, > 2 cm from the resection margin.

Postoperative outcome was evaluated 1 year after surgery using the International League Against Epilepsy (ILAE) outcome classification scale.³³ Briefly, ILAE class 1 means completely seizure free, class 2 means only auras, class 3 means 1–3 seizure days per year, class 4 means 4 seizure days per year to a 50% reduction in baseline seizure days, class 5 means a less than 50% reduction in baseline seizure days to a 100% increase in baseline seizure days, and class 6 means a more than 100% increase of baseline seizure days. ILAE classes 1–2 were regarded as good surgical outcomes and classes 3–6 were regarded as poor surgical outcomes. We excluded “borderline” patients to calculate the sensitivity, specificity, positive predictive value, and negative predictive value, defined as follows: 1) sensitivity = patients with “concordant” and good outcome/patients with good outcome $\times 100\%$; 2) specificity = patients with “discordant” and poor outcome/patients with poor outcome $\times 100\%$; 3) positive predictive value = patients with “concordant” and good outcome/patients with “concordant” outcome $\times 100\%$; and 4) negative predictive value = patients with “discordant” and poor outcome/patients with “discordant” outcome $\times 100\%$.

Results

The clinical characteristics of patients with focal epilepsy are shown in Table 1. Seizure types in all patients were only focal seizures. The median age at the time of imaging was 22 years, and 7 of 11 patients showed structural abnormalities on MRI. The two pediatric patients (patients 1 and 11) were sedated in the drug-induced sleep condition during EEG-fMRI. Patient 9 displayed two types of IED (frequent right parietal sharps and sporadic right temporal sharps), but only the right parietal sharp IEDs showed significant BOLD responses; therefore, these IEDs were the ones analyzed. Other patients exhibited only one type of IED. No patients experienced seizures during scans. All patients took more than two antiepileptic drugs (AEDs) before surgery. Patient 1 discontinued 3 AEDs completely within 1 year after surgery based on the wishes of the patient's parents. The number of AEDs was not reduced in other patients at 1 year after surgery. No patients showed postoperative motor, sensory, or cognitive deficits.

Using conventional ER analysis, 4 (36%) of 11 patients had significant hemodynamic responses (Table 2). Patient 3 had both positive and negative BOLD responses, while the other 3 patients showed only positive BOLD responses. Because the primary cluster size was 28,412 voxels in patient 2, the level of significance was set at FWEp $p < 0.05$ for this patient. For all other patients, the significance level was set at FWEc $p < 0.05$. Patient 1 showed “concordant” BOLD responses and achieved good surgical outcomes. Patient 2 had “borderline” BOLD responses, but the BOLD cluster with the third-highest t-value ($t = 5.97$) overlapped the resection areas, and she too achieved good surgical outcomes (Fig. 2A). Patient 3 had “discordant” BOLD responses, but the BOLD cluster with the sixth-highest t-value ($t = 5.19$) was inside the resection area, and she experienced good surgical outcomes. Patient 7 had “discordant” BOLD responses and poor surgical outcomes. Other patients, including patient 5, showed no significant hemodynamic responses (Fig. 3A). The sensitivity, specificity, positive predictive value, and negative predictive value of conventional ER analysis were 50.0%, 100.0%, 100.0%, and 50.0%, respectively.

Using SSWAS maps, 10 (91%) of 11 patients had significant hemodynamic responses (Table 2). All 10 patients displayed positive BOLD responses only. Six of the 10 patients had “concordant” BOLD responses, and 5 of those 6 patients achieved good surgical outcomes (Figs. 2B and 3B). Widespread positive BOLD changes in patient 6 were observed bilaterally (right hemisphere dominant), and she showed poor surgical outcomes. The remaining 4 patients had significant hemodynamic responses distant from the resection area, and 3 of those 4 patients attained poor surgical outcomes. The sensitivity, specificity, positive predictive value, and negative predictive value of SSWAS maps were 83.3%, 75.0%, 83.3%, and 75.0%, respectively.

Discussion

In this prospective study of a tertiary epilepsy center cohort, we demonstrated the clinical utility of SSWAS maps for presurgical evaluation in pharmacoresistant focal epilepsy. Subsecond analysis can detect significant hemodynamic responses in approximately 90% of patients, while conventional ER analysis can only detect responses in one-third of patients. In the comparison of significant BOLD responses with the resection areas and surgical outcomes, SSWAS maps showed adequate sensitivity and specificity for presurgical evaluation. This suggests that subsecond EEG-fMRI analysis would be helpful to surgeons in identifying the optimal placement of icEEG electrodes to achieve good surgical outcomes.

SSWAS maps were able to detect the significant BOLD changes of epileptic foci where conventional ER analysis failed. EEG recordings inside the MRI scanner contain many artifacts, including those due to gradient and ballistocardiography. Although improvements in artifact removal techniques are reducing the difficulty of detecting IEDs, some IEDs are still easily missed, which affects the accuracy of statistical analysis.^{10,31} Grouiller and colleagues showed that use of the reference topographic map on scalp EEG outside the scanner could help improve the

TABLE 1. Clinical characteristics of patients with focal epilepsy

Patient No., Sex	Age (yrs)	At Onset of Epilepsy	Epilepsy Syndrome	Structural MRI	Hypometabolism on FDG-PET	SOZ on icEEG	Irritative Zone on icEEG	Operation	Histology	ILAE Class at 1 Yr
1, F	0	3	Lt FLE	Normal	NA	Lt OFC	Lt OFC	Corticectomy in lt OFC	FCD type IIB	1
2, F	13	19	Rt FLE	Rt frontal DNT	Rt middle frontal gyrus	Rt middle frontal gyrus	Rt frontal cortex	Lesionectomy in rt frontal cortex	DNT	1
3, F	21	33	Rt TLE	Rt temporal DNT	Rt lateral temporal cortex	NA	Rt inferior temporal gyrus	Lesionectomy in rt temporal cortex	DNT	1
4, M	21	63	Lt TLE	Lt HS	Lt temporal cortex	NA	Lt temporal cortex	Lt AHC	HS	1
5, F	22	24	Rt FLE	Rt frontal hemorrhage (AVM) scar	Rt OFC	NA	Rt OFC	Lesionectomy in rt OFC	Nonspecific findings	1
6, M	15	22	Rt TLE/OLE	Normal	Rt lateral temporal cortex	Rt temporoparietal junction	Rt occipitotemporal cortex	Corticectomy in rt occipitotemporal cortex	Nonspecific findings	5
7, M	14	21	Lt FLE	Normal	None	NA	Lt frontal cortex	Corticectomy in lt frontal cortex	FCD type IC	4
8, M	45	55	Rt TLE	Rt temporal cavernous hemangioma	Rt temporal cortex	NA	Rt temporal cortex	Lesionectomy in rt temporal cortex	Cavernous hemangioma	3
9, F	43	58	Rt PLE	Brain contusion scar in rt hemisphere	Rt cerebral hemisphere	Rt supramarginal gyrus	Rt parietal cortex	Lesionectomy in rt parietal cortex	Nonspecific findings	5
10, F	4	11	Rt TLE	Normal	Rt anterior temporal cortex	NA	Rt temporal cortex	Rt anterior temporal lobectomy	FCD type IC	1
11, M	7	12	Lt TLE	Lt amygdala enlargement	Lt temporal cortex	Lt hippocampus	Lt hippocampus, lt amygdala	Lt AHC	FCD type IC	1

AHC = amygdalohippocampectomy; AVM = arteriovenous malformation; DNT = dysembryoplastic neuroepithelial tumor; FCD = focal cortical dysplasia; FLE = frontal lobe epilepsy; HS = hippocampal sclerosis; NA = not available; OFC = orbitofrontal cortex; OLE = occipital lobe epilepsy; PLE = parietal lobe epilepsy.

TABLE 2. EEG-fMRI findings in patients with focal epilepsy

Patient No.	Type of IEDs	No. of IEDs	BOLD Changes Using Conventional ER Analysis (peak location, t-value)				Comparison of BOLD Responses w/ the Resection Areas	BOLD Changes Using SSWAS Map (peak location, activation frequency)			Comparison of BOLD Responses w/ the Resection Areas
			Global Max	2nd Highest	3rd Highest			1st Highest	2nd Highest	3rd Highest	
1	Lt-F Sp	60	Lt-I-F gyrus, 8.53	Corpus callosum, 4.87	Lt-A cingulate gyrus, 4.83	Concordant	Concordant	Lt-I-F gyrus, 80	None	None	Concordant
2	Rt-F SpW	30	Rt thalamus, 6.14	Rt-M-F gyrus, 6.03	Lt-A cingulate gyrus, 5.97	Borderline	Borderline	Rt-M-F gyrus, 91	Rt-I-F gyrus, 87	Rt precentral gyrus, 76	Concordant
3	Rt-F Sh	30	Rt-M-F gyrus, 7.27	Lt cerebellum, 6.58	Rt cerebellum, 5.77	Discordant	Discordant	Rt-M-F gyrus, 69	Rt-I-F gyrus, 65	Rt-I-T gyrus, 55	Concordant
4	Lt-T Sh	16	None	None	None	NA	NA	Lt-M-T gyrus, 13	None	None	Concordant
5	Rt-F SpW	39	None	None	None	NA	NA	Lt-M-O gyrus, 83	Rt-M-O gyrus, 49	Rt-S-F gyrus, 19	Concordant
6	Rt-T Sh	6	None	None	None	NA	NA	Rt precuneus, 54	Rt-M-O gyrus, 48	Lt-M-T gyrus, 32	Concordant
7	Lt-F SpW	53	Lt-M-F gyrus, 4.88	Lt angular gyrus, 4.60	Rt cerebellum, 4.47	Discordant	Discordant	Rt cerebellum, 73	Lt-M-F gyrus, 62	Lt-M-O gyrus, 27	Discordant
8	Rt-F SpW	41	None	None	None	NA	NA	Rt-S-F gyrus, 11	None	None	Discordant
9	Rt-P Sh	15	None	None	None	NA	NA	Lt-S-T gyrus, 67	Rt parahippocampal gyrus, 58	Rt-M-F gyrus, 49	Discordant
10	Rt-T Sh	14	None	None	None	NA	NA	Rt-A cingulate gyrus, 16	Rt-M-F gyrus, 15	Rt-I-F gyrus, 14	Discordant
11	Lt-F Sp	20	None	None	None	NA	NA	None	None	None	NA

A = anterior; F = frontal; I = inferior; M = middle; O = occipital; P = parietal; S = superior; Sh = sharp wave; Sp = spike; SpW = spike and slow wave; T = temporal.

FIG. 2. Case 2. A case with nonconcordant hemodynamic responses using conventional ER analysis and concordant hemodynamic responses using subsecond analysis. This patient was a 19-year-old woman with right frontal lobe epilepsy and a dysembryoplastic neuroepithelial tumor. During fMRI recording, EEG showed frequent F4 spikes and slow waves (red outline). She underwent a lesionectomy of the right frontal cortex (resection area bounded by green outline). At 1 year after surgery, the outcome was consistent with ILAE outcome class 1. **A:** The result of conventional EEG-fMRI analysis using an ER approach. The voxel of the third-highest t-value ($t = 5.97$, MNI space $[x, y, z] = [-10, 26, 30]$, arrow) was outside the resection area but within 2 cm from the resection margin and therefore judged as “borderline.” The significance level was set at $p < 0.05$ corrected for multiple comparisons using an FEWp. **B:** The result of subsecond EEG-fMRI analysis using the SSWAS map. The voxel of the first-highest activation frequency (activation frequency = 91, MNI $[x, y, z] = [2, 32, 34]$, arrow) was inside the resection area and considered “concordant.” The significance level was set at $p < 0.05$ corrected for multiple comparisons using an FWEc. R = right, s = second. Figure is available in color online only.

identification of hemodynamic responses related to epileptic foci.¹³ We extended their method, using the sequence of topographic maps during IEDs from EEG data recorded inside the scanner as a reference to detect dynamic activation changes with millisecond-level temporal resolution, from which SSWAS maps could be constructed for epileptic focus detection. Unlike the study of Grouiller et al., we did not use EEG data outside the scanner as a reference. This was to avoid mismatching IED morphology and differences in spatial sampling inside and outside the scanner. In addition, we used canonical HRF, a common practice in EEG-fMRI analysis. Although the use of multiple HRFs can further increase the percentage of patients with significant BOLD responses,⁶ this approach may demonstrate various phenomena, including artifacts and propagated epileptic activities.¹⁹ Furthermore, all fMRI was recorded in a single continuous 15-minute session, which is shorter than previous studies.^{4,7} A longer recording time can further improve the detection rate of significant BOLD responses due to the potential increase in the number of IEDs occurring within the scan period, but imposes a greater burden on patients who have to endure the restrictions on body movement and loud noise for a longer time.

The sensitivity and specificity of the SSWAS map compared with resection areas and good surgical outcomes were adequate for presurgical evaluation in focal epilepsy, comparable to existing findings. In a previous ER-based analysis study using multiple HRFs for focal epilepsy, the sensitivity and specificity were 87.5% and 76.9%, respectively.⁴ In a recent topography-based analysis using canonical HRF for temporal lobe epilepsy (TLE), the sensitivity and specificity were 81% and 79%, respectively.⁷ The primary cluster that contains the voxel with maximum t-value has also been shown to be consistent not only with the irritative zone, but also with the seizure onset zone (SOZ) in 24 (77%) of 31 patients with drug-resistant focal epilepsy.¹⁷ In this study, both SOZ and significant BOLD responses using SSWAS maps were detected in 4 patients and the SOZ was concordant with the cluster containing the voxel with the highest activation frequency in 2 patients (patients 1 and 2) for whom surgical outcome was ILAE class 1. This suggests that the highest activation frequency of the BOLD response may predict the SOZ as well as the location of the maximum t-value, and contribute to adequate sensitivity and specificity of SSWAS maps. Other useful imaging modalities include magnetic source imaging, high-density electric source imaging, FDG-PET, SPECT,

FIG. 3. Case 5. A case with no significant hemodynamic responses using conventional ER analysis and concordant hemodynamic responses using subsecond analysis. This patient was a 24-year-old woman with right frontal lobe epilepsy and hemorrhagic scar from an arteriovenous malformation. During fMRI recording, EEG showed frequent F8/C4 spikes and slow waves (red outlines). She underwent a lesionectomy of the right orbitofrontal cortex (resection area bounded by green outline). At 1 year after surgery, the outcome was consistent with ILAE outcome class 1. **A:** The result of conventional EEG-fMRI analysis using an ER approach. There was no significant hemodynamic response. The significance level was set at $p < 0.05$, corrected for multiple comparisons using an FWEc. **B:** The result of subsecond EEG-fMRI analysis using the SSWAS map. The voxel with the third-highest activation frequency (activation frequency = 19, MNI space [x, y, z] = [32, 62, 4], arrow) was inside the resection area and therefore considered “concordant.” The significance level was set at $p < 0.05$, corrected for multiple comparisons using an FWEc. Figure is available in color online only.

and ultra-high-field MRI.^{8,14,16} EEG-fMRI and these modalities are complementary, and combining these methods may enable precise assessment of the epileptic foci before invasive icEEG recording to improve postoperative outcomes for intractable focal epilepsy.

Subsecond analysis can help avoid human bias and minimize efforts at manual IED detection in EEG-fMRI analyses. EEG data recorded inside the scanner contain various artifacts that could lead to some true IEDs being missed and some spikelike waveforms being selected by mistake, even for experienced EEG experts interpreting the EEG recordings.^{23,26,30} This, in turn, could affect the statistical analysis of the simultaneously recorded fMRI data and reduce the performance of EEG-fMRI analyses, such as ER-based approaches, in localizing epileptic foci among patients with epilepsy. The method evaluated in this study avoids this problem and only requires experienced epileptologists to mark several clear IEDs for it to work. This could save large amounts of time and money in obtaining the final results and could boost EEG-fMRI analysis as a more practical neuroimaging modality for evaluating epilepsy patients. Moreover, when no spikes are visible on EEG recorded inside the scanner, the method also allows the use of EEG data recorded outside the scanner to make the reference topographic map for detect-

ing latent IEDs, for which voltages are usually lower than those of artifacts. More studies are needed to validate the utility of this method under such conditions.

When we used SSWAS maps, we defined clusters containing voxels of the first- to the third-highest activation frequencies as significant. Khoo and colleagues showed that IEDs on the icEEG electrode adjacent to the voxel of the maximum t-value tended to precede IEDs on the other icEEG electrodes, and the region of the maximum t-value was consistent with the origin of IEDs, called “the spike onset zone.”¹⁸ On this basis, it is ideal to define only the cluster with the voxel of highest activation frequency as significant. Under that condition, the sensitivity and specificity of SSWAS maps were 50.0% and 100.0%, respectively. However, SSWAS maps can increase the candidates of significant BOLD clusters for focus detection from 36% to 91% using the sequence of topographic maps during IEDs. For that reason, it is reasonable that clusters with the voxels of the first- to third-highest activation frequency were significant when we used a subsecond approach for EEG-fMRI analysis in patients with focal epilepsy. The research task was to find how to detect the true epileptic focus from the three clusters and the epileptic network architecture spanning between them.

The findings of the present study were limited by the

small sample size, the short follow-up period, and the fact that SOZ on icEEG was not detected in all patients. More participants, longer follow-up, and comparison with other neuroimaging modalities may lead to a better understanding of the utility of subsecond EEG-fMRI analysis methods. In addition, we believe that subsecond analysis could be generalized to other types of epilepsy. Studies using subsecond analysis in the investigation of benign epilepsy with centrotemporal spikes, epileptic encephalopathy with continuous spike waves during slow-wave sleep, and West syndrome are currently underway.

Conclusions

We have demonstrated the clinical utility of SSWAS maps as effective tools for presurgical evaluation of pharmacoresistant focal epilepsy. Our findings showed that SSWAS maps offer a higher detection rate of spike-related significant BOLD signals than conventional ER-based analysis approaches and can be predictive of surgical outcomes. This approach also reduces the burden of manual IED detection on EEG recorded inside the scanner. Taken together, these findings have provided additional evidence for the usefulness of EEG-fMRI as a more practical modality in diagnosing patients with epilepsy that could potentially reduce the necessity for invasive icEEG recordings.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ito, Maesawa. Acquisition of data: Ito, Maesawa, Okai, Nakatsubo. Analysis and interpretation of data: Ito, Maesawa, Bagarinao, Okai. Drafting the article: Ito. Critically revising the article: Maesawa, Bagarinao. Reviewed submitted version of manuscript: Yamamoto, Kidokoro, Usui, Natsume, Hoshiyama, Wakabayashi, Sobue, Ozaki. Administrative/technical/material support: Yamamoto, Kidokoro, Usui, Natsume, Hoshiyama, Wakabayashi, Sobue, Ozaki.

Correspondence

Yuji Ito: Brain & Mind Research Center, Nagoya University, Aichi, Japan. yuji.ito@med.nagoya-u.ac.jp.