Localizing Seizure-Onset Zones in Presurgical Evaluation of Drug-Resistant Epilepsy by Electroencephalography/fMRI: Effectiveness of Alternative Thresholding Strategies

BACKGROUND AND PURPOSE: Simultaneous EEG/fMRI is an effective noninvasive tool for identifying and localizing the SOZ in patients with focal epilepsy. In this study, we evaluated different thresholding strategies in EEG/fMRI for the assessment of hemodynamic responses to IEDs in the SOZ of drug-resistant epilepsy.

MATERIALS AND METHODS: Sixteen patients with focal epilepsy were examined by using simultaneous 92-channel EEG and BOLD fMRI. The temporal fluctuation of epileptiform signals on the EEG was extracted by independent component analysis to predict the hemodynamic responses to the IEDs. We applied 3 different threshold criteria to detect hemodynamic responses within the SOZ: 1) PA, 2) a fixed threshold at $P < .05$ corrected for multiple comparison (FWE), and 3) FAV (4000 ± 200 activated voxels within the brain).

RESULTS: PA identified the SOZ in 9 of 16 patients; FWE resulted in concordant BOLD signal correlates in 11 of 16, and FAV in 13 of 16 patients. Hemodynamic responses were detected within the resected areas in 5 (PA), 6 (FWE), and 8 (FAV) of 10 patients who remained seizure-free after surgery.

CONCLUSIONS: EEG/fMRI is a noninvasive tool for the presurgical work-up of patients with epilepsy, which can be performed during seizure-free periods and is complementary to the ictal electroclinical assessment. Our findings suggest that the effectiveness of EEG/fMRI in delineating the SOZ may be further improved by the additional use of alternative analysis strategies such as FAV.

ABBREVIATIONS: BOLD = blood oxygen level–dependent; EEG = electroencephalography; FAV = fixed numbers of activated voxels; FWE = family-wise error; FWHM = full width at half maximum; IC = independent component; IED = interictal epileptic discharge; LTLE = lateral temporal lobe epilepsy; MTLE = mesial temporal lobe epilepsy; PA = peak activation; SOZ = seizure-onset zone
coactivations) without eliminating the hemodynamic responses at the SOZ. Currently, 2 strategies are used. The first applies a fixed threshold of \( P < .05 \) corrected for FWE and commonly results in variable interpretations of BOLD signal correlates from “no activation” to “widespread clusters” of activation.\(^{10,11}\) Both no activation and widespread activation patterns provide no reliable clues for delineating a focal SOZ. The second, the PA strategy, identifies the cortical zone of the maximum correlation between the BOLD signal and the IEDs. The PA criterion is thought to reflect the most active hemodynamic response to IEDs, which is reported to be confined to epileptogenic brain areas.\(^{19,20}\) Previous studies applying the PA criterion reported convergence between BOLD responses and the SOZ.\(^{19-24}\) However, the BOLD signal change due to IEDs is not uniform, as indicated by variously positive or negative BOLD correlates co-localizing to the SOZ in focal epilepsies.\(^{22,25}\)

The potential disadvantage of using these 2 approaches is an increased risk of missing the true effects at the SOZ. The largest study of EEG/fMRI in presurgical work-up to date recommended analysis of recordings at alternative thresholds in equivocal cases to enhance the localizing value of EEG/fMRI.\(^{26}\)

Materials and Methods

Subjects

Patients (11 women, 5 men; mean age, 40 years; range, 20–68 years) with drug-resistant focal epilepsies were prospectively recruited from our presurgical epilepsy program. An inclusion criterion for evaluation by EEG/fMRI recordings was the detection of IEDs on previous electroclinical data.

Setup, Recording, Preprocessing, and Data-Analysis Procedures

Setup, recording, preprocessing, and data analysis of the EEG and fMRI data were performed as described in Jann et al.\(^{7}\) The PA predictor was used as the event-related predictor for the fMRI BOLD signal in the correlation estimation (see On-line Appendix for a detailed description of the methods).

Correlation Estimation

Voxelwise correlations between the BOLD signal and the IC-based predictor were computed by using a general linear model. Volumes with artifacts in the corresponding EEG epoch (eg, motion and so forth) were excluded.

Peak Activation

The cluster with the maximum correlation to the IEDs was determined. Concordance of the SOZ with the identified BOLD signal correlate was defined as presence of the PA cluster within the area of resection in surgical patients with good clinical outcomes (Engel class I/II, 10 patients) and, in all patients, within the SOZ as defined by electroclinical data.

Family-Wise Error

Correlation maps were thresholded at \( P < .05 \) corrected for multiple comparisons (FWE). Consistent with previous studies, BOLD signal correlates with \( t < 3.1 \) and a minimum cluster size of 40 mm\(^3\) were considered significant.\(^{20,21}\) Concordance of the SOZ with BOLD signal correlates was defined as the presence of an activated cluster within the resected area and/or SOZ. For patients with MTLE, the analysis was determined to be equivocal if BOLD signal correlates in the mesiotemporal lobe were found bilaterally.

Fixed Numbers of Activated Voxels

The analysis was performed at an individual statistical threshold (\( P \) values), resulting in a total volume of activated BOLD clusters of \( 4000 \pm 200 \) mm\(^3\) within the brain tissue. Correction for multiple comparisons and false-positives was done by estimating the minimal cluster sizes for a given threshold.\(^{32,33}\) Concordance was defined as the presence of an activated cluster within the SOZ as defined above. For patients with MTLE, the analysis was rated equivocal if BOLD signal correlates in the mesiotemporal lobe were bilateral.

Results

Two patients with MTLE (patients 5 and 8) lacked IEDs during EEG/fMRI recordings. In 14 patients, an IC-factor coding
for the IEDs was identified on the basis of temporal dynamics and spatial distribution. Patients 1 and 2 were included in a previous methodologic study of IC-based EEG/fMRI.6

**BOLD Correlates in MTLE**

Results are summarized in the Table. Figure 1 summarizes findings in patient 6.

**Peak Activation**

The PA was detected within the resected tissue in 3 of the 6 patients with good postoperative outcomes. When the electroclinical definition of the SOZ was used, the PA matched the SOZ in 5 of 10 patients (Fig 1). In 3 patients, the PA was detected outside the mesiotemporal lobe (contralateral precentral gyrus, patient 3; contralateral anterior cingulate gyrus, patient 4; and posterior cingulate gyrus, patient 9).

**Family-Wise Error**

The FWE criterion resulted in a variable number of activated clusters (mean, 46; range, 0–106), covering an average brain volume of 109 cm³. BOLD signal correlates were present in the resected area in 3 of 6 patients with good postoperative outcomes and in 6 of 10 patients in which the electroclinical definition was used. Bilateral mesiotemporal lobe activations were detected in patient 2; in patient 3, no voxels exceeded the threshold. The average volume of the BOLD signal cluster within the SOZ was 1.3 cm³, comprising 1.2% (range, 0%–17.6%) of the volume of the total activated voxels.

**Fixed Numbers of Activated Voxels**

The FAV threshold criterion resulted in BOLD signal correlates within the resected tissue in 5 of 6 patients with good clinical outcomes. In 8 of 10 patients in whom the electroclinical definition was used, a BOLD response was present within the SOZ (Fig 1). On average, the cluster within the SOZ contained 0.4 cm³ of the total of 4 cm³ of activated brain parenchyma, comprising 9.8% (range, 3.6%–14.6%) of the activated volume. Clusters outside the mesiotemporal lobe (mean, 15) were mainly distributed among brain areas with known ictal functional connectivity to the mesiotemporal lobe in MTLE.34,35

In patients 4 and 7, BOLD responses within the SOZ were negative. Negative BOLD signal correlates within the presumed SOZ have been reported in ictal EEG/fMRI recordings in approximately 30% of cases.10,25

**BOLD Correlates in Neocortical Epilepsies**

**Peak Activation**

The PA was found inside the resected tissue in 2 of 4 surgical patients and in the SOZ (defined electroclinically) in 4 of 6 patients. In patient 12 (Fig 2), the PA lay in the right inferior parietal lobe, distant from the resected dysplastic cortex as indicated by postoperative outcome (Engel class Ia). In patient 16, the PA was found in the contralateral occipital lobe, as part of widespread bi-hemispheric negative BOLD signal correlates. In a patient with dual pathology in the temporal lobe (patient 15), PA and FAV pointed to focal cortical dysplasia and not to the mesiotemporal lobe.

**Family-Wise Error**

The FWE criterion resulted in extensive and multifocal clusters (mean, 111 cm³; range, 9–198 cm³; mean number of clusters, 37; range, 6–50). BOLD signal correlates were present in the resected area in 3 of 4 patients and in the SOZ (defined electroclinically) in 4 of 6 patients. On average, the cluster within the SOZ covered 5.6 cm³, corresponding to 5.0% (range, 0%–23%) of the activated voxels.

**Fixed Numbers of Activated Voxels**

BOLD signal correlates were present in the resected area in 3 of 4 patients and in the SOZ (defined electroclinically) in 5 of 6 patients. The portion of activated voxels located within the SOZ was 20.7% (range, 0%–45%), and the average number of distant clusters was 13 (range, 6–21). Notably, in 2 patients without lesions detectable on structural MR imaging (patients 11 and 14), the results of EEG/fMRI recording facilitated the placement of the invasive EEG electrodes.
ictal paroxysms are not detected by scalp EEG.36,37 These specific properties of MTLE create challenges for EEG/fMRI recordings because IEDs in the surface EEG are usually restricted. Most of the IEDs in the mesiotemporal lobe have no correlate on visual scalp EEG and may thus erroneously be attributed to the baseline signature of the fMRI correlation. Incorporating epileptic activity extracted by an IC may partially overcome this limitation. The IC-factor coding for epileptic activity is selected on the basis of the temporal and spatial distribution of a subset of unequivocal IEDs and represents a statistically independent pattern of time courses fluctuating during the acquisition period. Thus, the identified IC factor represents not only the IEDs fulfilling surface EEG criteria but also temporal fluctuations of epileptic activity, which would otherwise be ignored. In our series, 8 of 10 patients with MTLE showed BOLD signal correlates represented by the IC-factor, facilitating the calculation of hemodynamic responses within the SOZ.

The selection of the strongest cluster (PA) matched the SOZ in a limited number of patients (5 of 10). Three recordings localized the PA outside the SOZ within the cingulate gyrus and ipsilateral precentral gyrus, cortical areas embedded...
in a distant part of the MTLE network. The cluster with the highest correlation may thus represent the effects of propagation. Although the SOZ is usually considered to generate the most intensive increase in blood flow and consequently the
The most robust BOLD signal change, the magnitude of the BOLD response in the hippocampal formation is smaller than that in neocortical areas. Hence, epileptic activity in the mesiotemporal lobe may result in a less significant correlation with the hemodynamic responses.

The FWE threshold (t > 3.1 and cluster size > 40 mm³) produced a variable spatial extent of the resulting BOLD clusters. In 1 patient, no significant cluster cleared the threshold, and in another patient, bilateral mesiotemporal lobe activation hindered interpretation. Fixed threshold strategies referring to an alternative definition (ie, t > 4.7) may result in concordant results in individual patients but may obscure otherwise concordant results in patients with less significant correlation estimations. These findings corroborated results from previous studies applying a fixed statistical threshold and motivated the application of an alternative threshold as proposed by earlier presurgical EEG/fMRI studies. FAV is based on a predefined volume (4 cm³) of the BOLD signal cluster correlating with the IEDs. The selected volume is based on results of previous work. Among the 3 threshold criteria we compared in MTL, the FAV yielded the best matches of the BOLD signal correlates to the SOZ (8 of 10 patients). The localization of the SOZ was confirmed in 5 patients by surgery and good clinical outcome and in 3 patients by ictal video telemetry. These results are comparable with findings from ictal SPECT and interictal PET studies.

Neocortical Epilepsies

In all patients with focal cortical dysplasia, the invasive EEG recordings confirmed a tight spatial relationship with the corresponding structural epileptogenic lesion. PA matched the SOZ in 4 of 6 patients in our series. In 1 patient (Fig 2), the PA criterion identified a region beyond the dysplastic cortex, in agreement to an alternative definition (ie, PA matched the PA beyond the dysplastic cortex). In 1 patient, no significant cluster cleared the threshold, producing a variable spatial extent of the resulting BOLD clusters. Thus, EEG/fMRI should be used to determine the propagation speed of seizures, and pathways of ictal discharge spreading. Therefore, EEG/fMRI brings additional costs and limitations, such as the need for ictal injections and radiation exposure, and seizure localization by such techniques is influenced by the duration of seizures, propagation speed of seizures, and pathways of ictal discharge spreading. Thus, EEG/fMRI should be strongly considered as an important complement to EEG and clinical semiology.

In the present study, the FAV strategy provided the best localization value, accurately detecting the SOZ in 5 of 6 patients with neocortical epilepsies. An inherent limitation of FWE and FAV thresholding strategies is the fact that the presence of multifocal hemodynamic responses requires a pre-existing clinical hypothesis for the interpretation. Given a proper hypothesis, EEG/fMRI offers better spatial resolution and spatial specificity than scalp EEG and is comparable with PET and ictal SPECT. The use of functional imaging in the localization of the SOZ has been shown to benefit from the synthesis of multiple imaging modalities, these include EEG/fMRI incorporating standardized approaches of interpretation, as proposed in this study.

Conclusions

We have demonstrated that simultaneous EEG/fMRI by using IC-based extraction of epileptic activity is a valuable tool for delineating hemodynamic responses related to IEDs in the presurgical work-up of patients with epilepsy. The procedure can be performed during seizure-free periods, and its effectiveness in delineating the SOZ may be further improved by the additional use of alternative standardized analysis such as FAV.

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