Author/s:
Kowalczyk, MA;Omidvarnia, A;Dhollander, T;Jackson, GD

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MS. MAGDALENA KOWALCZYK (Orcid ID : 0000-0002-5410-0299)

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Dynamic analysis of fMRI activation during epileptic spikes can help identify the seizure origin.

Magdalena A. Kowalczyk[1], Amir Omidvarnia[1,2,3], Thijs Dhollander[1,4], Graeme D. Jackson[1,5#]

Affiliations:

1. Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne VIC 3010, Australia
2. Institute of Bioengineering, Center for Neuroprosthetics, EPFL, Campus Biotech, Chemin des Mines 9, 1202, Geneva, Switzerland
3. Department of Radiology and Medical Informatics, University of Geneva, Campus Biotech, Chemin des Mines 9, 1202, Geneva, Switzerland
4. ~~Murdoch Children's Research Institute, Royal Children's Hospital,~~ Developmental Imaging, Murdoch Children's Research Institute, Melbourne VIC 3052, Australia
5. Department of Neurology, Austin Health, Heidelberg VIC 3084, Australia

Corresponding author. Address: Melbourne Brain Centre, The Florey Institute of Neuroscience and Mental Health, Austin Campus, 245 Burgundy Street, Heidelberg 3084, VIC, Australia. Telephone number: +61 3 90357000, Fax number: +61 3 90355459. E-mail address: graeme.jackson@florey.edu.au.

E-mail addresses: magdalena.kowalczyk@florey.edu.au (M. A. Kowalczyk), amir.omidvarnia@gmail.com (A. Omidvarnia), thijs.dhollander@gmail.com (T. Dhollander), graeme.jackson@florey.edu.au (G.D. Jackson)

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Summary

Objective: We use the dynamic EEG-fMRI method to incorporate variability in the amplitude and field of the interictal epileptic discharges (IED) into the fMRI analysis. We ask whether IED variability analysis can 1) identify additional activated brain regions during the course of IEDs, not seen in standard analysis, and 2) demonstrate the origin and spread of epileptic activity. We explore whether these functional changes recapitulate the structural connections and propagation of epileptic activity during seizures.

Methods: Seventeen focal epilepsy patients with at least 30 IEDs of a single type during simultaneous EEG-fMRI were studied. IED variability and EEG source imaging (ESI) analysis extracted time-varying dynamic changes. General linear modelling (GLM) generated static functional maps. Dynamic maps were compared to static functional maps. The dynamic sequence from IED variability was compared ~~at a lobar level~~ to the ESI results. In a subset of patients, we investigated structural connections between active brain regions using diffusion-based fibre tractography.

Results: IED variability distinguished the origin of epileptic activity from its propagation in 15 out of 17 (88%) patients. This included two cases where no result was obtained from the standard GLM analysis. In both these cases IED variability revealed activation in line with the presumed epileptic focus. Two cases showed no result from either method. Both had very high spike rates associated with dysplasia in postcentral gyrus. In all 15 cases with dynamic activation, the observed dynamics were concordant ~~at a lobar level~~ with ESI. Fibre tractography ~~analysis~~ identified specific white matter pathways between brain regions active at IED onset and propagation.

Significance: Dynamic techniques involving IED variability can provide additional power for EEG-fMRI analysis, compared to standard analysis, revealing additional biologically plausible

information in cases with no result from the standard analysis and gives insight into origin and spread of IEDs.

Keywords: EEG, fMRI, IED variability, source imaging, fibre tractography, focal epilepsy

Key Points:

- IED variability method distinguished the origin of epileptic activity from its propagation in 88% patients included in the study.
- In two cases with no result ~~was~~ from the standard analysis, IED variability revealed activation in line with the presumed epileptic focus.
- In all cases with dynamic activation, the observed IED variability dynamics were concordant at a lobar level with ESI results.
- Fibre tractography visualised a potential trajectory of propagation of epileptic activity during seizures.

1. Introduction

Scalp-level electroencephalogram (EEG) of patients with focal epilepsy is characterized by brief interictal epileptogenic discharges (IEDs) that occur between seizures. Previous studies have confirmed that the seizure onset often lies within the cortical source area modelled by IEDs.[1-3] Since IEDs are less likely to be associated with artefacts in contrast to ictal events,[4] they are suitable for multimodal brain imaging studies. Among the different non-invasive methods, scalp EEG is considered to have a high temporal resolution, but poor spatial resolution. Thus, the traditional visual inspection of EEG data provides only imprecise localisation, indicating at best which lobe was involved during the epileptic events.

By combining EEG and functional MRI (fMRI), we are able to visualise the brain structures that show activity during IEDs.[5] The most common way of combining EEG and fMRI is based on general linear modelling (GLM) analysis of IEDs, where IEDs are considered as impulse functions and are convolved with a hemodynamic response function to detect the associated fMRI voxels, which are significantly correlated with the model time course.[6] The resulting blood-oxygen-level-dependent (BOLD) fMRI maps can either correspond to a single location of a presumed driver of

epilepsy, or show more extensive, multiregional activity.[7,8] Maximum BOLD signal change related to IEDs reflects the brain region generating the IEDs.[9]

The conventional GLM analysis of EEG-fMRI, however, is limited for several reasons:

- It reduces IEDs to their timing, ignoring their temporal morphology and spatial distribution. It leads to a 'static' picture of the brain functional maps associated with IEDs with no dynamic information about the propagation of epileptic activity within the cortex.
- The sensitivity of GLM analysis to detect activated brain region during IEDs varies between 38-82% in different studies,[8,10,11] which may reflect limitations in the standard fMRI signal modelling.
- Interpreting EEG-fMRI results is difficult when GLM analysis reveals extensive or multi-lobar activation. The multi-cluster activation patterns are reported in over two-thirds of EEG-fMRI studies.[8,12] Widely distributed BOLD changes appear to be associated with a widespread seizure onset zone and poor postsurgical outcome.[13]

Our previous study suggested that incorporating the amplitude and field of the IED into GLM analysis could increase its sensitivity to active brain regions during IEDs.[14] The temporal resolution of this IED variability technique is, however, limited to the repetition time of fMRI recordings, which is typically ~~on~~ in the order of seconds. On the other hand, EEG source imaging (ESI) can provide three-dimensional source representation of the IED activity with good temporal resolution[15] and reveal the spatial onset and spread of IEDs at the cortical level.[16-18]

This study aims to investigate whether dynamic EEG-fMRI method incorporating IED variability can provide additional power for EEG-fMRI analysis compared to static picture of focal epilepsy given by standard GLM analysis. Specifically, we will examine whether IED variability method can (*i*) identify additional activated brain regions during the course of IEDs, not seen in standard GLM analysis, and (*ii*) reveal the origin and spread of IEDs. The dynamic sequence from IED variability will be compared at a lobar level to the ESI results. We will also determine, whether these dynamic functional changes recapitulate the structural connections consistent with ~~and~~ propagation of epileptic activity during seizures, using diffusion-based fibre tractography ~~analysis~~.

2. Materials and methods

2.1. Subjects and data acquisition

From our database of 39 patients with refractory focal epilepsy who underwent 60 minutes of simultaneous resting state scalp EEG and fMRI in a 3T Siemens Skyra MRI system (Erlangen, Germany), we included 17 (44%) patients in this study (age range 11-60, eight females – see Table 1). Patients were included if they had at least 30 focal IEDs of a single type during the EEG-fMRI. We excluded 13 out of 39 (33%) patients who did not have any IEDs and 9 out of 39 (23%) patients did not have enough IEDs of one type during the study.

In the included cohort of 17 participants, 13 patients had one type of focal IED. Four patients had multiple focal IEDs types, however, their number was lower than 30 events, and therefore we did not include them in the study. Eventually, 17 IEDs datasets from 17 patients were included.

All patients included in this study were in the process of pre-surgical assessment at the Comprehensive Epilepsy Program at Austin Health (Melbourne, Australia) between 2012 and 2019. The study was approved by the Austin Health Human Research Ethics Committee. All participants gave written consent to participate in the study.

Functional MRI data were obtained using a gradient-recalled echo planar imaging (EPI) sequence with ~~blood-oxygen-level-dependent imaging~~ BOLD weighting and whole-brain slice coverage with the following parameters: repetition time (TR) = 3 s, echo time (TE) = 30 ms, flip angle = 85^{o}, voxel size = 3×3×3 mm, 44 interleaved 3 mm slices, field of view = 216 mm and acquisition matrix size = 72×72. A total of 1200 fMRI volumes were recorded ~~used~~ for all patients. A T1-weighted image was acquired for anatomical reference.

Simultaneous EEG data were acquired at 5000 Hz using a 32-channel MR-compatible EEG cap (BrainCap MR, EasyCap GmbH, Germany) according to the 10-20 standard system of electrode placement using a BrainAmp recorder (Brain Products GmbH, Germany). Additional channels included echo-cardiogram and signals from three carbon-fibre motion coils[19] along with the EEG, for detection and suppression of head motion and ballistocardiographic artefacts.

Diffusion-weighted MRI (dMRI) data were acquired using a 3T Siemens Trio MRI (Erlangen, Germany) with a 32-channel head coil, and with the following parameters: TR = 84 ms, TE = 110 ms, flip angle = 90^{o}, voxel size = 2.5×2.5×2.5 mm, 44 interleaved 5 mm slices, parallel acceleration factor = 1, 60 (or 64 for some subjects) gradient directions diffusion-weighted images (b=3000 s/mm^2), and 7 non-diffusion weighted images (b=0) ~~were~~ acquired with an EPI sequence. The dMRI data were acquired in five out of 17 (30%) participants included in the study (see Table 1).

Table 1 near here

2.2. EEG-fMRI and dMRI data preprocessing

Preprocessing of fMRI data was performed in MATLAB (MathWorks Inc., United States) using the SPM12 toolbox (Welcome Department of Imaging Neuroscience, Institute of Neurology, London) and the iBrain Analysis Toolbox for SPM.[20] This included: slice timing correction, re-alignment of the EPI images for head motion, segmentation of the T1-weighted images into white matter (WM), grey matter (GM) and cerebrospinal fluid (CFS) areas, smoothing of the normalized images using a Gaussian kernel with full width at half maximum (FWHM) of 8 mm and high-pass filtering at a cut-off of 128 seconds.

EEG signals were preprocessed using the BrainVision Analyzer software (version 2.0, Brain Products) and EEGLAB.[21] Ballistocardiographic and head motion artefacts were corrected automatically using information obtained via motion artefact detection loops.[19] Gradient-switching artefacts were corrected by subtracting the averaged scanner artefact template from the continuous EEG recordings using the information of scanner markups.[22] The preprocessed EEG datasets were downsampled to 250 Hz. Acquired EEG recordings were then reviewed by two ~~epileptologists experienced in EEG interpretation~~ EEG experts for the manual mark-up of all epileptic activity.

Preprocessing of dMRI data was performed using MRtrix3,[23] followed by 3-tissue constrained spherical deconvolution (CSD) modelling using MRtrix3Tissue (https://3Tissue.github.io/). Preprocessing steps included: denoising,[24] removal of Gibbs ringing artefacts,[25] EPI and eddy-current distortion and motion correction,[26] log-domain intensity normalization and bias field correction. 3-tissue response functions for WM, GM and CSF were estimated from the data themselves using an unsupervised approach.[27,28] Using these response functions, Single-Shell 3-Tissue CSD (SS3T-CSD)[29] was performed to compute WM fibre orientation distributions (FODs) and GM/CSF compartments.

2.3. Dynamic EEG-fMRI analysis

IED variability

The IED variability method for the modelling of time-varying behaviour in brain functional maps of epilepsy patients has been described in detail previously[14] and is illustrated in Suppl.Figure 1. In short, the method uses linear classification of IED versus background EEG within narrow windows of IED and performs GLM at each window along the course of IEDs to derive a series of hemodynamic responses at successive time intervals. It leads to a sequence of independent statistical maps associated with temporal variability of the epileptic spikes. In this study, the

window length was set to -100 to 950 milliseconds relative to the IED onset, resulting in 43 statistical maps ~~for~~ per each fMRI dataset.

EEG source imaging

ESI analysis was performed using the Brainstorm toolbox (version 3.4) through the recommended procedure for resting-state EEG data.[30] Source level models were based on the individual cortical mesh triangulations, extracted by FreeSurfer from each subject's T1-weighted image. Head surface triangulations were then computed from the same MRI data. The forward model was based on Boundary Element Method (BEM) ~~head models computed~~ using OpenMEEG.[31] The standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the distributed source activity of each cortical location at each time point for average IEDs.[32] For each interictal EEG dataset, IEDs were aligned according to the peak of their global field power (GFP) and an epoch of ±500 milliseconds around this peak was averaged across spikes.

Choice of the time slice during IED activity for the dynamic analyses

Previous studies revealed that the early component of the IED most closely matches the location and field of the source activity estimated by ESI, while the peak of the IED reflects propagated activity. [16,33] We selected two time points during the course of IED for source reconstruction: 'IED onset' and 'IED propagation' ($\tau 1$ and $\tau 2$ respectively). The former was defined as the peak of the half maximum atof the first rising phase in GFP of the averaged IED. The latter was defined as the maximum source activity around the first and second GFP maximum (see Figure 1). These were previously reported to be the best estimation of IED components.[18,34]

Figure 1 near here

Assessment of dynamic EEG-fMRI results

We assessed whether the dynamic EEG-fMRI method incorporating IED variability into the fMRI analysis can provide additional power for the EEG-fMRI analysis compared to standard GLM-based analysis of this data in focal epilepsy cases. Specifically, we investigated whether the IED variability technique can identify additional active brain regions associated with IEDs, not seen in standard GLM analysis, and reveal the origin and spread of IEDs. For each patient, an experienced epileptologist (G.D.J) assessed whether the additional spatial information provided by the dynamic EEG-fMRI method were biologically plausible, i.e. in line with presumed epileptic focus. The presumed epileptic focus was defined for each patient non-invasively on the basis of available clinical information, i.e. EEG data, ictal semiology and MRI structural abnormality.

The dynamic sequence from the IED variability analysis was compared ~~at a lobar level~~ to the ESI results. We classified the IED variability and ESI maps as 'concordant' when the IED variability maximum activation was within the ESI activation, and as 'discordant' when IED variability maximum was remote from the ESI activation. ~~Specifically, for each patient an experienced epileptologist (G.D.J) examined whether the obtained IED variability maps share similar fluctuations in the spatial patterns of epileptogenic functional networks like the ESI results.~~

For both IED variability and ESI results, and based on the post-surgery outcome, we calculated sensitivity, defined as the percentage of patients with maximum of the IED variability/ESI activation within the area of surgical resection area of all patients with good outcome (ILAE 1), specificity, defined as the percentage of patients with IED variability/ESI maximum outside the resected area in patients with poor outcome (ILAE 4/5), positive predictive value (the probability of becoming seizure-free when the IED variability/ESI maximum was resected) and negative predictive value (the probability of continuing to have seizures if the IED variability/ESI maximum was not resected).

Figure 2 shows the analysis pipeline of this study for a typical dataset. All analyses were conducted for each patient separately and performed on the IEDs datasets acquired during the same fMRI acquisition.

Figure 2 near here

2.4. Static EEG-fMRI analysis: GLM analysis

The standard GLM analysis was used to investigate the significant changes of BOLD signal and extract static images of IED-induced brain functional maps from concurrent EEG and fMRI, with each IED type modelled as an independent column in the GLM design matrix. This was obtained as a boxcar function convolved with the SPM canonical haemodynamic response function. Twenty-four fMRI motion realignment parameters were also included in the model as confounds. Additional scan-nulling columns were included to *scrub* volumes at any time point where framewise displacement was greater than 0.5 mm. A high-pass filter at 1/128Hz was included and serial correlation of noise was modelled as an autoregressive process of order 1. Voxel-wise F-test was used for significance testing of the GLM parameters across fMRI voxels. The resulting F-maps were thresholded at a voxel-wise p-value of 0.001 and a cluster-wise p-value of 0.05 using

Gaussian Random Field Theory.[35] The thresholded F-maps were later compared with the spatial maps obtained from the ~~two following dynamic analyses~~ IED variability and ESI methods.

2.5. Structural connectivity analysis

Additionally, structural connectivity analyses were performed to explain patterns of epileptic spread revealed by dynamic techniques, and determine whether this functional change is in a network that recapitulates the structural connections and propagation of epileptic activity. Diffusion MRI data was available for five of 17 (30%) patients included in the study. To visualise the nerve tracts between activated brain regions at IED onset (τ1) and IED propagation (τ2), targeted probabilistic fibre tractography[36] guided by the WM FODs was performed. Two brain regions of interest (ROI) with maximum activation identified in IED variability analysis of EEG-fMRI data were selected for each patient. ROIs were drawn manually on coregistered datasets. The tractography results were visualised as sets of streamlines. These regions were specific for each subject and the midbody of the corpus callosum was excluded for all cases. For each tract 5000 streamlines were generated using mostly default parameters; only the FOD amplitude threshold was slightly increased to minimize the presence of false positive streamlines. These were visually assessed by an experienced epileptologist (G.D.J.) to determinate if these pathways are biologically plausible.

3. Results

3.1. Dynamic EEG-fMRI provides additional power for EEG-fMRI analysis

The mean number of IEDs marked up in EEG-fMRI recordings was 226 ±224 across 17 patients. Standard GLM analysis data led to statistically significant clusters of BOLD changes in 13 of 17 studies (77%); in four cases, there were no significant IED-related BOLD changes (Patients 14-17).

IED variability analysis distinguished the origin of the IED from its propagation in 15 of 17 (88%) cases included in the study. This included two cases where no result was obtained from the standard GLM analysis. In both these cases, IED variability revealed activation in line with the presumed epileptic focus. In Patient 14, IED variability revealed activation in the left frontal and central regions, in agreement with the seizure activity and frequent IEDs recorded in the left frontal region during the patient's video-EEG monitoring. In Patient 16, IED variability showed increased activation of the epileptic focus in right frontal lobe. These results are concordant with the Patient's nuclear imaging showing the right frontal involvement, and video-EEG monitoring data that revealed multiple seizures and IEDs raising from right frontal areas. Two cases (Patients 15 and

17) showed no result from either method. Both had very high spike rates associated with focal cortical dysplasia in right postcentral regions. See Table 2 for more details.

Table 2 near here

~~In all 15 cases with dynamic activation from IED variability analysis, the observed dynamics were concordant at a lobar level with ESI results.~~ IED variability maps were concordant with ESI in 13/15 (87%) cases at IED onset (τ1), and 15/15 (100%) cases at IED propagation (τ2). IED variability provided higher sensitivity and specificity values compared to the ESI (100% vs 67%, 100% vs 0%, respectively). The positive predictive value of IED variability for seizure localization was 100%, compared to 80% for ESI (see Suppl. Table 1).

Seven patients had BOLD response in same areas in standard GLM, and at the IED onset/propagation with IED variability analysis. Six patients had some discordance in areas of BOLD activation between the three responses; we observed concordance between standard GLM analysis and IED variability at IED propagation in five patients, and between standard GLM and IED variability at IED onset in one patient. The difference in BOLD concordance between those two groups was statistically significant (chi-squared test; $p < 0.05$).

We observed additional activated brain regions obtained from IED variability analysis at IED onset and/or propagation, not seen in standard GLM analysis. We identified several different situations:

- Expansion of epileptic activation related to IEDs: dynamic techniques revealed that the primary epileptic focus grows in strength and expands with time (Patients 1, 2, 5, 6, 7, 16).
- Order of brain activation during IEDs: dynamic techniques could differentiate the origin of the primary focus vs subsequent spread during IEDs (Patients 2, 4, 7, 8, 9, 10).
- The IED variability technique provided more extensive activations across subcortical areas than ESI analysis (Patients 3, 6, 12).

Figure 3 shows exemplary subjects with each of those situations. Remaining cases are shown in Suppl. Figure 2.

Figure 3 near here

3.2. Functional changes during IEDs recapitulate the structural connections

Fibre tractography ~~analysis confirmed~~ showed WM pathways between brain regions active at IED onset and propagation in all five patients with available dMRI data (see Figure 4). In Patients 2, 4, 7 the tractography results revealed connections from left to right temporal nodes via the anterior commissure (AC) across the midline. These connections of the bilateral temporal lobes through the

AC have been investigated previously.[37,38] In Patient 8, IED variability provided ROIs in the right temporal (τ1) and right frontal region (τ2). Tractography identified the temporal WM pathway via the superior longitudinal fasciculus (SLF) from the right temporal node to the abnormality in the frontal cortex. The SLF is an association tract present in both hemispheres.[39] In Patient 12, tractography identified the existing short-association tract[39] between left temporal cortical nodes with adjusted regions in temporal lobe in the ipsilateral hemisphere.

Figure 4 near here

4. Discussion

The aim of this study was to investigate the advantage of adding IED variability analysis into standard EEG-fMRI analysis of complex focal epilepsy cases.

Dynamic vs static analysis of EEG-fMRI

The IED variability technique was able to distinguish the origin of epileptic activity from its spread in 88% patients. This included two cases with no result from the standard analysis, in which IED variability revealed active brain regions related to IEDs, in line with the presumed epileptic focus.

Clinical utility of dynamic EEG-fMRI analysis

We demonstrate the clinical importance of IED variability fMRI analysis distinguishing the area of initial activation in some cases. In particular, in Patient 9 and 10, where static GLM analysis showed a multiregional activation, the focal regions that were initially activated at IED onset using the IED variability technique were ultimately selected as surgical targets for resection in those cases. Surgery of this area ~~lead~~ led to seizure freedom in both cases. Similarly, in Patient 9, intracranial EEG implantation revealed right frontal seizure origin, followed by epileptic propagation towards right parieto-temporal region. In contrast to static GLM analysis, IED variability identified the origin of the IED, and distinguished this from subsequent activation areas related to the later part of the IEDs.

Previous studies suggested that maximum BOLD is likely to be the critical seizure onset zone,[9] as the standard GLM analysis uses statistical significance to try to distinguish the IED origin from later spread. The IED variability method recognises that not all activity during EEG-fMRI needs to be resected for surgical control of seizures, implying that some areas are secondary spread. In Patient 8, the standard GLM analysis showed right temporal and right frontal activations, with maximum BOLD in a right temporal region. Based on stereo-EEG focussed on the frontal lobe, this

patient underwent resection of one of four subtle focal cortical dysplastic lesions in the right superior frontal gyrus. This had no impact on the seizures, which were ongoing. We hypothesise that the epilepsy in Patient 8 could have been driven by the right temporal region, which was activated at IED onset. Patient 8 is currently awaiting further investigations to explore the right temporal region and the margin of the previous resection.

Although IEDs and seizures are two fairly distinct phenomena, they both originate in the epileptic focus.[1] IEDs, just like seizures, may affect brain areas well beyond the presumed region in which they are generated.[40] We hypothesise that with a single IED we are able to differentiate the propagation of epileptic networks, and the IED spread appears to be the same as the sequence during seizures. The time course of a spike and a seizure is remarkably different, yet both seem to activate networks that include areas of the brain at a distance from the origin. Remarkably, the slow network of a seizure and the fast network of the IED seem to be the same. For example, in Patient 2, IED variability analysis showed right temporal activation followed by immediate bilateral temporal activation during the IED. This is consistent with Patient's ictal semiology, involving coughing, speech arrest, and left arm tonic contraction with a rapid evolution to bilateral convulsions.

Other recent studies involving implementing the scalp EEG data into the GLM analysis of fMRI showed dynamic activation changes within the duration of IEDs.[41,42] These studies showed that the sub-second analyses of EEG-fMRI have the potential to distinguish between the epileptic foci and other co-activated brain regions.

Structural connections underlying IED dynamics

Augmenting fMRI analysis of IEDs with a three-dimensional reconstruction of white matter tracts obtained *in vivo* and non-invasively from dMRI may also identify potential seizure propagation pathways. In this study, fibre tractography identified WM pathways between brain regions active at IED onset and later during the spike in all cases with dMRI data. In three patients with temporal lobe epilepsy (Patients 2, 4, 7), tractography showed inter-hemispherical connections between right and left mesial temporal structures. Such interhemispheric propagation is commonly seen in epilepsy.[38,43] There is electrophysiological connection between temporal structures.[44] Our study visualises directly a potential pathway that enables propogation of IEDs. Previous experiments in animal models have suggested that spontaneous seizures can be suppressed via stimulation of WM tracts connecting bilateral temporal structures. Knowledge of white matter connections may be important for considering the location of implanted stimulation devices used to prevent seizure activity and suppress epileptic foci.[45,46]

Limitations of dynamic imaging of spikes with IED variability imaging

The high resolution IED variability method used in this study was able to reveal focal activations in subcortical areas as well as pinpoint the origin of the IED. This technique, however, requires high IED counts. Specifically, ideally at least ~40 IEDs of one type of event are needed for IED variability analysis.[14] In this study, we included subjects with at least 36 IEDs. Our results apply only to patients in whom IEDs are detected during the EEG-fMRI session, and do not provide information for patients without an active interictal EEG. In two patients, IED variability did not reveal any significant activation, despite very frequent IEDs, which may be caused by low spike amplitude recorded in those cases.

Our study compared static and dynamic functional maps related to IED performed on the same set of IED from the same MRI acquisition session, which is an important step when comparing non-invasive modalities and helps to eliminate bias associated with different experimental and clinical conditions (e.g. medication status). Despite ~~visually assessed~~ agreement between results of ESI and fMRI in revealing similar activation pattern during the IEDs, a perfect "spatial overlap" is not expected, as there are different underlying mechanisms for each method: ESI images synchronise post-synaptic activity, while fMRI measures haemodynamic changes related to total synaptic activity.[18] As ESI explores the events at the time at which they occur on the scalp, it can correctly identify the source of the IEDs in the superficial neocortex.[47] Scalp EEG-fMRI of the same events, on the other hand, can find the maximum response even if the origin is deeper in the brain.[48] Nonetheless, in all patients in this study, the observed dynamics from IED variability analysis were concordant with ESI.

5. Conclusion

The dynamic EEG-fMRI method incorporates IED variability in the amplitude and field of the IED into the fMRI analysis. We show in this study that, when enough data exists to perform this analysis, it provides additional power for EEG-fMRI analysis, compared to standard GLM analysis. IED variability reveals additional biologically plausible information in cases with no result from the standard analysis and distinguishes the origin and spread of IEDs. Tractography can explain the pattern of epileptic propagation by providing information of structural connectivity between functionally identified regions. Integrating different analysis techniques of EEG, dMRI and fMRI is a useful adjunct in the evaluation of challenging epilepsy cases, which might aid the identification of potential surgical targets non-invasively.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Summary of the clinical information for all patients.

Patient	Age at	Sex	Age of seizure	Epilepsy semiology	Clinical manifestations	Structural MRI	Scalp EEG	PET/ictal SPECT	EEG-fMRI focal	Intracranial EEG investigati	Operation procedure /

	scan		onset			findings	focus	focus	events not include in the study – GLM standard analysis (BOLD response)	on	pathology/ ILAE outcome (follow-up time)
1	41y	M	10y	L TLE	FAS: anxiety, dysphasia FSAI: blank stares, head turn to L or R, R hand automatism, L hand held still and rigid	L HS, multiple tubers in the L temporal lobe, L parietal region and L anterior cingulate	L temporal	L temporal	-	-	L anterior temporal lobectomy/ dysplasia, multiple tubers/ ILAE 1 (5y)
2*	23y	M	16y	R TLE	FSAI: blank stares, but will continue to complete manual tasks repetitively Nocturnal sz: tongue bite, mouth frothing, moaning, sucking lips, L face and arm tonic contraction with rapid evolution to FTBTC	R PVNH, R temporal peri-sylvian and parietal polymicrogyria, regions of cortical dysplasia	R fronto-temporal	R temporal	Sharps (n=15): R temporal focus	-	-
3	40y	M	16y	R TLE	FAS: deja vu, nausea FSAI: motor and speech arrest, oral automatism FSAI with no aura: eyes glazed over, moves L leg, clenching things with hands	MRI negative, previous R HS resection	Bitemporal and R posterior temporal	R frontal, R temporal, L temporal	-	-	-
4*	42y	F	7y	L TLE	FSAI: deja vu, nausea, fear, myoclonic movements of the L side of face FSAI: humming, asymmetric stiffening, R arm and leg raise, automatism, developing into FTBTC	PVNH, more severe on left	L temporal	*NA*	-	-	-
5	27y	F	8y	R TLE	FSAI: butterflies in stomach, unusual smell, visual symptoms (vision loss, blank stares, blurry vision),	MRI negative	R posterior inferior temporal	R temporal	Sharps (n=16): R posterior temporal focus	R posterior temporal implantation revealed R posterior temporal sz	R posterior inferior temporal corticectomy / FCD type IIB / ILAE 1

					rubbing hands together, lip smacking, chewing, speaking gibberish Occasional FTBTC					focus	(3y)
6	41y	F	16y	L TLE	FAS: tingling sensation (R hand that spreads to shoulder) FSAI: moaning, blank stares, dystonic posturing of L arm with clenching of fist, head version to L with facial grimace Frequent FTBTC	MRI negative	L temporal	L temporal	-	-	-
7*	60y	M	26y	R TLE	FAS: nausea, gustatory symptoms FSAI: blank stares, chewing, manual automatism Rare FTBTC	R insular surgical defect, previous right inferior frontal lesion resection	R temporal	R temporal	-	-	-
8*	39y	F	3mo	R FLE	FAS: eye and head deviation to L, raises L arm, stands and turns counter clockwise, progressing to FTBTC FSAI: behavioural arrest, ongoing compulsion to turn to L, rocking backwards/forwards, laughing, hand automatism	Four subtle focal cortical dysplastic lesions in R superior frontal gyrus	R frontal	R frontal, R temporal	-	R frontal implantation revealed R frontal sz focus	R frontal lobectomy/ normal pathology/ ILAE 5 (1y)
9	26y	M	13y	R FLE	FAS: discomfort sensation in chest, stands and R head version, circling sz to the R, swearing repetitively FSAI: pacing back and forth, behavioural arrest, blank stares FTBTC	MRI negative	R central and frontal	R temporal, R frontal	Sharps (n=17): R frontal parietal, midline activation	R frontal implantation revealed R frontal sz focus followed by parieto-temporal propagation	R frontal corticectomy /*NA*/ ILAE 1 (1y)
10	24y	M	23y	R parietal	FSAI: behavioural arrests, felling to the R then FTBTC	R posterior mesial cavernoma	R fronto-parietal	R frontal	SSW (n=22): R parietal focus	-	R posterior mesial gyrectomy/ cavernoma /ILAE 1 (2y)
11	53y	M	16y	L FLE	FSAI: dysphasia, eyes glazed over, motor sz (legs + arms bilat slow flexion and	Left superior-frontal dysplasia, previous left	L frontal	L frontal	-	-	-

					extension), moaning FTBTC	superior frontal resection					
12*	29y	F	16y	L TLE	FAS: rising sensation in stomach, blank stares, speech arrest, lip smacking FSAI: vocalising, then FTBTC	MRI negative	L temporal	L temporal	-	-	-
13	16y	F	13y	L TLE	FSAI: altered behaviour, confusion, blank stares, head movements R and L, oral automatism FTBTC	L temporal-occipital PVNH	L posterior and L temporo-occipital	L posterior quadrant, L temporal	-	-	-
14	11y	F	10y	L FLE	FSAI: blank stares, head/eye deviation to the R, periocular twitching FTBTC	MRI negative	L frontal, rare R frontal	*NA*	-	-	-
15	19y	F	12y	R parietal	FAS: L hand numbness FSAI: L arm movement with abnormal posturing, dystonia FTBTC	R postcentral BOSD	R centro-temporal	R postcentral	-	R centro-parietal implantation revealed R postcentral sz focus	R postcentral corticectomy / FCD type IIA /ILAE 1 (1y)
16	25y	M	11y	R FLE	FAS: visual symptoms (twinkling lights in L visual field, then R visual field, dots, colours, then complex visual hallucinations), head and eye deviation to L, stiffening L hand, automatism R hand, sensitivity to noise FSAI: speech and behavioural arrest FTBTC	Diffuse atrophy, abnormality in the inferior bank of the calcarine sulcus around the right fusiform gyrus	R frontal	R frontal	-	-	-
17	40y	M	9y	R parietal	FAS: premonitory feeling, then loss of sensation and weakness of L arm FTBTC	R postcentral BOSD	R central	R postcentral	-	-	R postcentral corticectomy / FCD type IIB / ILAE 1 (2y)

Abbreviations: BOSD = bottom of the sulcus dysplasia, EEG = encephalography, F = female, FAS = focal aware seizures, FCD = focal cortical dysplasia (type II: malformation resulting from disrupted cortical lamination and specific cytological abnormalities; type IIA with dysmorphic neurons, type IIB with dysmorphic neurons and balloon cells), FLE = frontal lobe epilepsy, FSAI = focal seizure awareness impaired (formerly complex partial seizure), FTBTC = focal to bilateral tonic–clonic (formerly generalized tonic–clonic seizure), HS = hippocampal sclerosis, ILAE 1 = International League Against Epilepsy outcome scale: Class 1 - completely

seizure-free, no auras, Class 5 - less than 50% reduction of baseline seizure days; ± auras, L = left, M = male, mo = month, MRI = magnetic resonance imaging, *NA* = not available, PET = Positron Emission Tomography, PVNH = periventricular nodular heterotopia, R = right, SPECT = Single Photon Emission Computed Tomography, SSW = sharp-slow waves, sz = seizures, TLE = temporal lobe epilepsy, y = year.

* Diffusion-weighted magnetic resonance imaging (dMRI) data available.

Table 2. Results of BOLD response in GLM analysis and IED variability at IED onset and propagation.

Patient	IED type	Number of IEDs	Standard GLM analysis: BOLD response	IED variability at IED onset (τ1)	IED variability at IED propagation (τ2)
1	Sharp	154	L orbito-frontal	L orbito-frontal	L orbito-frontal (along TS)
2	SSW	38	R temporal (posterior part of PVNH)	R temporal (posterior part of PVNH)	R temporal (posterior part of PVNH), L temporal
3	Sharp	211	Bilateral thalamus, bilateral superior temporal	Bilateral thalamus, left superior temporal	Bilateral thalamus, bilateral superior temporal
4	Sharp	444	Bilateral temporal-occipital	L temporal	Bilateral temporal, R occipital
5	Sharp	43	R posterior temporal	R posterior temporal	R posterior temporal
6	Sharp	93	L temporal-occipital	L temporal-occipital	L temporal-occipital
7	Sharp	259	R temporal	R temporal	Bilateral temporal, occipital
8	Sharp-slow	45	R temporal, R frontal	R temporal	R temporal, R frontal
9	SSW	36	R frontal, parietal and occipital	R frontal	R frontal, parietal and occipital
10	Sharp	150	R parietal, R frontal	R parietal	R parietal, R frontal
11	Sharp	109	L frontal	L frontal	L frontal, L temporal
12	Sharp	587	L temporal	L temporal	L temporal
13	Slow	133	L temporal (part of PVNH)	L temporal (part of PVNH)	L temporal (part of PVNH)
14	Sharp-slow	414	*NA*	L fronto-central	L fronto-central, R temporal
15	Sharp	254	*NA*	*NA*	*NA*
16	Sharp	42	*NA*	R frontal	R frontal
17	Sharp	830	*NA*	*NA*	*NA*

Abbreviations: BOLD = Blood-oxygen-level-dependent, EEG = electroencephalogram, GLM = general lineal modelling, IED = interictal epileptic discharge, L = left, PVNH = periventricular nodular heterotopia, R = right, TS = tuberous sclerosis; *NA* = not available (no statistically significant result), SSW = sharp-slow waves.

Supp. Table 1. The number of patients classified as TP (true positive), FP (false positive), TN (true negative), and FN (false negative), as well as sensitivity and specificity, positive/negative

predictive values for the IED variability and the ESI methods. Analysis conducted for surgical cases.

	TP	FP	TN	FN	Sensitivity = TP/ (TP + FN)	Specificity = TN/ (TN + FP)	Positive predictive value = TP / (TP + FP)	Negative predictive value = TN / (FN + TN)
IED variability (n=5)	4	0	1	0	100%	100%	100%	100%
ESI (n=7)	4	1	0	2	67%	0%	80%	0%

Abbreviations: ESI = electroencephalography source imaging, FN = false negative (the seizure-free patients in whom the maximum of the IED variability/ESI activation was outside the resected area), FP = false positive (the non-seizure-free patients in whom the maximum of the IED variability/ESI activation was within the resected area), IED = interictal epileptic discharge, TN = true negative (the non-seizure-free patients in whom the maximum of the IED variability/ESI activation was outside the resected area), TP = true positive (the seizure-free patients, in whom the maximum of the IED variability/ESI activation was within the resected area).

Figure legends

Figure 1. Time points τ1 and τ2 marked on spike average (n=154). Time point τ1 was defined as the peak of the half maximum of the first rising phase in the global field power (GFP) of the averaged epileptic spike, τ2 was defined as the maximum source activity around the first and second GFP maximum.

Figure 2. The analysis pipeline for an exemplary subject (Patient 8): dynamic analysis of EEG-fMRI. Left top panel: static approach - GLM analysis based on IED-related BOLD response. Right panel: (A) Average of IEDs marked at two time points during the IED interval (τ1, τ2), (B, C) Dynamic approaches: IED variability and EEG source imaging results, retrospectively.

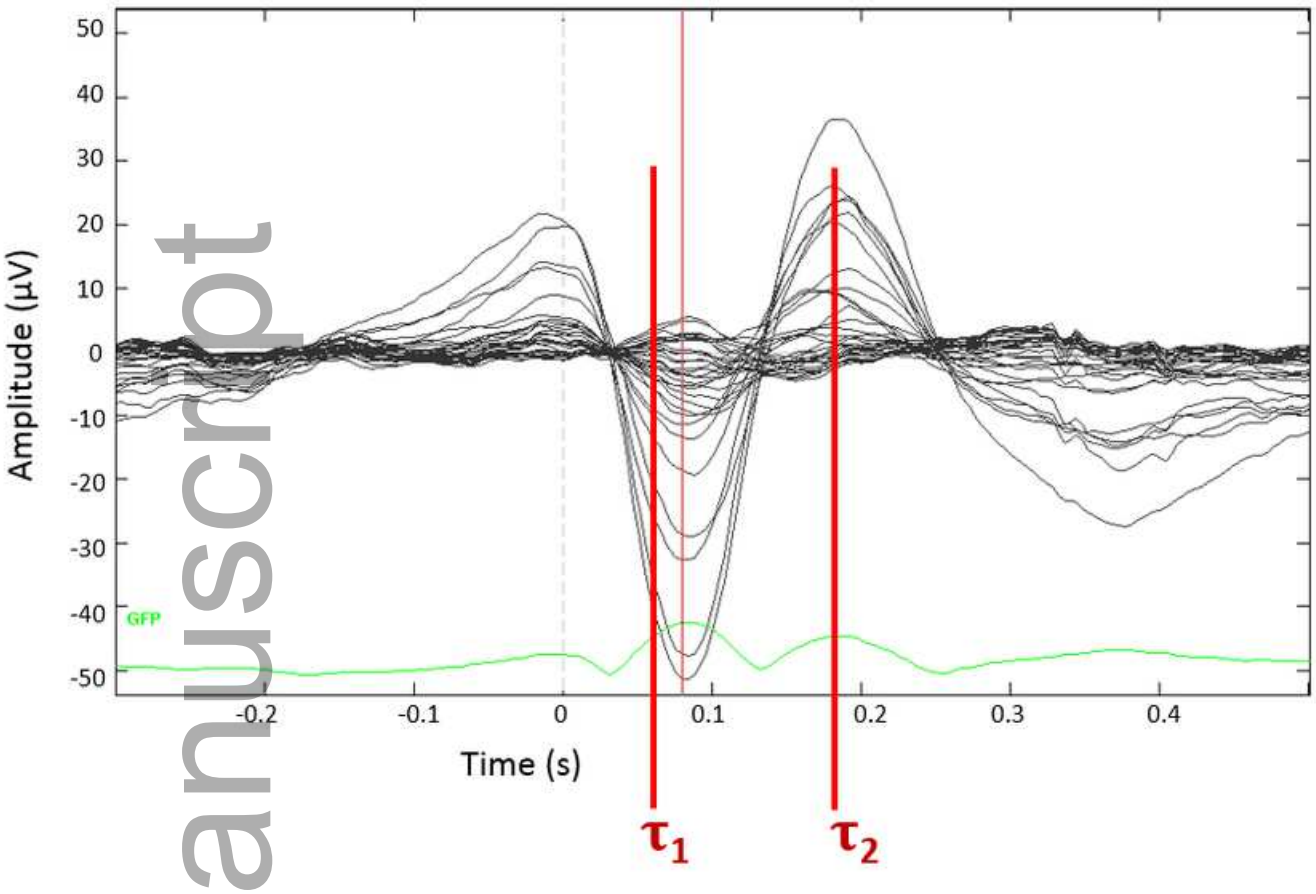
Figure 3. Evolution of brain activation during epileptic spikes: dynamic snapshots and static functional maps for exemplary subjects. Selected cases show different situations: expansion of primary epileptic focus (Patient 1), sequence of brain activation during IEDs (Patient 9), activation across subcortical regions revealed by IED variability (Patient 3), and a patient with a results from dynamic analysis despite no significant BOLD response from GLM analysis (Patient 16).
Abbreviations: EEG = electroencephalography, EEG-fMRI = simultaneous electroencephalography with functional magnetic resonance imaging, GLM = general lineal modelling, IED = interictal epileptic discharge, FLE = frontal lobe epilepsy, L = left, NA = not available (no statistically significant result), R = right, sLORETA = standardized low resolution

brain electromagnetic tomography, TLE = temporal lobe epilepsy, τ1 = IED onset, τ2 = IED propagation. Surgical resection regions marked in Patients 1 and 9 (schematic only).

Figure 4. Fibre tractography results displayed on the coregistered T1 image in a subset of cases. For reference, IED variability results with ROIs (schematic) are shown for each case. The convention for colour coding: red: transverse fibre, green: anteroposterior fibres, blue: craniocaudal fibres.
Abbreviations: FLE = frontal lobe epilepsy, L = left, R = right, ROI = regions of interest, temp = temporal, TLE = temporal lobe epilepsy.

Suppl. Figure 1: IED variability analysis – an overview. Shown is an example for a given temporal EEG window. A: Narrow windows of EEG data, x(t) (red), and randomly selected periods of the background activity (blue bars). B: We estimated the linear weighting (w) on the EEG channels that maximally discriminates the IEDs (red) vs the background activity (blue). C: From w, we compute ȳi, which is the demeaned classifier output. This was used to design the functional MRI model based on known event timing (D). We built two regressors for fMRI model, including event-related average BOLD response to targets (E), and regressor incorporating IED variability (F, G). We convolved each regressor with the canonical haemodynamic response function. H: Brain regions that are strongly coupled with the IED at the selected latency. Figure modified from Walz et al 2017.[14]
Abbreviations: BOLD = Blood-oxygen-level-dependent, EEG = electroencephalography, fMRI = functional magnetic resonance imaging, IED = interictal epileptic discharge, L = left, MRI = magnetic resonance imaging, R = right.

Suppl. Figure 2. Evolution of brain activation during epileptic spikes: dynamic snapshots and static functional maps for all remaining cases.
Abbreviations: EEG = electroencephalography, EEG-fMRI = simultaneous electroencephalography with functional magnetic resonance imaging, GLM = general lineal modelling, IED = interictal epileptic discharge, FLE = frontal lobe epilepsy, L = left, NA = not available (no statistically significant result), R = right, sLORETA = standardized low resolution brain electromagnetic tomography, TLE = temporal lobe epilepsy, τ1 = IED onset, τ2 = IED propagation. Surgical resection regions marked in Patients 5, 8, 10, 15 and 17 (schematic only).



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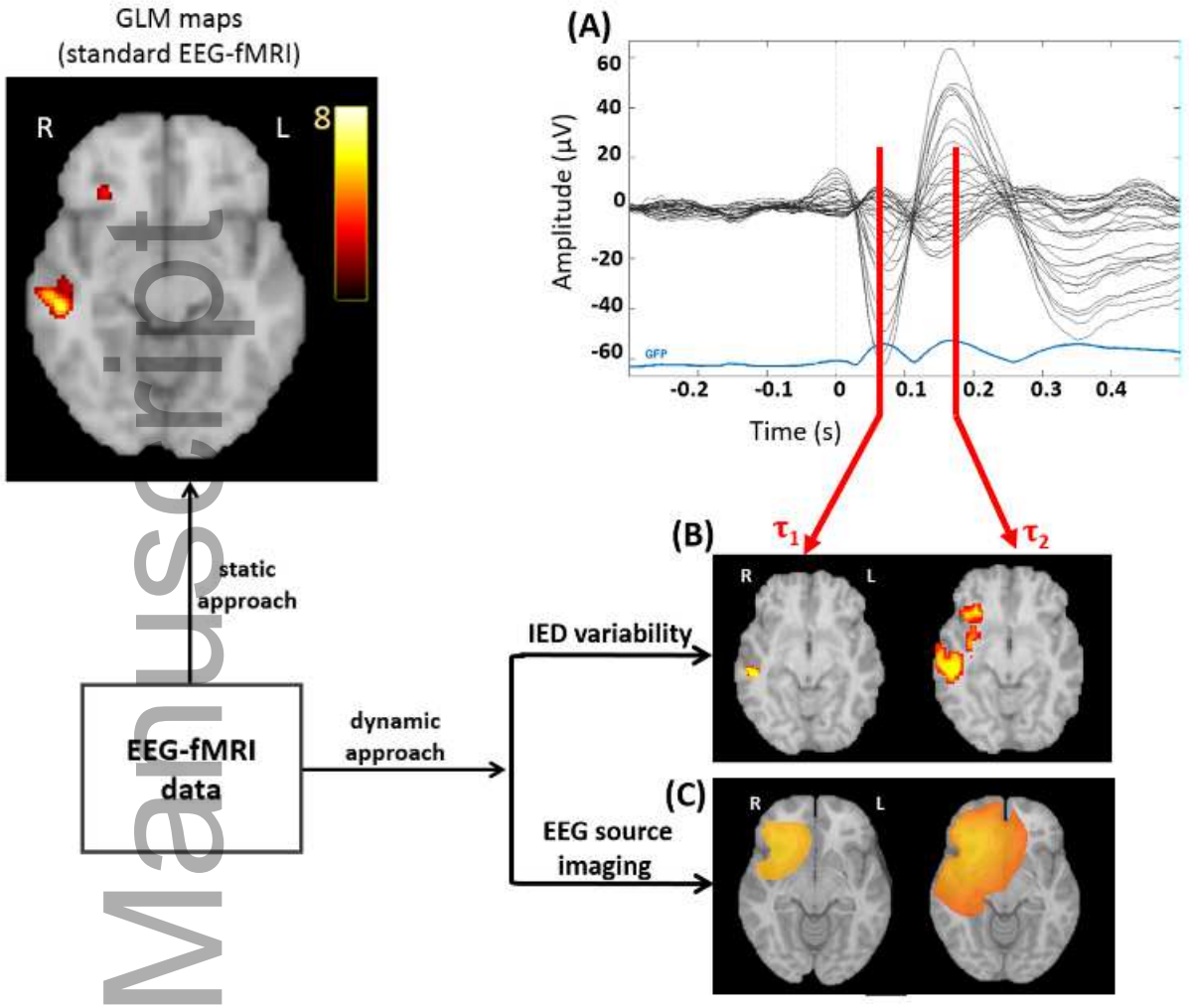

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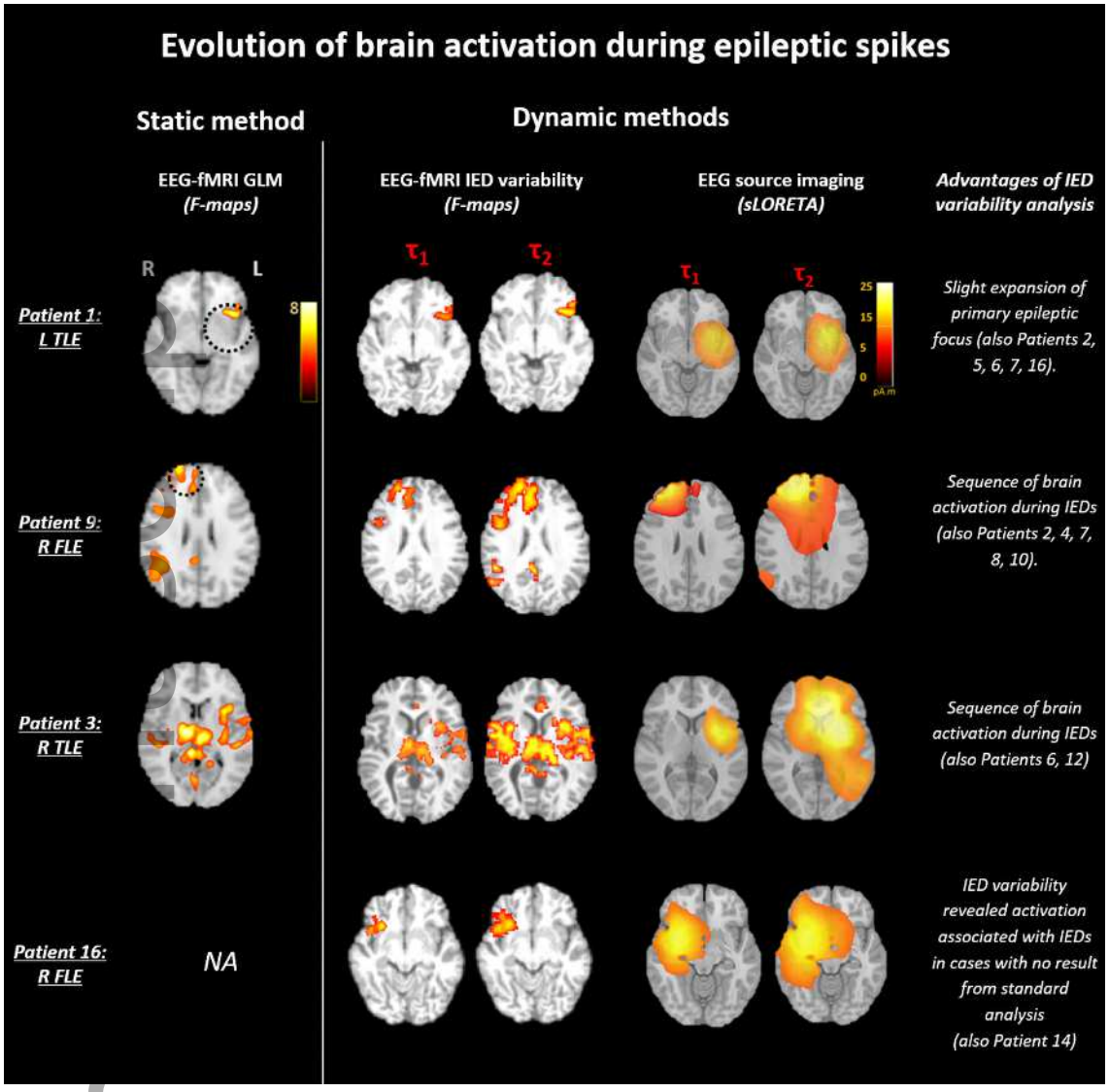

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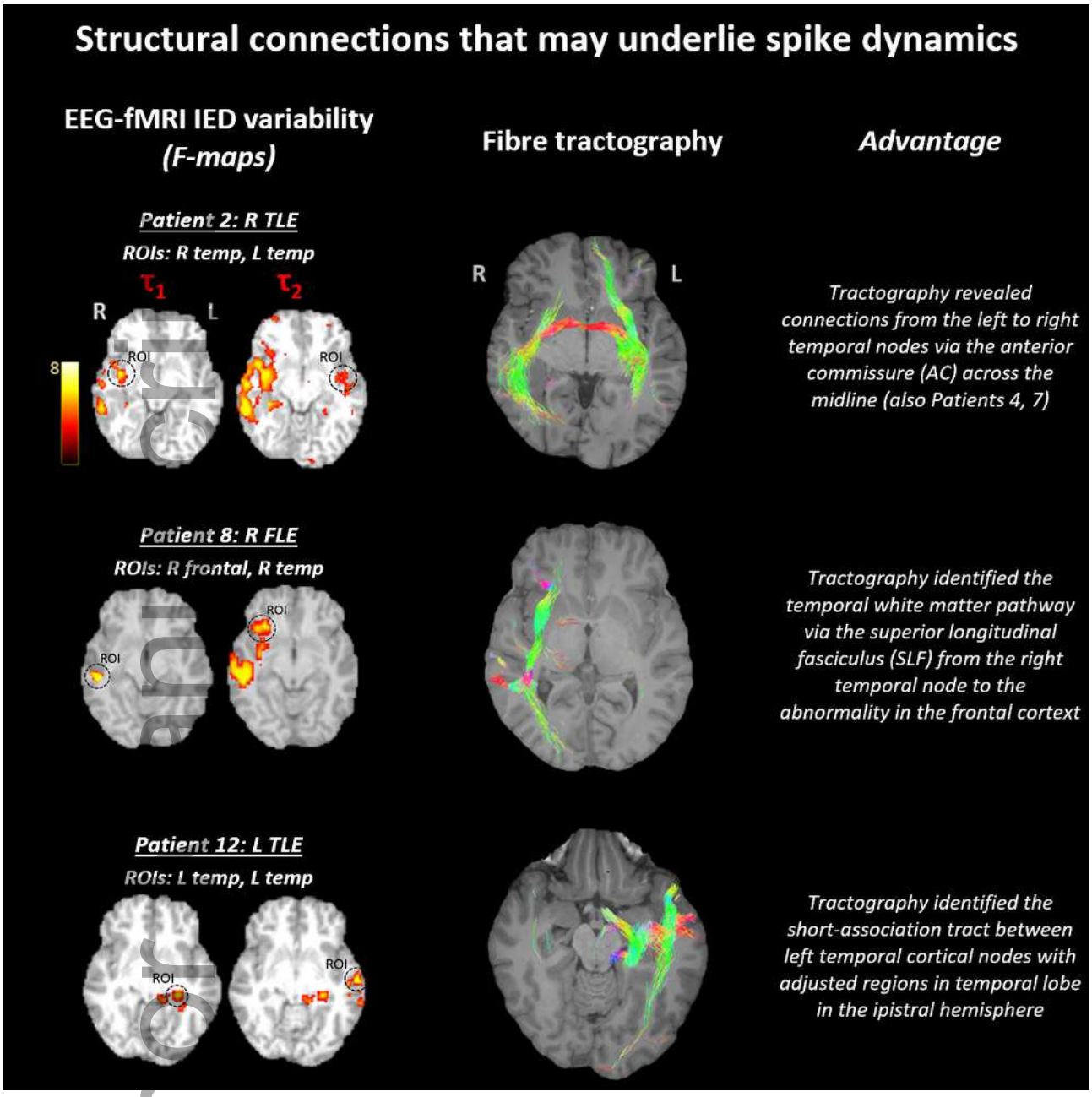

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