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# Identifying the structures involved in seizure generation using sequential analysis of ictal-fMRI data

Antonio Donaire [a,*], Nuria Bargallo [a,b], Carlos Falcón [b], Iratxe Maestro [a], Mar Carreno [a,b], Javier Setoain [a,b], Jordi Rumià [a], Santiago Fernández [a], Luis Pintor [a,b], Teresa Boget [a,b]

[a] Hospital Clínic, Barcelona, Spain
[b] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

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ABSTRACT

The aim of this study was to investigate if sequential analysis of BOLD signal changes induced by seizures is useful for preoperative identification of the site of seizure onset in patients with pharmaco-resistant focal epilepsy.

*Method:* We analyzed BOLD raw data from 5 patients with focal medically refractory epilepsy who experienced partial seizures during fMRI as part of a preoperative evaluation. To sequence the changes in BOLD signal seizure-induced, each seizure epoch was divided into groups of five consecutive images (ten-second blocks). *t*-maps were calculated continuously from 120 s before the onset of clinical/EEG seizure onwards by comparing two consecutive groups of five images. Time lag between each comparison was 2 s. Relative changes in BOLD signal between two consecutive groups of five images along the seizure epoch were determined. Results were compared with those of subtraction ictal SPECT coregistered with MRI (SISCOM) and intracranial EEG (2 patients).

*Results:* A typical seizure was registered in each patient. After sequential analysis, a well-localized and statistically significant (*t*: 7–14) area of signal increase was consistently found at seizure initiation in each patient. This area invariably preceded the onset of clinical/electrical seizure by several seconds (6–52 s); was concordant with SISCOM results in all but one patient; and overlapped with the ictal onset zone determined by intracranial EEG in those 2 patients who underwent invasive-EEG recordings. Complete resection of this initial area of signal increase resulted in seizure remission. Three out of four patients who underwent epilepsy surgery remained seizure-free.

*Conclusion:* Sequential analysis of ictal-fMRI data may be useful to precisely and non-invasively delineate the ictal onset zone within the brain; and provide insights into the cerebral substrates involved in the generation and propagation of seizures.



## Introduction

The ultimate goal in epilepsy surgery is to determine the minimum amount of cortex to be resected (inactivated or completely disconnected) to produce seizure freedom (Luders et al., 2008). Seizure semiology, a potentially epileptogenic brain lesion, genetic background and particularly the cortical area involved in seizure generation ("seizure-onset zone" (SOZ)) must be considered to infer the location and extension of the epileptogenic zone (Carreño and Luders, 2008). The "gold standard" for SOZ localization in neocortical epilepsy has been surgical implantation of subdural electrodes (Carreño and Luders, 2008; Rosenow and Luders, 2001). A major limitation of these invasive electroencephalography (EEG) recordings is restricted spatial sampling, which can barely cover a limited portion of the brain. This makes good estimation of the location of the "epileptic focus" before electrode implantation very important, particularly in pharmaco-resistant epileptic patients without lesions on MRI (Koubeissi, 2008). Another methodology widely accepted to define/determine SOZ location is subtraction ictal single-photon emission computed tomography (SISCOM), which can non-invasively evaluate the relative increase in seizure-induced blood flow during the peri-ictal period (Van Paesschen et al., 2007; Van Paesschen, 2004). It is unclear if the areas of increased perfusion depicted by SISCOM represent the seizure-onset zone (SOZ), ictal propagation, or both (Ahnlide et al., 2007; Dupont et al., 2006). Accurate localization of the SOZ in neocortical epilepsy is therefore often quite challenging, yet critically important for successful surgical therapy. There is increasing interest in developing new non-invasive techniques to localize more precisely the SOZ that will translate into improved outcomes after surgery for neocortical epilepsy. Functional MRI (fMRI) with simultaneous-EEG

* Corresponding author. Epilepsy Unit, Hospital Clínic i Provincial, C/Villarroel 170, CP: 08036, Barcelona, Spain. Fax: +34 93 2275783.
*E-mail address:* donaire@clinic.ub.es (A. Donaire).

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recording has been used to evaluate metabolic and hemodynamic changes related to interictal epileptiform activity (Aghakhani et al., 2004; Archer et al., 2003; Bagshaw et al., 2004; Gotman, 2008; Jackson, 2008; Jacobs et al., 2007; Jann et al., 2008; Moeller et al., 2008; Salek-Haddadi et al., 2006), prolonged bursts of interictal epileptiform discharges (Aghakhani et al., 2004; Bagshaw et al., 2005; Detre et al., 1995; Hamandi et al., 2008) and even focal epileptic seizures (Archer et al., 2006; Detre et al., 1995; Di et al., 2006; Federico et al., 2005; Jackson et al., 1994; Kobayashi et al., 2006a,b; Krings et al., 2000; Kubota et al., 2000; Liu et al., 2008; Morocz et al., 2003; Tyvaert et al., 2008). It could be a good tool for detecting functional changes occurring at seizure initiation within the epileptogenic zone because it can detect subtle changes in cerebral activity with very high spatial and temporal resolution. Epilepsy is an abnormal brain state, but available evidence suggests preserved neurovascular coupling between neuronal activity and the metabolic and hemodynamic processes underlying changes in blood oxygen level-dependent (BOLD) signal in response to epileptic activity (Carmichael et al., 2008; Hamandi et al., 2008; Stefanovic et al., 2005). This assumption is fundamental to the application of BOLD-fMRI to the study of the complex hemodynamic changes that occur during epileptic seizures. Ictal-fMRI studies have shown widespread changes in BOLD signal related to seizures reflecting the SOZ and ictal propagation precluding precise delineation of the cortical area from which epileptic seizures are arising. In these studies, epileptic seizures were usually modeled as single events, which prevented elucidation of the temporal and spatial sequence of these signal changes that were seizure-related. Our hypothesis was that sequential analysis of seizure-induced changes in BOLD signals may enable investigation of the successive hemodynamic and metabolic changes associated with focal seizures with high spatial and temporal resolution. This could be applied to locate precisely and non-invasively the exact location of the SOZ.

We analyzed five independent focal seizures from five patients with pharmaco-resistant focal epilepsy who experienced epileptic seizures during ictal-fMRI as part of their preoperative evaluation. We segmented each seizure into ten-second blocks. Each block represented a unique experimental condition that was contrasted continuously with the contiguous ten-second blocks from the onset of seizure onwards to gain access to temporal development of the BOLD signal changes induced by epileptic seizures. The initial seizure-related activations should correspond to the initial changes in neuronal activity within the SOZ. We compared these initial regions of seizure-related activation with the results from invasive subdural evaluation and SISCOM to evaluate the utility of sequential analysis of ictal-fMRI data in the anatomic location of the SOZ.

## Methods and patients

This study is part of a larger prospective research program aimed to image the cerebral structures involved in epileptic activity generation using functional MRI. The study design involved patients who experienced simple partial or complex partial seizures during fMRI. From 2004 to 2007, 36 from 356 patients admitted for presurgical evaluation underwent ictal or interictal-fMRI, 25 with simultaneous recording of EEG. All patients underwent comprehensive preoperative evaluation, including clinical history, neurologic examination, long-term monitoring of video–EEG, neuropsychologic assessment, high-resolution structural MRI, SISCOM, and invasive-EEG evaluation with subdural electrodes (if needed). Patients had to have frequent partial seizures (at least one seizure every to 2–3 h) with or without loss of consciousness to be considered for ictal-fMRI. Patients with secondary generalized tonic–clonic seizures, or hypermotor seizures or complex motor automatisms, were excluded. Patients had to have at least one clinical seizure similar to their typical seizures, with or without simultaneous-EEG coregistration, during fMRI to be included in the study. Patients also had to have (i) an ictal single-photon emission computed tomography (SPECT) with a radioisotope injection time of <40 s from the beginning of the seizure; or (ii) undergone invasive-EEG evaluation with subdural grids to compare the results obtained from ictal-fMRI with those from well-established diagnostic techniques for SOZ localization.

Written informed consent was obtained from all patients. The study protocol was approved by the ethics committee of our hospital.

### *Acquisition of fMRI data*

fMRI was done on a Signa 1.5-Tesla General Electric Magnetic Resonance Scanner (GE Medical Systems, Milwaukee, WI, USA). A structural high-resolution axial three-dimensional T1-weighted image was acquired using a fast spoiled gradient-recalled acquisition (FSPGR) sequence (thickness, 1.5 mm).

Functional images were acquired as a series of single-shot gradient-echo planar imaging (EPI) volumes providing T2-weighted BOLD contrast (repetition time/echo time (TR/TE), 2000/34 ms; field of view (FOV), 24×24 cm, 64×64 pixel matrix; flip angle, 90°; slice thickness, 5 mm; gap, 1.5 mm; 20 axial slices per scan). Continuous whole-brain EPI-BOLD volumes were acquired over runs of 11 min 20 s, corresponding to 340 scans, until at least one seizure was registered. A maximum of four runs were scheduled per patient. Antiepileptic medication was reduced (one antiepileptic drug was reduced or suppressed) 24 h before scanning to prompt seizures inside the scanner.

The EEG signal was continuously acquired inside the MRI scanner using 27 MRI-compatible electrodes. Data were transmitted from a BrainAmp amplifier (sampling rate, 5 kHz; Brain Products, Munich, Germany) via an optic-fiber cable to the EEG monitor located outside the scanner room.

EEGs recorded during MRI were post-processed using Vision Analyzer software (Brain Products). ECG/EOG electrodes were also used. Ballistocardiogram and scanner artifacts were removed, and EEGs reviewed by three experienced epileptologists (M.C., I.M., A.D.); the onset and end of seizures were manually marked. Patients were monitored (I.M., A.D.) during imaging to ensure that the seizures recorded corresponded to their typical seizures.

Patients with epileptic auras (simple partial seizures) were asked to indicate the onset and the end of ictal events by pressing a response button. Times of seizure onset and seizure end were automatically registered, and could be correlated with functional images. Seizure onset and seizure end were determined by simultaneous-EEG recordings if consciousness was impaired.

### *fMRI analysis*

fMRI was processed and analyzed using SPM2 (Wellcome Department of Cognitive Neurology, University College London, London, UK) running on MATLAB (Mathworks Incorporated, Natick, MA, USA). Preprocessing involved realignment of fMRI series for motion correction, normalization to the Montreal Neurological Institute (MNI) template

**Fig. 1.** Schematic representation of the method to analyze successive changes in BOLD signal seizure-related. The seizure epoch is divided in blocks of five scans (segmentation process). Comparisons (*t*-maps) were continuously obtained by contrasting two consecutive blocks of five scans (arrows). The entire procedure was repeated as many times as the number of the scans contained in each block (segmentation #01–05) but starting one scan further with respect to the previous segmentation process. Each *t*-map was labeled with the number (*n*) of the first scan contained in that comparison. To facilitate visualization of the final sequence of seizure-related changes in BOLD signal obtained after continuously comparing two consecutive blocks of five scans every 2 s, *t*-maps (overlaid on axial T1-weighted MRIs) corresponding to each segmentation process were framed with different colors (green, red, blue, yellow, magenta).