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Continuous EEG source imaging enhances analysis of EEG-fMRI in focal epilepsy ☆

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ABSTRACT

Introduction: EEG-correlated fMRI (EEG-fMRI) studies can reveal haemodynamic changes associated with Interictal Epileptic Discharges (IED). Methodological improvements are needed to increase sensitivity and specificity for localising the epileptogenic zone. We investigated whether the estimated EEG source activity improved models of the BOLD changes in EEG-fMRI data, compared to conventional « event-related » designs based solely on the visual identification of IED.

Methods: Ten patients with pharmaco-resistant focal epilepsy underwent EEG-fMRI. EEG Source Imaging (ESI) was performed on intra-fMRI averaged IED to identify the irritative zone. The continuous activity of this estimated IED source (cESI) over the entire recording was used for fMRI analysis (cESI model). The maps of BOLD signal changes explained by cESI were compared to results of the conventional IED-related model.

Results: ESI was concordant with non-invasive data in 13/15 different types of IED. The cESI model explained significant additional BOLD variance in regions concordant with video-EEG, structural MRI or, when available, intracranial EEG in 10/15 IED. The cESI model allowed better detection of the BOLD cluster, concordant with intracranial EEG in 4/7 IED, compared to the IED model. In 4 IED types, cESI-related BOLD signal changes were diffuse with a pattern suggestive of contamination of the source signal by artefacts, notably incompletely corrected motion and pulse artefact. In one IED type, there was no significant BOLD change with either model.

Conclusion: Continuous EEG source imaging can improve the modelling of BOLD changes related to interictal epileptic activity and this may enhance the localisation of the irritative zone.

Introduction

Around 30% of patients with epilepsy suffer from recurring seizures despite treatment with multiple anti-epileptic drugs (Sillanpaa, 2000). Some of these patients can benefit from epilepsy surgery if the epileptogenic focus can be precisely localised. EEG-correlated fMRI (EEG-fMRI) is a non-invasive imaging technique that may indicate regions of increased or decreased cerebral oxygenation (Blood Oxygen Level Dependant, BOLD, signal) correlated with Interictal Epileptiform Discharges (IED) (Al-Asmi et al., 2003; Salek-Haddadi et al., 2006). At present, EEG-fMRI has limited sensitivity, with 40–70% of EEG-fMRI datasets containing focal IED showing significant BOLD changes. The regions of significant BOLD change have been shown to be generally concordant with the findings of conventional electro-clinical and imaging data, and in particular with intracranial electrodes recording of IED (Benar et al., 2006).

Most interictal EEG-fMRI studies are based on event-related fMRI designs with identification of IED by expert observers and the representation of the IED as idealised (and usually uniform) 'stick functions', convolved with a model of the haemodynamic response function (Al-Asmi et al., 2003). For prolonged runs of IED, a block design that takes into account the duration of the discharges has been shown to increase sensitivity of EEG-fMRI analysis (Bagshaw et al., 2005; Salek-Haddadi et al., 2006). These models, however, do not account for variations of the BOLD response to individual IED, although amplitude and morphology of IED on scalp EEG have been reported to be different in patients with and without BOLD response to IED (Krakow et al., 1999). Moreover, modelling only IED detected on scalp EEG would often not reflect the abundant underlying epileptic activity that can be recorded by intracranial EEG (Tao et al., 2005).

In the present study, we used continuous Electrical Source Imaging (cESI) to obtain a continuous estimate of the activity of the IED source.

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We then used this activity function as a parametric model of the BOLD signal changes to address the following questions:

(1) Does the proposed parametric modelling of epileptic activity explain additional variance of the BOLD compared to a modelling of IED as discrete events?
(2) Is there spatial concordance between the ESI-correlated BOLD signal changes, the source of IED onset defined by ESI and other non-invasive or invasive imaging modalities? In other words, does cESI reflect ongoing epileptic activity?

Methods

Patients and electro-clinical data

Patients with refractory focal epilepsy undergoing pre-surgical assessment were selected from the pool of EEG-fMRI data acquired on a 3 T MR scanner between January 2004 and October 2008 according to the following criteria: (1) intra-MRI EEG recording with 32 electrodes or more; (2) presence of spikes, spike-waves or sharp waves on the intra-MRI EEG. Epileptic transients in the form of short runs of low amplitude high frequency poly-spikes were not considered as they have poor signal-to-noise ratio for ESI.

In the 10 patients who fulfilled the criteria (one EEG-fMRI recording each), we identified 15 separate IED types that were used for analysis, resulting in 15 IED-type specific analysis. Clinical, electrophysiological and imaging data of the patients are given in Table 1. All patients had cryptogenic focal epilepsy except for patient 4 who had focal cortical dysplasia in the left occipital cortex, patient 7 who had left hippocampal sclerosis and patient 10 who had a left frontal sub-cortical lesion (detectable as increased signal on FLAIR images). The study was approved by the Research Ethics Committee of the UCL Institute of Neurology and UCL Hospitals. Written informed consent was obtained from all patients.

EEG-fMRI set-up and acquisition

EEG in resting state with closed eyes outside (15 min prior to scanning) and inside the scanner was acquired using MR-compatible EEG system (Brain Products, Munich, Germany). A 32- or 64-electrode EEG cap was used according to the 10–20 or 10–10 electrode position convention. All patients underwent EEG-fMRI on a 3 T Signa Excite HDX scanner (GE Medical Systems, Milwaukee) and were asked to lie still in the scanner with their eyes closed and no specific instruction regarding vigilance. EEG was recorded continuously during fMRI. ECG was recorded with a single lead. Each patient underwent two or three 20-min blocks of EEG-fMRI acquisition. Each fMRI dataset consisted of 404 T2*-weighted single-shot gradient-echo echo-planar images (EPI; TE/TR 30/3000 ms, flip angle 90, FOV 24×24 cm^2, 43 or 44 interleaved slices with in-plane resolution 3×3 mm^2 and 3 mm thickness). For the purpose of anatomical localisation and EEG source localisation a T1 FSPGR image (TE/TR/TI = 3.1/8.2/450 ms; $256\times256\times170$ matrix, resolution: $1.1\times1.1\times1.1$ mm^3) including nasion and inion (resampled offline to $1\times1\times1$ mm^3 voxels for comparison with isotropic images created with the head model for ESI).

EEG analysis and electrical source imaging (ESI)

The EEG was corrected offline for gradient artefact and pulse-related artefacts using average artefact subtraction methods described elsewhere (Allen et al., 2000, 1998). IED were identified and marked by two experienced electro-encephalographers (SV, RT) (Salek-Haddadi et al., 2006).

The IED used for fMRI modelling were analysed using an ESI methodology implemented in *Cartool* (http://brainmapping.unige.ch/Cartool.htm). After filtering (high-pass: 0.3 Hz, low-pass: 35 Hz), IED were averaged and channels containing artefacts were interpolated. We used a Spherical head Model with Anatomical Constraints (SMAC) based on a 3-shell spherical realistic head model and the patient's individual MRI (Spinelli et al., 2000). The source space was limited to the grey matter, segmented using the Statistical Parametric Mapping software SPM5 (www.fil.ion.ucl.ac.uk/spm). A standard localisation of the electrodes according to the 10–20 system was assumed to obtain electrode coordinates. Estimation of the generator location was carried out using a linear distributed inverse solution (LAURA) (Grave de Peralta Menendez et al., 2001). This source imaging algorithm incorporates the physical law that the strength of a source regresses regularly with distance by a local autoregressive average with coefficients depending on the distance between solution points (Michel et al., 2004). The parameters used for the LAURA calculation were fixed to a neighbourhood size of 26 solution points and a regression with the inverse of the cubic distance (for vector fields). The

Table 1
Clinical, electrophysiological and imaging data. R/L/Bil: right/left/bilateral; T: temporal; F: frontal; Par: parietal; Occ: occipital; post: posterior; SPS/CPS: Simple/Complex Partial Seizure, SGS: Secondarily Generalised tonic–clonic Seizure, FCD: Focal Cortical Dysplasia, HS: Hippocampal Sclerosis. # not considered for further analysis as good quality ESI was not possible, see text.

IED type	Gender, age	Seizure semiology	MRI	IED focus (scalp EEG)	Number of IED during fMRI (Number of 20-min fMRI sessions)	Intracranial EEG
1	M, 31 years	Bizarre vague sensation, CPS with dystonic posture L hand	N	R T	189 (2)	R T lat post
2	M, 30 years	Aphasic SPS No aura, CPS	N	L T	161 (2)	na
3	F, 48 years	No aura, CPS with oral and manual automatisms	N	L T	197 (2)	na
4a	M, 21 years	CPS, oral automatisms, R clonic jerks, SGS	FCD L medial occipital	L T	312 (2)	L Occ medial
4b				R T	56 (2)	
5	M, 27 years	Cloni R face/arm→SGS	N	R F	2239 (2)	R F medial ant
6a	M, 19 years	Epilepsia partialis continua L leg→rare SGS	N	Central midline	206 (3)	R medial
6b				R F-central	121 (3)	F-Par
6c				R F	10 (3)	
7	M	Olfactory-gustatory aura, CPS	L HS	L T	33 (2)	na
8a	M, 22 years	No aura, CPS with L head version	N	Bil F	269 (3)	na
(8b)				Bil F polyspikes#	101 (3)	
9a	M, 25 years	Epigastric, auditory, gustatory or heautoscopic aura, tonic posture R hand	N	L F-T	38 (3)	na
9b				L F polar	35 (3)	
9c				L Par	23 (3)	
10a	F, 37 years	No aura, CPS	L F white matter lesion	L F and Bil F L>R	72 (2)	na
(10b)				R F#	11 (2)	