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EEG–fMRI in focal epilepsy: Local activation and regional networks

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HIGHLIGHTS

- EEG/fMRI is an important new tool for studying patients with focal epilepsy and the electrographic field of the interictal epileptiform discharges (IEDs) is reflected in the fMRI results with focal and diffuse IEDs providing novel and important localization information.
- Amongst patients with a heterogeneous array of focal epilepsies, the piriform cortex is a common node in the underlying networks associated with focal IEDs.
- In cases of diffuse IEDs we noted involvement of subcortical structures, in particular the thalamus and cerebellum.

ABSTRACT

Objective: To identify features of BOLD signal change associated with interictal epileptiform discharges (IEDs) in a heterogeneous group of focal epilepsy patients.
Methods: EEG/fMRI studies in 27 focal epilepsy patients were reviewed with attention given to the extent and location of the IED and the resulting pattern of BOLD signal change. Second order group analysis was used to identify common features.
Results: fMRI results provided novel clinical information for individual patients. We identified a significant common node within the ipsilateral piriform cortex as well as patterns involving distant cortical or subcortical areas.
Conclusion: Despite the heterogeneity of IEDs in focal epilepsy, there are important common features underpining IEDs with a highly significant fMRI node in the ipsilateral piriform cortex.
Significance: There are important common features in the networks involved in IEDs in patients with a heterogeneous range of epileptogenic foci. We confirm that the piriform cortex is a common node underlying IEDs in patients with focal epilepsy and so provides a target for further study and potential therapy. We describe important features of BOLD signal change that accompany focal and diffuse IEDs that will help researchers and clinicians navigate the sometimes complex findings revealed by these studies.

1. Introduction

EEG combined with fMRI (EEG–fMRI) is increasingly available to investigate interictal epileptiform discharges (IEDs) in patients with presumed focal epilepsy (Lazeyras et al., 2000; Diehl et al., 2003; Bagshaw et al., 2004; Aghakhani et al., 2006; Salek-Haddadi et al., 2006; Bonaventura et al., 2006; Zijlmans et al., 2007; De Tiege et al., 2007; Lui et al., 2008; Manganotti et al., 2008; Tyvaert et al., 2008; Jacobs et al., 2008; Moeller et al., 2009; LeVan et al., 2010; Rathakrishnan et al., 2010; Thornton et al., 2010; Borelli et al., 2010; Pesaresi et al., 2011; Grouiller et al., 2011; Laufs et al., 2011; van Houdt et al. 2013) One reason this difficult to obtain data is important is the hope that results from these studies will provide an insight into the substrates underlying focal epilepsy thereby improving patient management (Zijlmans et al., 2007; Moeller et al., 2009; Thornton et al., 2010; Van Houdt et al., 2013).

The focal epilepsies are a group of conditions that account for 60% of all epilepsies (Banerjee et al., 2009), and some of these patients can be rendered seizure free by resection of the epileptic focus. For this reason the aim of the extensive and detailed investigations that are routinely carried out on patients with focal

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epilepsy (e.g. EEG, MRI, SPECT and PET) is to provide information that may help identify the epileptogenic zone. This zone is defined as "the minimum amount of cortex that must be resected (or completely disconnected) surgically to produce seizure freedom" (Luders et al., 2006) and so accurate identification of the anatomical limits of this zone is the dominant issue in the presurgical work-up of patients with focal epilepsy, but this has proven to be an elusive goal and there is no single 'gold standard' test to define this area.

EEG–fMRI is a powerful new tool in this quest and is typically used to study IEDs. IEDs are ideally suited for fMRI studies because they are the most common marker of epilepsy and are abundant, easily recognized EEG events that elicit identifiable and reproducible BOLD signal changes (Benar et al., 2002; Gholipour et al., 2011; Pesaresi et al., 2011). Furthermore, they are typically sub-clinical, that is to say that the subject will not move because of one of these events and therefore the fMRI data will not be confounded by event related motion.

While IEDs are ideally suited to EEG–fMRI studies, they may not delineate the epileptogenic zone (Marsh et al., 2010). IEDs arise from a region defined as the irritative zone (Luders et al., 2006) that may (or may not) overlap with the epileptogenic zone. IEDs may be more extensive, sometimes spreading into other cerebral lobes, and even into the contralateral hemisphere (Alarcon et al., 1997; Labate et al., 2004; Marsh et al., 2010; Vulliemoz et al., 2010). Furthermore a variety of IEDs may arise from adjacent normal cortex in the 'irritative zone'. Understanding the reasons for the variety of IEDs and the pathways by which they spread across lobes and hemispheres will have consequences for our understanding of basic epileptic processes as well as direct implications when trying to use EEG–fMRI as a clinical tool.

In the current study we review our experience acquired from all patients with focal epilepsy studied at high field (3T) in our centre over a seven year period paying particular attention to electrographic field of the IEDs and the common structures and therefore potential networks involved in the generation, spread and regulation of these events. We reviewed individual results and assessed their utility in the management of individual cases, hypothesising that the fMRI result would largely reflect the EEG discharge but provide better spatial information. We also conducted group analysis to examine the hypothesis that focal IEDs have a common underlying substrate.

2. Materials and methods

2.1. Patients

In our centre, a total of 218 patients with a presumptive diagnosis of epilepsy (any type, including focal) were studied with EEG–fMRI at 3T between the years 2003–2010. From that data set we reviewed the data for all the patients with an electro-clinical diagnosis of focal epilepsy studied during that time (79 patients). The patients were mostly referred from the Comprehensive Epilepsy Programs at the Austin Hospital as well as some from the Royal Melbourne Children's Hospital. These are tertiary referral venues for characterization of epilepsy syndromes and assessment of suitability of patients with refractory focal epilepsy for surgery. Diagnosis was based on ILAE criteria for focal epilepsy and was confirmed by reviewing the clinical, imaging and EEG data in detail for those patients.

The basis of the current report is the findings in 33 patients with a confirmed diagnosis of focal epilepsy (16 females; mean age: 28 years, range 10–49 years) who had a successful EEG–fMRI study (the remaining 46 patients did not have IEDs during the monitoring period). A successful EEG–fMRI study was one defined as having typical IEDs during the fMRI scan together with good quality MRI and EEG. Patients with an electro-clinical diagnosis of focal epilepsy who did not have any epileptiform discharges recorded inside the scanner or with unsatisfactory technical quality of the EEG recording are not included. Clinical details are summarized in Table 1.

Clinical features were based on review of patient's clinical notes.

The study was approved by the ethics committee of our institution and all subjects gave informed consent, including parental consent from subjects under the age of 18 years.

2.2. EEG recording

Eighteen non metallic scalp electrodes with carbon fibre leads were attached to the scalp in the conventional '10–20' locations (with the exception of Fz). ECG was recorded from 1 or 2 electrodes placed on the chest. EEG data were acquired using a custom built amplifier with fibre optic transfer of data to a computer in the MR control room to allow on line monitoring of the EEG signal. MR gradient artifacts in the EEG signal was minimized by hardware design, and residual artifact removed off line, and in more recent studies, ballistocardiogram and movement artifacts were also reduced using head movement detection coils (Masterton et al., 2007). Real-time display, filtering and recording were performed using software developed in-house running on a Windows XP computer. The entire recording was conducted without activation procedures, and the patient was encouraged to sleep. EEG was recorded briefly outside the scanner to ensure good technical quality and identification of interictal discharges (IEDs) prior to continuous 3T EEG–fMRI acquisition for up to one hour.

2.3. MRI acquisitions

fMRI data were obtained using a 3-T GE Signa LX whole body scanner (General Electric, Milwaukee, Wisconsin) with continuous acquisition of gradient-recalled echo planar image volumes (TR = 3200 ms, TE = 40 ms, flip angle = 80° with axial oblique slices 3.2 mm thick + 0.2 mm gap, 22 cm FOV; 64 × 64 matrix). The first 4 image acquisitions were discarded to ensure steady state tissue magnetization. fMRI data were acquired for 20–60 min (average 53 min).

2.4. Data analysis

2.4.1. EEG

The whole EEG record was reviewed offline by an experienced electroencephalograher for identification of ictal and interictal epileptiform discharges (IEDs). IEDs were defined as events with the same field, duration and EEG waveform morphology as confirmed IEDs seen on routine EEG. Ambiguous EEG events which could not be confidently classified as epileptiform were identified and included in the subsequent analysis as 'events of no interest', but not considered further in the present study.

It is important to note that while patients with a diagnosis of focal epilepsy often have focal IEDs, many will also have a variety of more diffuse IED types. We have classified IEDs based on their spatial distribution. Because of the relative limited EEG cover (10–20 electrode positions with the exception of Fz) we have limited the specificity of our EEG localization (i.e. we do not claim any localization beyond the lobar level).

2.4.2. EEG classification

Focal discharges were defined as IEDs with a field that was consistent with an origin limited to a single lobe (i.e. they may be frontal, temporal, parietal or occipital). In this regard we also accepted