ARTICLE

The spike onset zone

The region where epileptic spikes start and from where they propagate

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Abstract

Objective

To determine whether the maximum hemodynamic response to scalp interictal epileptic discharges (IEDs) corresponds to the region where IEDs originate and from where they propagate.

Methods

We studied 19 patients who underwent first an EEG-fMRI showing responses in the gray matter, and then intracranial EEG (iEEG). We coregistered the hemodynamic responses to the iEEG electrode contacts and analyzed IEDs in the iEEG channel adjacent to a maximum response (labeled the *main channel*), in relation to IEDs in other channels during a widespread intracranial IED event. IEDs in the main channel were aligned at their peak, and IEDs in each channel were averaged time-locked to these instants. The beginning and peak of IEDs in the averaged trace were identified, blinded to the identity of the main channel. The latency of IEDs was computed between the earliest and all other channels.

Results

The median latency of IEDs in the main channel was significantly smaller than in other channels for either the peak (15.5 vs 67.5 milliseconds, $p = 0.00037$) or the beginning (46.5 vs 118.4 milliseconds, $p = 0.000048$). The latency of IED was significantly correlated to the distance from the maximum hemodynamic response ($p < 0.0001$ for either the peak or the beginning).

Conclusion

IED adjacent to a maximum hemodynamic response, which often corresponds to the seizure onset zone, is more likely to precede IEDs in remote locations during a widespread intracranial discharge. Thus, EEG-fMRI is a unique noninvasive method to reveal the origin of IEDs, which we propose to label the spike onset zone.

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Glossary

HRF = hemodynamic response function; **IED** = interictal epileptic discharge; **iEEG** = intracranial EEG.

Simultaneous EEG-fMRI of scalp interictal epileptic discharges (IEDs) is a noninvasive and powerful way to visualize with high spatial resolution neuronal activity (reflected in hemodynamic changes) across the whole brain during epileptic discharges.[1–3] Some correspondence between scalp IEDs–related EEG-fMRI hemodynamic responses and intracranial IEDs has been demonstrated.[2,4–6] However, these studies did not derive a general principle of correspondence.

Since the early work of Penfield and Jasper, IEDs are known to sometimes propagate from the generating regions,[7] and resection of these regions was associated with improved surgical outcome.[8,9] Penfield and Jasper also noted the apparent impossibility of reliably differentiating the original and the propagated IEDs. We demonstrated that the maximum response in EEG-fMRI to scalp IEDs often correctly localizes the seizure onset zone.[3,10] Resection of this maximum response was also correlated with good surgical outcome.[11,12] Focal intracranial IEDs are unlikely to be detectable on scalp EEG.[13,14] However, IEDs are often recorded at multiple brain regions with barely distinguishable latency, suggesting that IEDs could propagate rapidly across the cortex. Since scalp IEDs are detectable only when synchronous activation involves a large brain region (>10 cm^2),[14] they can represent almost-synchronous widespread intracranial IED events. We hypothesized that, in contrast to regions to which IEDs may propagate (reflected in the widespread irritative zone[15]), the scalp IED-related maximum hemodynamic response reflects the region in which these widespread intracranial IED events originated. We sought to determine whether the IED recorded close to the maximum response does indeed occur earlier during a widespread intracranial event (figure e-1, links.lww.com/WNL/A626).

Methods

Study population

From the database of patients who participated in EEG-fMRI studies between April 2006 and July 2017, we retrospectively identified consecutive patients with drug-resistant focal epilepsy who subsequently underwent intracranial EEG (iEEG) study as part of their presurgical evaluation.

Standard protocol approvals, registrations, and patient consents

Each patient gave written informed consent for the EEG-fMRI study approved by the research ethics committee of Montreal Neurological Institute and Hospital.

Intracerebral EEG and EEG-fMRI acquisition, processing, and analysis, and localization of iEEG electrode contacts, were identical to previous studies[1,3] and are described briefly below (see appendix e-1 for details, links.lww.com/WNL/A628).

Intracranial EEG acquisition

Multicontact stereo-EEG electrodes were implanted using image-guided stereotaxy with or without robotized surgical assistant[16,17]—the deepest contacts aimed at the mesial structures and the most superficial placed in the lateral cortical mantle. Clinical diagnostic data (seizure semiology, scalp EEG, neurocognitive evaluation, structural MRI, [^{18}F]-fluorodeoxyglucose–PET and ictal SPECT when available) were considered when determining electrode placement. EEG-fMRI was not integrated in the image-guided stereotaxy system for implantation in all but 2 recent cases (patients 10 and 18). iEEGs were recorded using the Harmonie EEG system (Stellate, Montreal, Canada) prior to September 2016 and the Neurofax EEG-1200A system (Nihon Kohden, Tokyo, Japan) thereafter. iEEG recordings were bandpass-filtered at 0.3–500 Hz (Harmonie) or at 0.016–600 Hz (Neurofax) except for patient 4 (0.3–300 Hz), and acquired at a sampling rate of 2,000 Hz in all patients.

EEG-fMRI acquisition, processing, and analysis

Scalp EEG was recorded inside a 3-tesla MRI scanner with 25 magnetic resonance–compatible electrodes. fMRI data were collected in 6-minute runs for a total of 6 to 15 runs with patients at rest. The IEDs with the same spatial distribution (similar or different morphologies) were grouped, whereas IEDs with different spatial distributions (e.g., patients with independent bilateral temporal IEDs) were considered different IED types and analyzed separately. Thus, some patients had more than one study. fMRI data were analyzed as an event-related design[18]; each type of IED was built as a regressor with all regressors included in the same general linear model and convolved with 4 hemodynamic response functions (HRFs) peaking at 3, 5, 7, and 9 seconds.[6] IED-related hemodynamic responses can be positive or negative with respect to the baseline: a positive correlation between the actual BOLD (blood oxygen level–dependent) signal and the time course of the expected IED-related HRFs results in a positive response and an anticorrelation results in a negative response. A statistic t map was created for each regressor using the other regressors as confounds for each event type. A combined t map was created by taking, at each voxel, the highest t value (or the lowest for a negative response) from the 4 t maps created with the 4 HRFs (t value = contrast value divided by the standard error).[6] This single combined t map was first thresholded at an uncorrected $t > 3.0$ (or $t < -3.0$ for a negative response) and the responses with t value higher (or lower for a negative response) than the significance threshold corresponding to corrected whole-brain

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topological false discovery rate of 0.05 were then identified (resulted in a study-specific absolute *t* value threshold between 4.1 and 5.3).[1]

EEG-fMRI hemodynamic maxima selection

We used a semiautomated approach to select hemodynamic responses in the gray matter and lesions (table e-1, links.lww.com/WNL/A627). First, the anatomical image (MPRAGE [magnetization-prepared rapid-acquisition gradient echo]) of each patient was segmented using FreeSurfer (freesurfer.net/). The gray and white matter segments were used to retain hemodynamic responses in the brain and exclude those in the basal ganglia. The surviving responses were then visually verified. Responses in the cortical gray matter and a lesion were accepted.[1] The voxel with the highest positive *t* value (labeled the *positive maximum*) and the lowest negative *t* value (labeled the *negative maximum*) were then selected from these surviving responses. Each study can have up to 2 maxima selected (one positive and one negative).

Coregistration of fMRI *t* maps and postimplantation images for localization of electrode contacts

Postimplantation MRI or CT and the fMRI *t* maps were coregistered. The trajectory and localization of each electrode was manually indicated in the postimplantation MRI or CT. Then the coordinates of each electrode contact were computed from the distance between contacts and the coordinates of the entry and endpoints of the electrodes.[1,19]

Selection of iEEG channel closest to the EEG-fMRI maxima

We selected the iEEG channel closest to the maximum using the following procedure: (1) the midpoint between 2 adjacent intracranial electrode contacts was considered the physical location of a bipolar iEEG channel, and (2) the iEEG channel closest to and located within 10 mm of an EEG-fMRI maximum was identified and labeled as *main channel*.

Marking of IEDs on iEEG recordings

For marking of intracranial IEDs, we selected a continuous 2-hour iEEG recording at least 72 hours postimplantation to avoid the acute effect of electrode placement and the potential influence of anesthesia.[1] iEEG recordings were visually inspected, and channels contaminated with artifacts were excluded. All iEEG data were analyzed offline in bipolar montage using MATLAB (MathWorks, Natick, MA) for automated analysis and Stellate reviewer for visual marking.

For each hemodynamic maximum, we visually marked the intracranial IEDs using the following criteria: (1) IEDs seen in the main channel (closest to the hemodynamic maximum, as defined above), (2) IEDs must also be present in multiple other channels at approximately the same time by visual inspection at 30 mm/s (to select the almost-synchronous IEDs involving widespread regions), (3) IEDs with different morphology were marked separately (e.g., IEDs with positive peak and negative peak were considered different even if they were both seen in the main channel), and (4) only the IEDs with predominant morphology were selected. We aimed to mark the first 100 to 120 IEDs for main channels with frequent IEDs, or the largest number of IEDs found within the 2-hour recording for main channels with less frequent IEDs. We aligned the IEDs in the main channel at their first clear peak and averaged the iEEG in each channel time-locked to these instants (figure 1A). We only used channels showing an IED on the resulting averaged trace in the subsequent analysis. We visually marked the first clear peak (labeled as *peak*) in each channel, blinded to the identity of the main channel. We also automatically detected the trough[9,20] before the peak (labeled as *beginning*) (figure 1B) (see appendix e-1 for details, links.lww.com/WNL/A628). The channel showing the earliest peak or beginning (labeled as *first channel*) may not be the main channel (figures e-2 and e-3, links.lww.com/WNL/A626), and the first channel may not be the same for the peak and the beginning. We computed the latency of the IED in each channel (averaged trace) referenced to the first channel for the peak and the beginning of IED.

Statistical analyses

Results are reported in median (interquartile range) unless stated otherwise. We tested whether the median IED latency in the main channel among all the hemodynamic maxima was significantly different from the median latencies of other channels, using a permutation test (1 million repetitions; see appendix e-1 for details, links.lww.com/WNL/A628). If the main channels have shorter latency, the median latency would be shorter than that of randomly selected channels, resulting in a low *p* value. Correlation coefficients were computed using Pearson correlation. A p value <0.05 was considered statistically significant. All statistical analyses were performed using MATLAB (MathWorks).

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator, subject to approval by the research ethics board of the Montreal Neurological Institute and Hospital.

Results

Between April 2006 and July 2017, among patients with focal epilepsy who underwent EEG-fMRI, 68 subsequently underwent iEEG implantation. Twenty-seven were excluded for the following reasons: no scalp IEDs during EEG-fMRI in 18, technical issues (EEG or fMRI artifacts) prevented EEG-fMRI analysis in 6, and postimplantation imaging was not available in 3. We included 41 patients (16 male; mean age at evaluation 28 ± 8 years, range 17–51): 19 had one, 8 had 2, 12 had 3, and 2 had 4 types of IED, for a total of 79 IED-related

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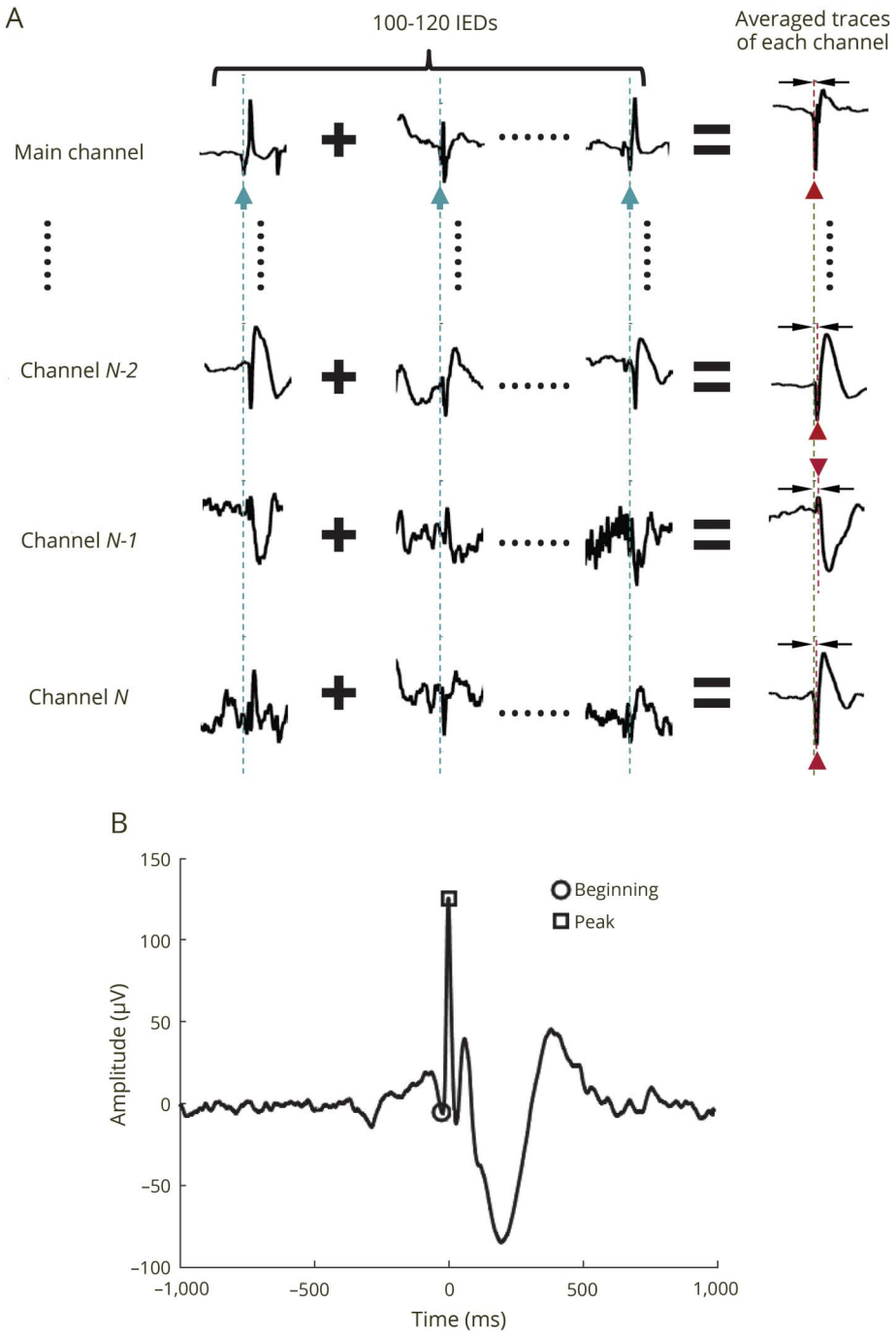
Figure 1 Methods to yield the averaged traces of intracranial EEG



(A) Approximately 100 IEDs were marked on the main channel and aligned at their first clear peak (blue arrows). Then, the intracranial EEG at other channels were averaged time-locked to these instants (blue dashed lines), resulting in averaged traces in which time 0 was aligned at the peak of the main channel (green dashed line). The first clear peak of the IED on each of the averaged traces was marked during the second marking (red dashed line with arrowhead), which was performed blinded to the identity of the main channel. Latencies were calculated as the time difference of peaks between the first channel (the channel showing the earliest peak; in this example, the first channel is the main channel) and each of the remaining channels (the differences between the green and red dashed lines as indicated by pairs of the black arrows). (B) Example of an IED on an averaged trace of an intracranial EEG channel. The peak was visually marked and the beginning was automatically detected. IED = interictal epileptic discharge.

studies. Fifty-three IED-related studies were excluded because the closest channel recorded was located further than 10 mm from the hemodynamic maxima in 41 and there was no significant hemodynamic response in 12. Therefore, 26 studies resulting in 28 maxima from 19 patients were finally analyzed: 24 studies with one maximum (19 positive and 5 negative maxima) and 2 with 2 maxima (each study contains a positive and a negative maximum). Six to 13 electrodes (equivalent to 48–131 contacts) were implanted in each patient. See tables e-1 and e-2 (links.lww.com/WNL/A627) for electroclinical characteristics and findings of EEG-fMRI maxima and intracranial IEDs.

Distance between channels analyzed and hemodynamic maxima

In total, 997 channels (median 32.5 [17.5–54]) showing an IED on the average trace were analyzed. The median distances from hemodynamic maxima were 6.25 (5.15–8.7) mm for the

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main channels and 29.6 (22.7–39.5) mm for all channels showing an IED.

Latency of IEDs

For each EEG-fMRI maximum studied, a median of 105 (103–111) IEDs were marked on the main channel. Referenced to the first channel, the median latency of the main channel was significantly smaller than the latencies of other channels for either the peak (p = 0.00037) or the beginning (p = 0.000048) of an IED (table 1). Figures 2 and 3 and figures e-2 and e-3 (links.lww.com/WNL/A626) show representative EEG-fMRI maxima and the averaged traces with IEDs in the main, first, and the other channels.

Correlation of IED latency with distance from the hemodynamic maximum

The latency of peak and latency of beginning of IED of each channel were significantly correlated with the distance between each channel and the hemodynamic maximum: the closer the channel is located to a hemodynamic maximum, the earlier the IED (table 2).

Discussion

The brain region where IEDs are present in patients with focal epilepsy, called the irritative zone,[15] is often widespread and for this reason considered a poor marker of the epileptogenic zone. We showed that during a widespread intracranial IED event, the IED recorded close to the EEG-fMRI maximum hemodynamic response is more likely to precede the IEDs recorded in remote locations, and that the IED delay in a particular channel is correlated with the distance between its location and the maximum hemodynamic response. We propose, supported by the results of this study, that a widespread intracranial IED event occurs as the result of an IED originating in a small region and propagating within 70 to 120 milliseconds (ms) (table 1; median latency of all channels showing an IED) over wide regions. We demonstrated that EEG-fMRI is a noninvasive tool that likely points to this region of IED origin, which we call the *spike onset zone*.

Why is the spike onset zone important? It is important because it is a possible explanation for the commonly seen widespread irritative zone in the context of focal epilepsy. It is more important, however, because it often is the same as the seizure onset zone. A study using iEEG demonstrated good correspondence between the zones of the earliest spike and seizure origin.[9] We have demonstrated an excellent correspondence between the maximum hemodynamic response to scalp IEDs and the iEEG-defined seizure onset zone.[3,10] In particular circumstances, the maximum response can predict the seizure onset zone with more than 90% accuracy.[3] The maximum response to scalp IEDs is also a good predictor of surgical outcome,[11,12] which we explain by the fact that it points to the seizure onset zone.

The concept of spike onset zone is supported by the frequent observation that deep epileptogenic lesions, in mesial temporal or mesial frontal regions, often result in IEDs visible on the scalp despite the fact that an IED generated in such a deep lesion cannot physically be seen on scalp EEG[21,22]: the IED generated in the depth propagates neuronally to the superficial neocortex, arriving 70 to 120 ms later, and it is the propagated event that is visible on the scalp. In such a situation, an EEG or magnetoencephalography source analysis will correctly find the source of the neocortical event in the superficial neocortex because it analyzes the event at a time at which it occurs on the scalp,[23] whereas the EEG-fMRI study of the same neocortical event will find the maximum response in the depth, where the IED originated. The low temporal resolution of EEG-fMRI is advantageous in this case: it finds hemodynamic changes that occur anytime in the temporal vicinity of the superficial neocortical (scalp) event. In this situation, it is important to distinguish the source obtained by EEG/magnetoencephalography analysis of the instantaneous electrical field and the neuronal source or origin found by EEG-fMRI.

In the above situation, one can ask why there is not a hemodynamic response in the deep structures *and* in the superficial neocortex since both regions show an IED, one original and one propagated. Indeed, a hemodynamic response in deep

Table 1 Latency of the IED of the main channel and all channels showing an IED on averaged iEEG trace, referenced to the first channel

	Latency, ms		
IED parameter	**Main channel**	**All channels showing an IED**	***p* Value[a]**
Peak[b]	15.5 (2.5–31)	67.5 (33.5–104.6)	0.00037[c]
Beginning[d]	46.5 (27.25–140.25)	118.4 (92.9–177.7)	0.000048[c]

Abbreviations: IED = interictal epileptic discharge; iEEG = intracranial EEG.
Data represent median (interquartile range).
[a] Permutation test (1 million permutations).
[b] Peak-to-peak latency.
[c] Statistically significant.
[d] Beginning-to-beginning latency.

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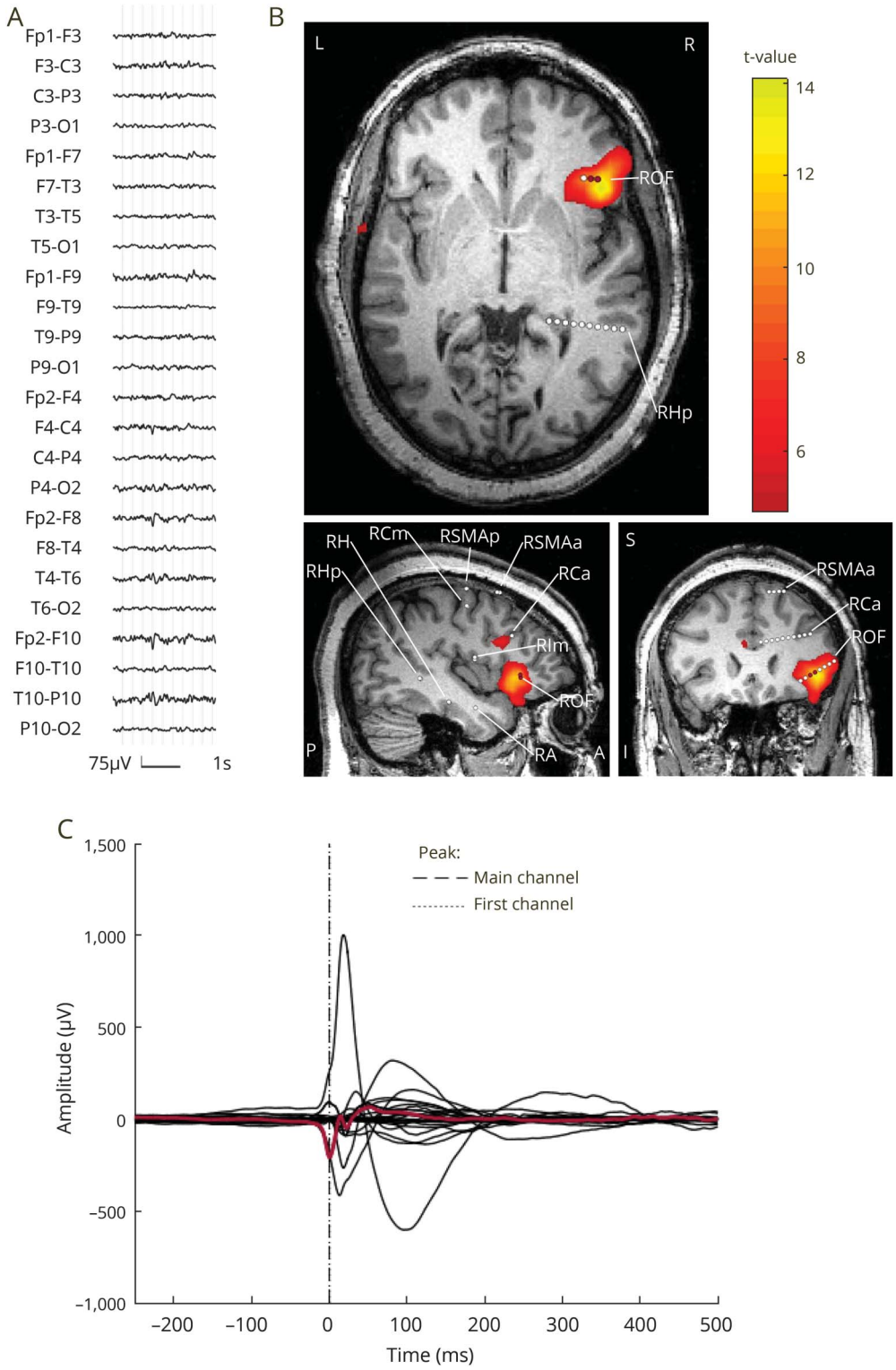
Figure 2 Example of IED recorded closest to the maximum hemodynamic response being the earliest (patient 13)



(A) Scalp EEG, bipolar montage, spikes with equipotentiality at F8-T4 and F10-T10. (B) White circles indicate the contacts visible in these slices. Contacts corresponding to channels closest to fMRI maximum (*main channel*) were marked in red (2 adjacent contacts make 1 channel on intracranial EEG). Yellow-red scale corresponds to *t* values of positive hemodynamic responses. (C) IEDs of all intracranial EEG channels. Each line corresponds to an averaged trace of an intracranial EEG channel. Red = main channel. Dashed black line = peak of IED in the main channel. Dotted black line = peak of IED in the first channel. The scalp IEDs (see panel A) resulted in a maximum hemodynamic response in the right lateral orbitofrontal gyrus (*t* value = 14.1). The patient underwent stereo-EEG with a suspicion of right frontal lobe epilepsy. Nine electrodes were inserted in the right hemisphere: 6 in the frontal lobe, 3 in the temporal lobe. In the frontal lobe, ROF aimed the mesial orbitofrontal, RCa the anterior cingulate, RCm the midcingulate, RSMAa the anterior supplementary motor area, and RSMAp the posterior supplementary motor area, RIm the insula through the frontal lobe; in the temporal lobe, RA the amygdala, RH the hippocampus, RHp the posterior hippocampus. The intracranial study revealed very active IEDs in the lateral orbitofrontal region. The peak of IED in the main channel was the earliest (among 25 channels showing IEDs in the averaged traces). IED = interictal epileptic discharge.

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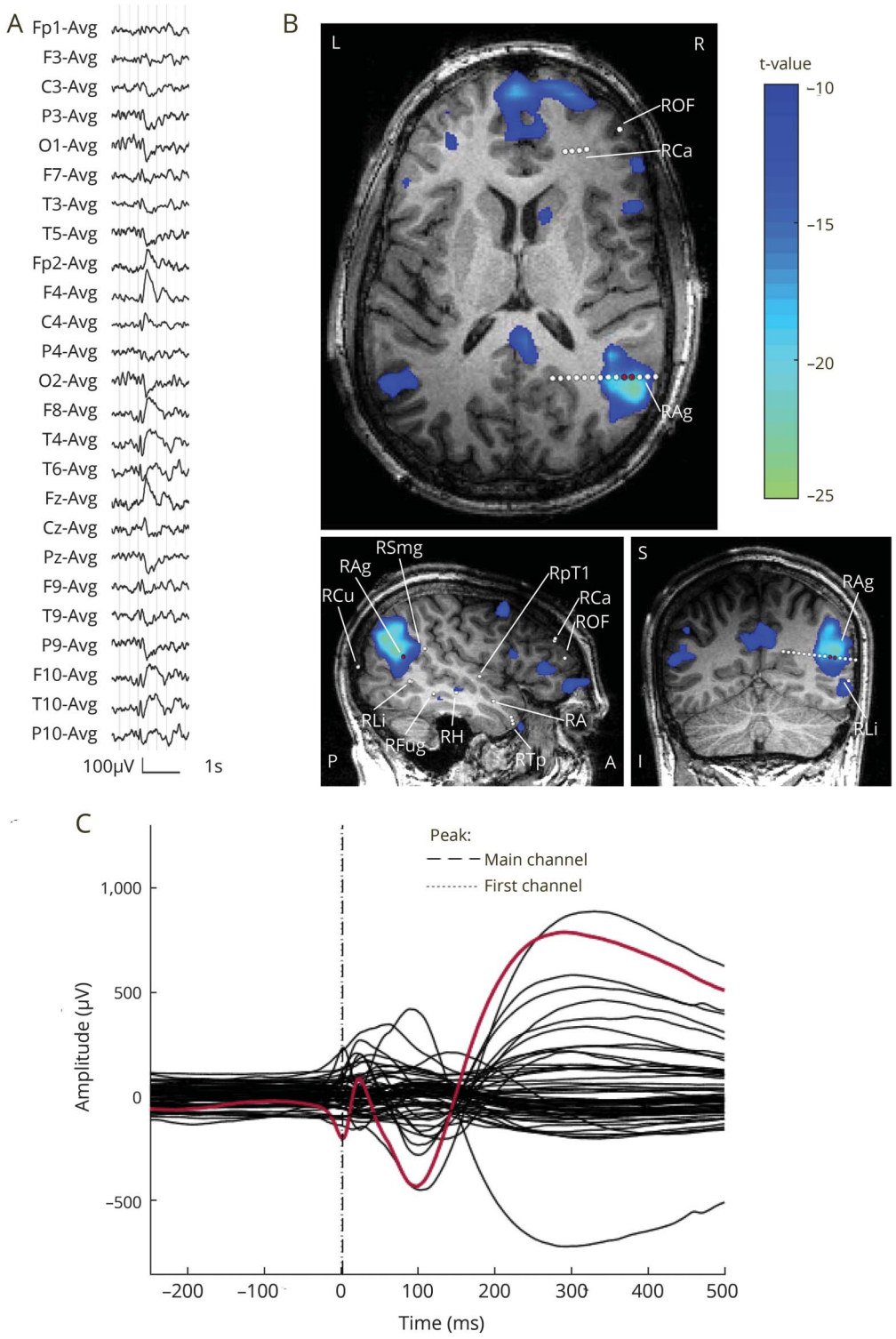
Figure 3 Example of IED recorded closest to the maximum hemodynamic response being the earliest (patient 10)



(A) Scalp EEG, average montage, Fp2, F4, F8, T4, T6, F10, T10, P10 spike and waves. (B) White circles indicate the electrode contacts visible in these slices. Contacts corresponding to channels closest to fMRI maximum (*main channel*) were marked in red (2 adjacent contacts make 1 channel on intracranial EEG). Green-blue scale corresponds to *t* values of negative hemodynamic responses. (C) IEDs of all intracranial EEG channels. Each line corresponds to an averaged trace of an intracranial EEG channel. Red = main channel. Dashed black line = peak of IED in the main channel. Dotted black line = peak of IED in the first channel. The scalp IEDs (see panel A) resulted in a maximum hemodynamic response in the right angular gyrus (*t* value = −24.2). The patient underwent stereo-EEG with a suspicion of right posterior quadrant epilepsy. Eleven electrodes were inserted in the right hemisphere: 2 in the frontal lobe, 9 in the temporal lobe and posterior quadrant structures. In the frontal lobe, ROF aimed the mesial orbitofrontal, RCa the anterior cingulate; in the temporal lobe and posterior quadrant, RTp aimed the temporal pole, RA the amygdala, RH the hippocampus, RpT1 the inferior insula, RFug the fusiform gyrus, RSmg the supramarginal gyrus, RAg the angular gyrus, RLi the lingual gyrus, and RCu the cuneus. The intracranial study revealed very active IEDs in the right posterior quadrant structures. The peak of IED in the main channel was the earliest (among 56 channels showing IEDs in the averaged traces). IED = interictal epileptic discharge.

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Table 2 Correlation coefficient between latency of an intracranial IED[a] and distance between the location of its recording intracranial EEG channel and the maximum EEG-fMRI hemodynamic response

IED parameter	Correlation coefficient[b] (95% CI)	*p* Value
Peak	0.35 (0.30–0.41)	<0.0001[c]
Beginning	0.26 (0.21–0.32)	<0.0001[c]

Abbreviations: CI = confidence interval; IED = interictal epileptic discharge.
[a] Referenced to the IED of the first channel.
[b] Pearson correlation.
[c] Statistically significant.

structures is often accompanied by a weaker response in superficial neocortex.[24] We propose that the region generating an IED requires more energy than a region where an IED is propagated. It is conceivable that for an IED to propagate, its source must involve a more intense neuronal discharge than an IED that is the *result* of propagation.[24] The concept of a propagating IED requiring more energy than a nonpropagating IED may also explain another apparent paradox of EEG-fMRI studies: such studies frequently show a clear maximum response in a region of focal cortical dysplasia, often distant from the scalp,[11] while iEEG studies often show continuous IEDs restricted to the lesion.[25] The EEG-fMRI findings can result from an infrequent IED generated in the lesion that propagates to reach the superficial cortex and become visible on scalp EEG. When this event is compared to the continuous IEDs (invisible on scalp and thus treated as background) during EEG-fMRI analysis, an increased response is found in the lesion because the propagating IEDs require more energy than the continuously occurring but nonpropagating IEDs. Further study using combined iEEG-fMRI would elucidate this hypothesis.[26]

We included negative maximum hemodynamic responses in this study because we had not found any difference between positive and negative responses in localizing the seizure onset zone,[3,12] and synchrony in intracranial IED activity exists even between positive and negative responses in our previous studies.[1] A negative response was reported as the result of an earlier positive hemodynamic response peaking before the spike[27] or a decrease in neuronal activity in the epileptogenic zone,[28] especially when the IED includes a large slow wave.[29] Of note, we did not find a significant difference between the latency of IEDs recorded close to a negative and a positive maximum response (for the peak of an IED, the median latencies were 17 [7.5–36.0] ms for the positive responses and 9 [0.5–12.8] ms for the negative responses, $p = 0.092$; for the beginning of an IED, 63.5 [33.5–140.5] ms for the positive responses and 32 [18.8–52.8] ms for the negative responses, $p = 0.091$). This supports the fact that a negative response, similar to positive ones, can represent the origin of IEDs.

Despite that intracranial IEDs recorded close to the maximum hemodynamic response are likely to occur earlier, not all of them are the earliest (32% of them are among the earliest if the shortest 10th-percentile IED peak latencies are considered or 68% if 25th-percentile latencies are considered; table e-2 [links.lww.com/WNL/A627]). Indeed, the IEDs with the earliest peak and earliest beginning were recorded in channels not too far from the maximum response (at a median distance of 21.6 [10.6–33.2] mm and 24.5 [9.4–37.8] mm, respectively). This can probably be explained by several factors with small effects that can be compounded. They include the lack of perfect overlap between electrophysiologic activity and the related hemodynamic changes,[30,31] the degradation in fMRI localization accuracy caused by distortion and fMRI signal dropout, and imperfect coregistration between anatomical images and fMRIs.

Studying the IEDs using iEEG recordings and scalp EEG-fMRI performed separately can cause possible sampling mismatch. We cannot be sure that the scalp IEDs recorded during EEG-fMRI correspond to the intracranial IEDs analyzed later with iEEG. Thus, the link between the 2 studies is presumptive. Given a widespread intracranial IED event having its source in the region of maximum hemodynamic response and given that this maximum response was obtained from the analysis of a scalp IED, we infer that it is very likely that the source is that of the scalp IED. Simultaneous iEEG, scalp EEG, and fMRI may be the most direct way to study the electrophysiologic basis of IED-related hemodynamic response.[26,32,33] Simultaneous scalp EEG and iEEG is possible but it is difficult to have a large number of scalp EEG electrodes because of the scalp incision and the entry point of iEEG electrodes. Simultaneous iEEG and fMRI is unavailable in our institution and also has limitations because of fMRI signal dropout near intracranial electrodes,[34] which is critical for this type of study.

Because this is a retrospective study, the data pool was heavily distilled to get to the analyzable dataset and this may have introduced some bias: findings are only applicable in patients with IEDs on the scalp and only for IEDs resulting in significant hemodynamic responses. Although we also rejected a large number of patients in whom there was no iEEG channel near the maximum response, this should not be a source of bias because this occurred randomly as EEG-fMRI was not integrated in the image-guided stereotaxy implantation system in most patients. The validity of our findings will be better determined in a larger prospective study, where EEG-fMRI findings are utilized to guide electrode placement and simultaneous iEEG-fMRI is performed.

Author contributions

H.M.K., N.v.E., and J.G. were responsible for conception and design of the study. H.M.K., N.Z., and F.D. were responsible for data acquisition. H.M.K., N.v.E., N.Z., F.D., and D.H. were responsible for analysis of data. H.M.K., N.v.E., F.D., and J.G. were responsible for drafting a significant portion of the manuscript or figures.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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