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# Simultaneous EEG-Correlated Ictal fMRI

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**The ability to continuously acquire simultaneous EEG and fMRI data during seizures presents a formidable challenge both clinically and technically. Published ictal fMRI reports have so far been unable to benefit from simultaneous electrographic recordings and remain largely assumptive. Unique findings from a Continuous EEG-correlated fMRI experiment are presented in which a focal subclinical seizure was captured in its entirety. For the first time dynamic and biphasic Blood Oxygen Level Dependent (BOLD) signal changes are shown using statistical parametric mapping time-locked to the ictal EEG activity localizing seizure generation and propagation sites, with millimeter resolution, to electroclinically concordant gray matter structures. Though presently of limited clinical applicability, a new avenue is opened for further research.** 

## INTRODUCTION

Intravoxel fluctuations in deoxyhaemoglobin influence the focal short-term changes in magnetic susceptibility to which blood oxygen level-dependent (BOLD) fMRI is sensitive and these fluctuations appear to result from a complex interplay between blood flow, blood volume, and oxygen metabolism as orchestrated by the neurovascular coupling (Buxton *et al.,* 1998). There is a growing literature on EEG-correlated fMRI (Schomer *et al.,* 2000) employing an interleaved method of data acquisition due to various technical limitations. EEG-triggered fMRI hence allows for the BOLD response to EEG events to be intermittently sampled at a number of discrete time points in order to detect areas of relative activation (Krakow *et al.,* 2000). In patients with partial epilepsy, spike-triggered fMRI has yielded promising results broadly consistent with electroclinical data (Krakow *et al.,* 1998; Warach *et al.,* 1996; Lazeyras *et al.,* 2000), but more recently we have been able to apply a technique to acquire good quality EEG/fMRI data continuously and simultaneously (Allen *et al.,* 2000) to reveal the temporal characteristics of hemodynamic response to interictal events (Lemieux *et al.,* 2001) and the potential exists to investigate the extent and further characteristics of such changes in relation to different pathologies. Within this context, fMRI activations are felt to anatomically reflect areas involved in spike generation and propagation, the "irritative zone" (Luders *et al.,* 1993), the anatomical definition of which is an important part of the multidisciplinary presurgical evaluation of patients with medically refractory partial epilepsy.

By contrast ictal fMRI activation would be expected to reflect changes within the epileptogenic region itself (and propagation sites) but there have been no EEG-correlated ictal fMRI studies and otherwise few anecdotal reports of ictal fMRI, all in patients with an abnormal structural MRI and none employing statistical hypothesis testing. An outline of this literature is provided in Table 1 and reviewed below.

Jackson *et al.* (1994) used a FLASH sequence to obtain susceptibility-weighted images from a 4-year-old child experiencing partial motor seizures. Images were obtained every 8 s from a single slice only. No motion correction was applied and analysis was by way of visual inspection only. Signal increases of up to 40% were depicted occurring over 4–5 min in positive areas, though not exclusively in association with clinically observable seizure activity. Changes unaccompanied by observable seizure activity were attributed to subclinical seizure activity and other similar changes (delayed by 1.5 min) within the sagittal sinus and surrounding veins were attributed to venous drainage. Positive areas identified on subtraction images appeared concordant with other investigations and it was concluded that "functional MRI enables the time course, spatial distribution and spread of ictal activation to be observed during the seizure."

Detre *et al.* (1995, 1996) described a patient with a history of partial motor seizures but with neither clinical nor electrographic evidence of seizure activity during fMRI. They nonetheless identified an area of signal change, concordant with ictal SPECT and intracranial EEG localizations of an epileptogenic focus, exhibiting



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**TABLE 1**

Summary of Published Ictal fMRI Time Series

| Reference | Clinical data | Seizure detection | Functional MRI | Simultaneous EEG | Motion correction | Statistical analysis |
|---|---|---|---|---|---|---|
| Jackson *et al.* (1994) | 4-year-old male; right-sided partial motor seizures of body and face<br>**Diagnosis:** Rasmussen's encephalitis<br>**MRI**<br>Thickened cortex with abnormal signal in left hemisphere gray matter<br>**Routine EEG**<br>Interical: Widespread slow and occasional L parietal spikes<br>Ictal: Irregular slow waves over anterior front of emporal regions Preceding twitching by 8–20 s<br>**Sedation:** IV Diazepam | Facial movement | **Scanner**<br>1.5T Siemens SP4000<br>**Sequence**<br>Multi hot FLASH (TE/TR 60/85 ms, Matrix 64×128, FOV 230 mm, flip angle 40°)<br>**Coverage:** Single 8 mm slice<br>**Time resolution:** 8 s | None | None | None<br>Visual inspection of subtraction images and time courses extracted from subsequently selected areas<br>Concordant activations with up to 40% signal increases reported |
| Detre *et al.* (1995, 1996) | 25yr old male: right-sided partial motor seizures of face<br>**Diagnosis:** Chronic gliosis<br>**MRI**<br>Widespread left hemisphere atrophy<br>**Routine EEG**<br>Interictal: Increased theta during wakefulness<br>Ictal: No definite ictal findings<br>**Sedation:** Phenytoin and Phenobarbitone with significant sedation | None | **Scanner**<br>1.5T GE signa<br>**Sequence**<br>Single shot GE-EPI (TE/TR 50/4000 ms, 64×64 matrix, FOV 240 mm, 16×5 mm slices no gap).<br>**Coverage:** Whole brain<br>**Time resolution:** 4 s | None | Yes | None<br>Visual inspection of thresholded percentage change images and time courses extracted from selected cluster<br>Concordant areas with 3–4% signal increases reported |
| Krings *et al.* (2000) | 62-years-old female; left-sided Jacksonian marches involving leg<br>**Diagnosis:** Glioblastoma multiforme<br>**MRI**<br>Right central space occupying lesion<br>**Routine EEG**<br>Ictal and interictal EEG normal<br>**Sedation:** Primidone 625 mg daily | Leg movement | **Scanner**<br>1.5T Phillips Gyroscan<br>**Sequence**<br>Multishot GE-EPI (TE/TR 35/2200ms, Voxel size 3×3×5-mm flip angle 35°<br>**Coverage:** Whole brain<br>**Time resolution:** 2.2 s | None | Yes | None<br>Visual inspection of thresholded percentage change images and time courses from interesting clusters<br>Concordant regions with either positive or negative signal changes of 3–4%. |

a 3–4% signal increase and return to baseline over 100 s. These were assumed to represent subclinical seizure activity based mainly on temporal homology and spatial concordance but the degree of "surprise" (Cover and Thomas, 1991) was not characterized statistically.

Krings *et al.* (2000) performed fMRI on a patient during a 33-s Jacksonian march involving the left leg with "calf shaking." They described three perilesional (glioma) regions of interest based on the visual inspection of subtraction images. These three areas each appeared to show variable (bidirectional) signal changes of +2.2%, −3.5%, and +3.1% beginning 65, 30, and 0 s prior to seizure onset, respectively. Initial changes were attributed to subclinical seizure activity and negative changes to a "mismatch between oxygen consumption and delivery." It was concluded that "functional MRI allows for demonstrating seizure evolution and spread."

Ictal fMRI is not routinely feasible for a number of reasons. BOLD-fMRI is not sensitive to detecting low frequency state-related changes due to large intersessional effects and scanner noise characteristics. Together with the sluggish haemodynamic response function (HRF), this limits detection power to the narrow frequency band within which most conventional fMRI paradigms operate and in the current context will tend to necessitate capturing both seizure onset and termination. Seizures, however, are generally short lasting, unpredictable and it may not be practical to keep patients in the scanner for long enough even where subclinical seizures are known to be occurring frequently,

given the risks of seizure evolution and generalization within the scanner environment. Most ictal EEG phenomena are in addition associated with impairment of consciousness usually to a degree that the required level of cooperation for an MRI scan cannot be achieved even where consent may have been obtained in advance. Any significant degree of head and body motion is also likely to render the imaging [and EEG] data uninterpretable and EEG-correlated studies, where appropriate facilities exist, are complicated further by the extra time involved in attaching electrodes, patient positioning, and equipment set-up.

Despite these drawbacks, however, EEG-correlated Ictal fMRI does offer the necessary spatiotemporal resolution theoretically required to study seizure generation and propagation *in vivo* and knowledge of ictal BOLD changes may contribute clinically both to seizure localization at an individual level and to an understanding of the generators of ictal EEG changes routinely recorded in other patients for example during video-EEG telemetry. There is also potential for scientific insights into the complex accompanying blood flow and metabolic changes to which this signal is sensitive (Buxton *et al.,* 1998). We present here the first successful attempt at continuous and simultaneous EEG-correlated whole-head fMRI at short TR in a patient who fortuitously experienced an unequivocal subclinical electrographic seizure. Statistical parametric mapping (Friston *et al.,* 1995b) was used to characterise the fMRI data, make systematic inferences and help protect against bias, type 1 error, and motion-related artefact.

## METHODS

### *Case Report*

A 47-year-old right-handed gentleman with a 2-year history of intractable generalized tonic-clonic seizures underwent an EEG-correlated fMRI study. He also experienced frequent simple partial seizures characterised by cessation of activity and sitting still but without falls and did not report any auras. His past medical history was unremarkable and the aetiology of the epilepsy unknown. Structural MRI was normal[1] but interictal EEGs had consistently revealed focal left anterior temporal spikes, more pronounced in sleep. Neurological examination was unremarkable but the patient complained of poor memory and occasional word finding difficulties. Treatment was with Lamotrigine 400 mg daily and Gabapentin 1200 mg daily. Written informed consent was obtained in accordance with local ethics committee approval with an initial study aim of establishing a spike-related activation through interictal EEG/MRI.

### *Data Acquisition*

Imaging was performed on a GE Horizon Echospeed 1.5 Tesla Scanner using a continuous BOLD-fMRI sequence (TE/TR 40/3000, 21×5-mm interleaved slices, FOV = 24×24 cm, 64×64 matrix). Seven hundred such scans were acquired over a 35-min period. Eleven channels of referential scalp EEG were recorded simultaneously with online and offline pulse (Allen *et al.,* 1998) and imaging (Allen *et al.,* 2000) artefact subtraction using MR-compatible equipment.

### *Processing and Analysis*

The SPM99 package [http://www.fil.ion.ucl.ac.uk/spm99] was used for all image preprocessing and voxel-based statistical analysis, within the context of the general linear model. A slice-timing correction (Henson *et al.,* 1999) was performed prior to realignment (Friston *et al.,* 1995a) to correct for the staggered order of slice acquisition. Spatial smoothing followed with an isotropic Gaussian kernel of 12 mm FWHM to both boost signal[2] and conformity with the assumptions underlying Gaussian random field theory (see below). The seizure event was initially modelled flexibly with a windowed Fourier set of basis functions (8 sines and 8 cosines) spanning 45 s (Josephs *et al.,* 1997) making no assumptions about the shape of an underlying response, only that this period will likely explain a critical proportion of the overall variance encountered within the voxels being searched for. The six rigid-body motion correction parameters were included as confounding covariates within the design matrix (Friston *et al.,* 1996) to regress out any possible motion-correlated signal change, regardless of the seizure. Both data and design matrix were high-pass filtered at 1/200 seconds cut-off, dictated by the noise characteristics of the scanner and the subsequent need to limit inferences to frequencies that may be reliably inferred about with fMRI. An AR(1) model was used to estimate the intrinsic autocorrelation structure of the data (Friston *et al.,* 2000) and derive the effective degrees of freedom. An F-contrast was specified to test for the additional variance explained by the subspace of the model embodying the "effects of interest" (i.e., the seizure) and the computed SPM{F}thresholded at $P < 0.05$ using a correction for multiple comparisons based on Gaussian random field theory (Friston *et al.,* 1991).

[1] Epilepsy protocol structural imaging included T1-weighted Coronal 3-D IR-Prepared Spoiled GRASS, T2-weighted conventional dual spin echo, and Fluid Attenuated Inversion Recovery sequences (Liu *et al.,* 2001).

[2] The matched filter theorem states that optimal resolution of signal from noise will be achieved by matching the filter to the signal. The assumption here is that plausible seizure-related BOLD activations are unlikely to involve fewer than three neighboring voxels (Cooper *et al.,* 1965).

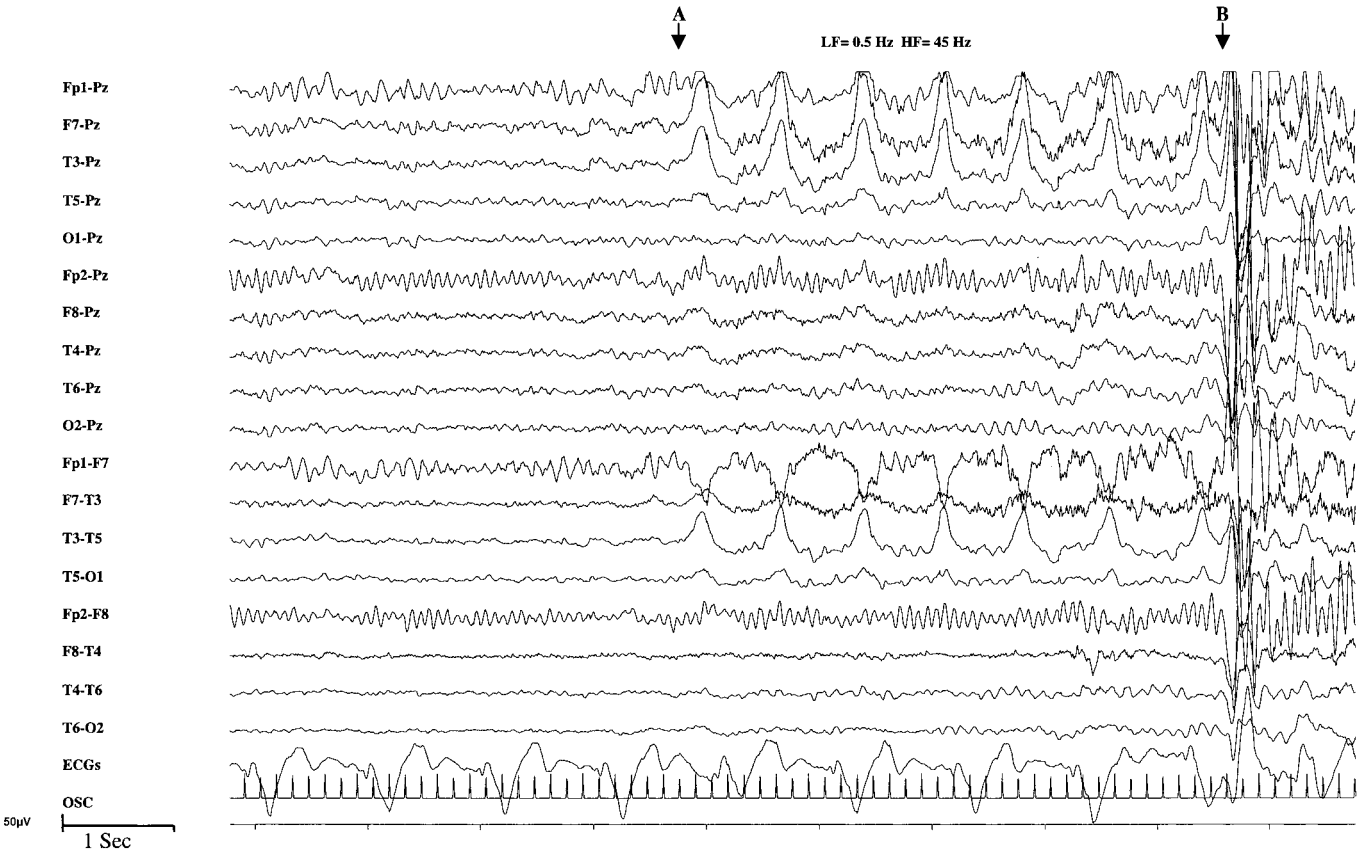


**FIG. 1.** EEG recorded during the experiment. Two bitemporal chains are shown, referenced to Pz in the top ten channels, followed by a bipolar montage in the next eight. ECG and slice timing signals (OSC) are shown at the bottom. fMRI was carried out continuously throughout the recording as indicated by the timing signals. Pulse and imaging artifact were subtracted online. Focal seizure activity begins at point A. Brief movement artifact is evident at point B.

A second step was performed to ascertain the spatial extent specifically of the dominant temporal pattern. A volume of interest (VOI) was therefore defined by the entirety of the cluster containing the maximum of the SPM{F} and a time series accounting for the most variance (i.e., the first eigenvariate), filtered and adjusted for the above contrast, was extracted from this VOI. The seizure related signal change was well approximated by a sine wave cycle of 102 s, used for simplicity to model the seizure next as a single regressor (alongside the motion parameters). A T-contrast was specified as a unidirectional test of significance for the parameter estimate pertaining to this individual regressor, as orthogonalized with respect to all other covariates. The computed SPM{T} was thresholded as above. No cluster thresholds were applied and the result overlaid onto a high-resolution T1-weighted anatomical scan (Coronal 3-D IR-Prepared Spoiled GRASS, TR/TE/TI 17/4.2/450, 124 × 1.5-mm slices, FOV 240 × 180 mm, matrix 256 × 192) for orientation. Coregistration was to the mean EPI image, using mutual information (Collignon *et al.*, 1995); part of the SPM99 package.

## RESULTS

The patient was visually observed and monitored throughout the experiment with good quality simultaneous and continuously acquired EEG (& ECG). Shortly into the experiment focal rhythmic delta activity was seen to emerge abruptly and unilaterally maximum over the $F_7/T_3$ electrodes (see Fig 1). This activity was sustained for the next 15 s prior to evolving into a localised ($F_7/T_3$) 5 Hz theta rhythm and decaying slowly over the next 26 s to constitute an electrographic seizure. Brief motion artefact was evident in the EEG 5 s into the seizure but there were no visible clinical accompaniments or subsequently reported symptoms. The rigid body motion correction parameters are given in Figs. 3b and 3c for the entire session.

The SPM{F}, obtained from the initial analysis step, reveals a principal cluster of 917 voxels as displaying significant amounts of time-locked variance (Fig. 2a), the dominant temporal nature of which was captured by the first eigenvariate shown in Fig. 3a. The SPM{T} obtained from the next step (Fig. 2b), is in excellent agreement with the SPM{F} and further reveals those

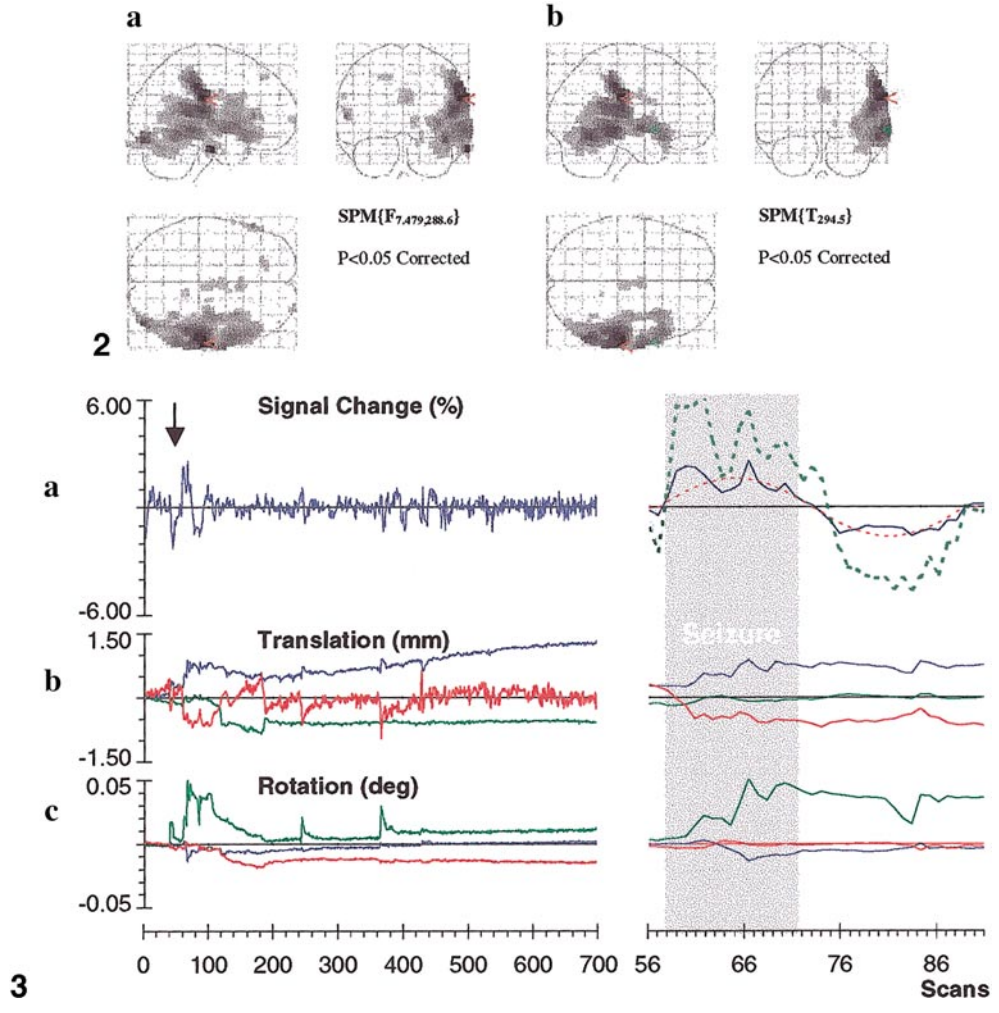


**FIG. 2.** (a) SPM {F}: These results were obtained using a Fourier set of basis functions spanning the seizure event. Realignment parameters were included as confounds. The statistical maximum is shown in red. (b) SPM{T}: These results were obtained using a single sine wave regressor spanning the seizure (see text). Realignment parameters were included as confounds. The statistical maximum is shown in red but the maximum parameter estimate for the regressor of interest (the beta image maximum) is shown in green.

**FIG. 3.** (a) Regional time series. On the left, the first eigenvariate is shown as extracted from the principal cluster of the SPM {F} for the entire experiment. Seizure onset is indicated by the arrow. On the right and rescaled, the maximum signal change is also shown (green) along with the sine wave regressor (red). The seizure interval is shaded in grey. Percentage changes are with respect to the grand session mean. (b,c) Realignment parameters. The X, Y, and Z translations in units of millimeters are shown in red, green, and blue, respectively, and the corresponding rotations given underneath in degrees.

particular voxels to share the same pattern and direction of signal change (described by the sine wave). Figure 3a, illustrates the rise in signal (approximately 2.5% mean) peaking at around 6 s into the seizure followed later by a prolonged undershoot. The greatest signal rise (approximately 5.5%) is also shown.

The anatomy of the seizure related activation is clear from Fig. 4. The principal cluster extends posteroinferiorly from the left insular grey matter, through the temporal lobe insula, along the superior and middle temporal gyri to the left fusiform gyrus; anteriorly to the left inferior frontal gyrus; and superiorly up to the left inferior parietal lobule. A smaller cluster (18 voxels) is also evident within the grey matter of the ipsilateral cingulate gyrus. The statistical maximum ($P < 1 \times 10^{-13}$) overlies the left inferior parietal lobule but the maximum of the parameter estimate (beta) images, representing signal as opposed to signal:noise, falls within the anterior segment of the middle temporal gyrus.

## DISCUSSION

The physiological impact of seizure activity on cerebral blood flow has been appreciated for some time (Gibbs *et al.*, 1934; Penfield *et al.*, 1939), indeed ictal SPECT has proved a useful technique for the clinical localization of epileptogenic areas as a consequence

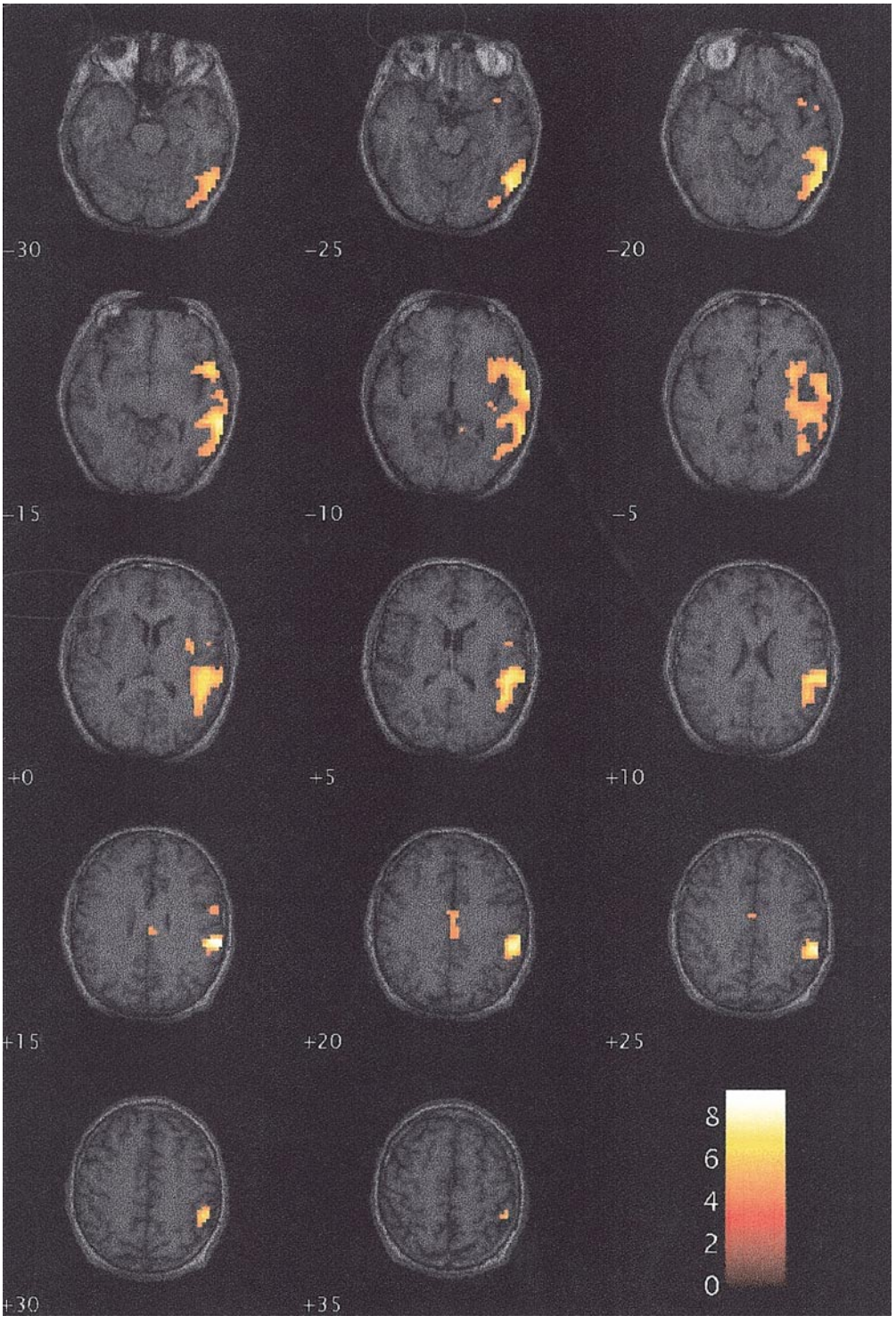


**FIG. 4.** Anatomical overlay. The seizure related activation obtaining from Fig. 2b is shown overlaid onto consecutive slices of a coregistered T1-weighted scan.

(Duncan, 1997; Cascino, 2001). In brief, ictal SPECT studies using $^{99m}$Tc-HMPAO (technetium 99 m hexamethylene propylene amine oxime) demonstrate sustained hyperperfusion within seizure foci surrounded by a rim of hypoperfusion, followed later by a return through baseline to a period of sustained hypoperfusion (Duncan, 1997). A transition from increased regional cerebral blood flow (rCBF) to decreased rCBF is suggested to take place at around 90 s after seizure onset, independently of offset (Avery *et al.*, 2000, 1999),

but return to baseline may occur more rapidly for shorter durations of seizure activity (Zubal *et al.,* 1999). Such findings are in good keeping with the general time course of the BOLD changes demonstrated here.

In regard to magnitude, BOLD changes in isolation are difficult to quantify directly in terms of physiological variables and a more intricate knowledge of the underlying physiology is essential. Though quantitative PET measurements of ictal rCBF are difficult to obtain (Duncan, 1997), increases of around 150–200% are suggested (Theodore *et al.,* 1996), but while cerebral blood flow and metabolism are closely coupled under physiological conditions (Siesjo, 1978), the influence of seizure activity is far less clear.

Interictally, there is evidence for both unmatched reductions in the regional metabolic rate of glucose (rCMRGlc) as compared to rCBF within human epileptic foci (Gaillard *et al.,* 1995; Fink *et al.,* 1996; Duncan, 1997) and similar uncoupling in animal models (Bruehl *et al.,* 1998).

Ictally, Kuhl *et al.* (1980) report rCMRGlc increases of 82–130% using $^{18}$FDG-PET in association with smaller flow changes but Engel *et al.* (1982) found rCMRGlc increases of an order 2–6 times the measured interictal values for homotopic regions. Franck *et al.* (1986) have described disproportionate increases in CBF compared to $CMRO_2$ in five patients one of whom underwent $^{18}$FDG-PET but with an unchanged glucose extraction ratio. They conclude that the supply of oxygen by blood flow was sufficient to meet local metabolic demands in status epilepticus and that glucose utilization is more important that oxygen consumption in determining rCBF but Buxton and Frank (1997) have since provided a widely embraced explanation for such data compatible with an intact neurovascular coupling.

The "oxygen limitation model" of Buxton and Frank (1997) suggests blood flow and metabolism to be coupled in a non-linear fashion such that relatively small increments in the cerebral metabolic rate of oxygen ($CMRO_2$) necessitate disproportionately large increases in rCBF. Quantitative theoretical relationships between BOLD and rCBF were provided within which context the rCBF changes implied by our data are found to be broadly compatible with the PET literature (assuming true underlying rCBF increases of 100–200%).

An unexpected feature of the seizure-related BOLD change seen in the patient we report lies in its temporal relationship to the EEG. The BOLD changes shown in Fig. 3a might appear to precede the EEG changes by several seconds (as also suggested by others (Krings *et al.,* 2000)), but this cannot be reliably shown in relation to a single event and with the necessitated high-pass filter. Interestingly, a post stimulus undershoot is seen more markedly than would be predicted through conventional models of sustained neural activity (e.g., the convolution of a boxcar function with a canonical Hemodynamic Response Function (Aguirre *et al.,* 1998)). Assuming an underlying temporal mismatch between flow and volume (Mandeville *et al.,* 1999), a very sharp initial increase in flow (Buxton *et al.,* 1998) presumably second to a particularly potent BOLD-inducing aspect of the seizure activity might thereby be suspected.

Anatomically, our results demonstrate a large and highly significant grey matter signal change centred over the left temporal and insular cortices, starting at seizure onset. The electrographic seizure focus ($F_7/T_3$), concordant with previous interictal spike foci (left anterior temporal), was also concordant with the fMRI activation and even more so perhaps with the area of maximal signal change as demonstrated in Fig. 2b.

In this respect, the ictal rCMRGlc changes observed by Engel *et al.* (1982) did not always correspond to areas of maximal interictal hypoperfusion and were not confined to (though included) EEG sites of ictal onset and spread. There were also extensive differences across subjects ranging from activation of an entire left hemisphere with seizures generalizing from the left parietal area, to more selective activation of the left perisylvian area with seizures confined electrographically to the left temporal and central electrodes. Interestingly in one case, seizures involving the right temporal lobe were also associated with increased activity in limbic projection sites (hippocampus and cingulate cortex). Chugani *et al.* (1994) distinguished between three dominant ictal rCMRGlc patterns in 18 children including "hypermetabolism restricted to cerebral cortex" and taken together with such observations, the BOLD activation patterns presented are extremely plausible both anatomically and neurobiologically as well as being in keeping with the patients clinical picture and provide further support for similar activation patterns arising from subclinical and clinical seizure activity (Handforth *et al.,* 1994; Alfonso *et al.,* 1998).

The rigorous data analysis and use of stringent thresholds were motivated by a desire to minimise the risks of false positives and motion-related effects to every possible extent and indeed the spatial characteristics of our activation are quite distinct from "edge effects" traditionally associated with stimulus-correlated motion in fMRI (Hajnal *et al.,* 1994). It also differs markedly in spatial extent from those attributed to focal seizure activity by other groups (see Table 1) and further studies are clearly essential to resolving such disparities in terms of patient characteristics, seizure activity, scanner characteristics, and data acquisition and analyses techniques.

Our decision to model the EEG activity as a single neural event was primarily motivated by the theoretical signal to noise considerations. Sampling of an inherently noisy fMRI time series at low temporal resolution concealing a single relatively brief, undefined, and sluggish BOLD fluctuation would not permit inferences regarding the spatiotemporal cascade. Simi-

larly the relative length of an HRF in relation to the ictus prohibits any meaningful subdivision of the epoch for modelling as other than a single event without prior knowledge of subtle interactions and non-linearities for instance. Moreover, even were sequential activation to be evincible, any extrapolation of temporal relationships to the underlying neural activity would be hampered by interregional variability within the HRF (Lee *et al.*, 1995; Buckner *et al.*, 1996, 1998; Schacter *et al.*, 1997; Robson *et al.*, 1998; Kastrup *et al.*, 1999; Miezin *et al.*, 2000). To the best of our knowledge therefore sequential activation and propagation effects have never been convincingly demonstrated through fMRI in relation to a seizure.

In summary, we have demonstrated the ability to detect electrographic seizure activity during continuously acquired fMRI and the potential for EEG-correlated ictal fMRI to illuminate the spatial extent of the neural networks underlying a unilateral subclinical seizure. While not routinely feasible, this technique allows for the "BOLD signatures" of EEG phenomena to be established, providing unique perspectives into the complex perfusion and metabolic changes that accompany seizure activity with localizing information of immediate clinical interest.

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## REFERENCES

Aguirre, G. K., Zarahn, E., and D'Esposito, M. 1998. The variability of human, BOLD hemodynamic responses. *Neuroimage* **8:** 360–369.

Alfonso, I., Papazian, O., Litt, R., Villalobos, R., and Acosta, J. I. 1998. Similar brain SPECT findings in subclinical and clinical seizures in two neonates with hemimegalencephaly. *Pediatr. Neurol.* **19:** 132–134.

Allen, P. J., Polizzi, G., Krakow, K., Fish, D. R., and Lemieux, L. 1998. Identification of EEG events in the MR scanner: The problem of pulse artifact and a method for its subtraction. *Neuroimage* **8:** 229–239.

Allen, P. J., Josephs, O., and Turner, R. 2000. A Method for Removing Imaging Artifact from Continuous EEG Recorded during Functional MRI. *Neuroimage* **12:** 230–239.

Avery, R. A., Spencer, S. S., Spanaki, M. V., Corsi, M., Seibyl, J. P., and Zubal, I. G. 1999. Effect of injection time on postictal SPET perfusion changes in medically refractory epilepsy. *Eur. J. Nucl. Med.* **26:** 830–836.

Avery, R. A., Zubal, I. G., Stokking, R., Studholme, C., Corsi, M., Seibyl, J. P., and Spencer, S. S. 2000. Decreased cerebral blood flow during seizures with ictal SPECT injections. *Epilepsy Res.* **40:** 53–61.

Bruehl, C., Hagemann, G., and Witte, O. W. 1998. Uncoupling of blood flow and metabolism in focal epilepsy. *Epilepsia* **39:** 1235–1242.

Buckner, R. L., Bandettini, P. A., O'Craven, K. M., Savoy, R. L., Petersen, S. E., Raichle, M. E., and Rosen, B. R. 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **93:** 14878–14883.

Buckner, R. L., Koutstaal, W., Schacter, D. L., Dale, A. M., Rotte, M., and Rosen, B. R. 1998. Functional-anatomic study of episodic retrieval. II. Selective averaging of event-related fMRI trials to test the retrieval success hypothesis. *Neuroimage* **7:** 163–175.

Buxton, R. B., and Frank, L. R. 1997. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *J. Cereb. Blood Flow Metab.* **17:** 64–72.

Buxton, R. B., Wong, E. C., and Frank, L. R. 1998. Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magn Reson. Med.* **39:** 855–864.

Cascino, G. D. 2001. Advances in neuroimaging: Surgical localization. *Epilepsia* **42:** 3–12.

Chugani, H. T., Rintahaka, P. J., and Shewmon, D. A. 1994. Ictal patterns of cerebral glucose utilization in children with epilepsy. *Epilepsia* **35:** 813–822.

Collignon, A., Maes, F., Delaere, D., Vandermeulen, D., Suetens, P., and Marchal, G. (1995). Automated multi-modality image registration based on information theory. In *Proceedings of Information Processing in Medical Imaging* (Y. Bizais *et al.*, Ed.), Kluwer Academic Publishers.

Cooper, R., Winter, A. L., Crow, H. J., and Walter, W. G. 1965. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. *Electroencephalogr. Clin. Neurophysiol.* **18:** 217–228.

Cover, T. M., and Thomas, J. A. (1991). *Elements of Information Theory.* Wiley.

Detre, J. A., Alsop, D. C., Aguirre, G. K., and Sperling, M. R. 1996. Coupling of cortical and thalamic ictal activity in human partial epilepsy: Demonstration by functional magnetic resonance imaging. *Epilepsia* **37:** 657–661.

Detre, J. A., Sirven, J. I., Alsop, D. C., O'Connor, M. J., and French, J. A. 1995. Localization of subclinical ictal activity by functional magnetic resonance imaging: correlation with invasive monitoring. *Ann. Neurol.* **38:** 618–624.

Duncan, J. S. 1997. Imaging and epilepsy. *Brain* **120**(Pt 2): 339–377.

Engel, J., Jr., Kuhl, D. E., and Phelps, M. E. 1982. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science* **218:** 64–66.

Fink, G. R., Pawlik, G., Stefan, H., Pietrzyk, U., Wienhard, K., and Heiss, W. D. 1996. Temporal lobe epilepsy: Evidence for interictal uncoupling of blood flow and glucose metabolism in temporomesial structures. *J. Neurol. Sci.* **137:** 28–34.

Franck, G., Sadzot, B., Salmon, E., Depresseux, J. C., Grisar, T., Peters, J. M., Guillaume, M., Quaglia, L., Delfiore, G., and Lamotte, D. 1986. Regional cerebral blood flow and metabolic rates in human focal epilepsy and status epilepticus. *Adv. Neurol.* **44:** 935–948.

Friston, K. J., Ashburner, J., Poline, J. B., Frith, C. D., Heather, J. D., and Frackowiak, R. S. 1995a. Spatial registration and normalization of images. *Hum. Brain Mapp.* **2:** 165–189.

Friston, K. J., Frith, C. D., Iiddle, P. F., and Frackowiak, R. S. 1991. Comparing functional (PET) images: The assessment of significant change. *J. Cereb. Blood Flow Metab* **11:** 690–699.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., and Frackowiak, R. S. 1995b. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2:** 189–210.

Friston, K. J., Josephs, O., Zarahn, E., Holmes, A. P., Rouquette, S., and Poline, J. 2000. To smooth or not to smooth? Bias and efficiency in fMRI time-series analysis. *Neuroimage* **12:** 196–208.

Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., and Turner, R. 1996. Movement-related effects in fMRI time-series. *Magn. Reson. Med.* **35:** 346–355.

Gaillard, W. D., Fazilat, S., White, S., Malow, B., Sato, S., Reeves, P., Herscovitch, P., and Theodore, W. H. 1995. Interictal metabolism and blood flow are uncoupled in temporal lobe cortex of patients with complex partial epilepsy. *Neurology* **45:** 1841–1847.

Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. 1934. Cerebral blood flow preceeding and accompanying epileptic seizures in man. *Arch. Neurol. Psychiatr* **32:** 257–272.

Hajnal, J. V., Myers, R., Oatridge, A., Schwieso, J. E., Young, I. R., and Bydder, G. M. 1994. Artifacts due to stimulus correlated motion in functional imaging of the brain. *Magn Reson. Med.* **31:** 283–291.

Handforth, A., Cheng, J. T., Mandelkern, M. A., and Treiman, D. M. 1994. Markedly increased mesiotemporal lobe metabolism in a case with PLEDs: Further evidence that PLEDs are a manifestation of partial status epilepticus. *Epilepsia* **35:** 876–881.

Henson, R. N. A., Buchel, C., Josephs, O., and Friston, K. J. 1999. The slice-timing problem in event-related fMRI. *Neuroimage* **9:** 125.

Jackson, G. D., Connelly, A., Cross, J. H., Gordon, I., and Gadian, D. G. 1994. Functional magnetic resonance imaging of focal seizures. *Neurology* **44:** 850–856.

Josephs, O., Turner, R., and Friston, K. J. 1997. Event-related fMRI. *Hum. Brain Mapp.* **5:** 243–248.

Kastrup, A., Kruger, G., Glover, G. H., Neumann-Haefelin, T., and Moseley, M. E. 1999. Regional variability of cerebral blood oxygenation response to hypercapnia. *Neuroimage.* **10:** 675–681.

Krakow, K., Allen, P. J., Lemieux, L., Symms, M. R., and Fish, D. R. 2000. Methodology: EEG-correlated fMRI. *Adv. Neurol.* **83:** 187–201.

Krakow, K., Symms, M. R., Woermann, F. G., Allen, P. J., Fish, D. R., and Duncan, J. S. 1998. Reproducible localisation of interictal activation in epilepsy patients using spike-triggered fMRI. *Epilepsia* **39:** 199.

Krings, T., Topper, R., Reinges, M. H., Foltys, H., Spetzger, U., Chiappa, K. H., Gilsbach, J. M., and Thron, A. 2000. Hemodynamic changes in simple partial epilepsy: A functional MRI study. *Neurology* **54:** 524–527.

Kuhl, D. E., Engel, J., Jr., Phelps, M. E., and Selin, C. 1980. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of 18FDG and 13NH3. *Ann. Neurol.* **8:** 348–360.

Lazeyras, F., Blanke, O., Perrig, S., Zimine, I. G. X., Delavelle, J., Michel, C. M., de Tribolet, N., Villemure, J., and Seeck, M. 2000. EEG-Triggered functional MRI in patients with pharmacoresistant epilepsy. *Magn Reson. Imaging* **12:** 177–185.

Lee, A. T., Glover, G. H., and Meyer, C. H. 1995. Discrimination of large venous vessels in time-course spiral blood- oxygen-level-dependent magnetic-resonance functional neuroimaging. *Magn Reson. Med.* **33:** 745–754.

Lemieux, L., Salek-Haddadi, A., Josephs, O., Allen, P., Toms, N., Scott, C., Krakow, K., Turner, R., and Fish, D. R. 2001. Event-Related fMRI with Simultaneous and Continuous EEG: Description of the Method and Initial Case Report. *Neuroimage* **14:** 780–787.

Liu, R. S., Lemieux, L., Bell, G. S., Bartlett, P. A., Sander, J. W., Sisodiya, S. M., Shorvon, S. D., and Duncan, J. S. 2001. A longitudinal quantitative MRI study of community-based patients with chronic epilepsy and newly diagnosed seizures: Methodology and preliminary findings. *Neuroimage* **14:** 231–243.

Luders, H. O., Engel, J., Jr., and Munari, C. 1993. General Principles. In *Surgical Treatment of the Epilepsies* (J. Engel, Jr., Ed.), pp. 137–153. Raven Press, New York.

Mandeville, J. B., Marota, J. J., Ayata, C., Moskowitz, M. A., Weisskoff, R. M., and Rosen, B. R. 1999. MRI measurement of the temporal evolution of relative CMRO(2) during rat forepaw stimulation. *Magn Reson. Med.* **42:** 944–951.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., and Buckner, R. L. 2000. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage* **11:** 735–759.

Penfield, W., Kalman, V. S., and Cipriani, A. 1939. Cerebral blood flow during induced epileptiform seizures in animals and man. *J. Neurophysiol.* **2:** 257–267.

Robson, M. D., Dorosz, J. L., and Gore, J. C. 1998. Measurements of the temporal fMRI response of the human auditory cortex to trains of tones. *Neuroimage.* **7:** 185–198.

Schacter, D. L., Buckner, R. L., Koutstaal, W., Dale, A. M., and Rosen, B. R. 1997. Late onset of anterior prefrontal activity during true and false recognition: An event-related fMRI study. *Neuroimage* **6:** 259–269.

Schomer, D. L., Bonmassar, G., Lazeyras, F., Seeck, M., Blum, A., Anami, K., Schwartz, D., Belliveau, J. W., and Ives, J. 2000. EEG-Linked functional magnetic resonance imaging in epilepsy and cognitive neurophysiology. *J. Clin. Neurophysiol.* **17:** 43–58.

Siesjo, B. K. 1978. *Brain Energy Metabolism*. New York, Wiley.

Theodore, W. H., Balish, M., Leiderman, D., Bromfield, E., Sato, S., and Herscovitch, P. 1996. Effect of seizures on cerebral blood flow measured with 15O-H2O and positron emission tomography. *Epilepsia* **37:** 796–802.

Warach, S., Ives, J. R., Schlaug, G., Patel, M. R., Darby, D. G., Thangaraj, V., Edelman, R. R., and Schomer, D. L. 1996. EEG-triggered echo-planar functional MRI in epilepsy. *Neurology* **47:** 89–93.

Zubal, I. G., Spanaki, M. V., MacMullan, J., Corsi, M., Seibyl, J. P., and Spencer, S. S. 1999. Influence of technetium-99m-hexamethylpropylene amine oxime injection time on single-photon emission tomography perfusion changes in epilepsy. *Eur. J. Nucl. Med.* **26:** 12–17.