STUDYING SPONTANEOUS BRAIN ACTIVITY USING EEG-FMRI AND EVENT-RELATED ICA

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Introduction: Simultaneous EEG and fMRI recordings (EEG-fMRI) can detect haemodynamic changes associated with spontaneous events observed on the EEG, such as interictal epileptiform discharges ("spikes"). Event-related analyses of these studies typically assume a canonical HRF model and define the start of the event as the onset of EEG changes. There have been two recent reports, however, of BOLD signal changes starting several seconds before the appearance of an epileptiform spike on the EEG [1,2], which suggests there may be related brain activity, undetected by the EEG, that occurs prior to the spike. The analysis strategy adopted in both those reports was to retain the assumption of a canonical HRF model and simply shift the event-onset backward in time relative to the spike – an approach that may poorly represent the *unobserved* underlying activity that leads to the BOLD signal changes preceding the spike. For example, the unobserved activity may be sustained for several seconds or could be a slow network oscillation, which would result in evoked BOLD signal changes that are quite different from a standard HRF model shifted in time relative to the spike.

In this abstract we describe a new event-related independent components analysis (eICA) method for detecting BOLD signal changes associated with spontaneous EEG events. This data-driven analysis method does not rely upon a pre-defined HRF to model the expected response, which makes it ideal for detecting BOLD signal changes associated with unobserved activity that may precede the event observed on the EEG. We demonstrate this new method on an EEG-fMRI study of patients with benign epilepsy with centrotemporal spikes (BECTS).

Methods: eICA – Model: The fMRI signal, **Y**, acquired during an EEG-fMRI experiment is represented as a $t \times n$ matrix: the rows contain the spatial maps of BOLD signal intensities sampled at n voxel locations and the columns contain the voxel time-courses sampled at t time-points.

The event-related signal, **B**, models the BOLD signal changes associated with a *single isolated event* and is represented as a $p \times n$ matrix of whole-brain BOLD signal changes during a one-minute period centred around the event - i.e. from 30 seconds before to 30 seconds after. An estimate, $\hat{\mathbf{B}}$, of the event-related signal is formed by fitting a general linear model (GLM) to the observed fMRI signal, **Y**. The GLM design-matrix, **X**, is created by convolving a series of delta functions representing the event-timings (shifted backward by 30 seconds), with an orthogonal basis-set of p box-car functions spanning a one-minute period (i.e. an FIR basis-set of order p). The parameter estimates for this model at each voxel provide the columns of $\hat{\mathbf{B}}$, i.e.:

$$\hat{\mathbf{B}} = \mathbf{X}^{\dagger}\mathbf{Y} = \mathbf{B} + \mathbf{E}\,, \qquad (1)$$

where $\mathbf{X}^{\dagger}$ denotes the pseudo-inverse of **X**; and **E** is a matrix of errors. It can be shown [3] that $\mathbf{E} = [\mathbf{e_1}\,\mathbf{e_2}\ldots\mathbf{e_n}]$ and $\mathbf{e_i} \sim N(0, \sigma_i^2 \mathbf{X}^{\dagger}\mathbf{V}\mathbf{X}^{\dagger T})$, where $\mathbf{X}^{\mathrm{T}}$ denotes the transpose of **X**; and σ^2_i and **V** are the variance parameters (voxel-specific variance and pooled covariance respectively) of the residual errors after the GLM fit.

The eICA method assumes that the event-related signal, **B**, is the mixture of a small (unknown) number, q, of independent spatial sources (with the requirement that $q < p$). This model is represented as:

$$\mathbf{B} = \mathbf{A}\mathbf{S}\,, \qquad (2)$$

where **S** is a $q \times n$ matrix of spatial sources; and **A** is a $p \times q$ mixing matrix. Substituting (1) into (2) gives:

$$\hat{\mathbf{B}} = \mathbf{A}\mathbf{S} + \mathbf{E}\,, \qquad (3)$$

which describes how the estimated event-related BOLD signal changes, $\hat{\mathbf{B}}$, are modelled as the mixture of the true underlying spatial sources, **AS**, corrupted by additive voxel-specific Gaussian noise.

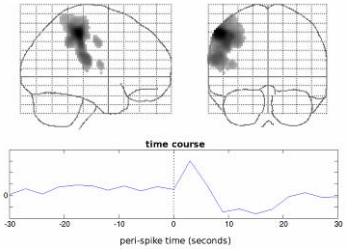

Figure 1

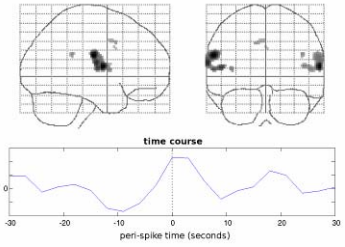

Figure 2

Two example spatial sources and associated time-courses estimated for a subject with left-sided spikes. The spatial maps are displayed as glass-brain views at a threshold of $p < 0.001$ (uncorrected) and the time of the spike ("time-zero") has been marked with a dotted line on the time-course. The first component (figure 1) shows a large area of spike-related BOLD signal changes in the ipsilateral post-central gyrus, with a time-course consistent with an activation related to the spike itself. The second component (figure 2) shows bilateral BOLD signal oscillations low in the central sulci that commence before the time of the spike. The time-course of this component shows marked differences compared to a canonical HRF model.

Estimates of **A** and **S** are obtained using ICA, after $\hat{\mathbf{B}}$ has first been projected into a q-dimensional sub-space using principal components analysis. The effect of the additive noise in (3), however, is to make the matrix $\hat{\mathbf{B}}$ of full rank, so determination of the correct number of sources, q, is non-trivial. Therefore, we estimate q from the eigenvalues of the sample covariance matrix, using the Laplace approximation to the Bayesian model evidence [4]. Before this estimation, however, the data must be pre-whitened and variance-normalised, to ensure i.i.d. errors. The pre-whitening filter, **K**, is formed via the Cholesky decomposition of the covariance matrix (i.e. $\mathbf{K}\mathbf{K}^{T} = \mathbf{X}^{\dagger}\mathbf{V}\mathbf{X}^{\dagger T}$) and the time-courses are normalised using the voxel-specific estimate of the standard deviation, σ_i.

eICA - Implementation: The eICA procedure was implemented in Matlab, using SPM2 [5] to perform the GLM estimation and the FastICA [6] and ICASSO [7] toolboxes to provide the ICA decomposition.

Results & Discussion: eICA was applied to EEG-fMRI studies from eight BECTS patients. In all subjects at least one of the estimated sources showed BOLD signal changes predominantly in the region of the central sulcus, which is concordant with the presumed source of the EEG spike in these patients. Furthermore, in each subject, at least one of these concordant sources showed a BOLD signal time-course beginning before the spike. In three patients, the eICA analysis provided two concordant sources: one showing BOLD signal changes beginning at the time of the spike, and another beginning before the spike (e.g. Figures 1 and 2). This demonstrates how the eICA analysis can effectively reveal the different networks underlying spontaneous EEG events in a completely data-driven manner. As illustrated in Figure 2, this can include BOLD signal changes that precede the EEG event and with time-courses that appear significantly different to a canonical HRF.

The eICA analysis also appeared effective at filtering sources of BOLD signal change originating from physiological (i.e. cardiac or respiratory) noise or motion, rather than true BOLD effects. These were estimated as separate sources, and easily identified by their spatial and/or temporal structure e.g. "activations" in the ventricles, sinuses or edges of the brain; or noisy, high-frequency time-courses. Thus the eICA method appears to provide a solution to the high rate of artefactual "activations" reported by other authors when using non-canonical HRF models in EEG-fMRI studies of epileptiform spikes [8].

Conclusion: eICA provides a data-driven approach for characterising the brain networks involved in the generation of spontaneous EEG events. We have demonstrated its use in the analysis of epileptiform spikes, but the method is equally suitable for the study of many other "spontaneous" brain phenomena – for example, EEG waveforms during sleep. Using eICA we were able to highlight regions of BOLD signal change that precede epileptiform spikes on the EEG. The ability to identify such regions will help provide new insights into the underlying causes of spike discharges in epilepsy.

References: [1] Hawco et al, Neuroimage, 2007, 35, p1450 [2] Moeller et al, Neuroimage, 2008, 39, p1839 [3] Worsley et al, Neuroimage, 1995, 2, p173 [4] Minka, MIT Technical Report 512, 2000 [5] http://www.fil.ion.ucl.ac.uk/spm/software/spm2 [6] Hyvarinen, IEEE Trans Neural Netw, 1999, 10, p626 [7] Himberg et al, Neuroimage, 2004, 22, p1214 [8] Lemieux et al. Human Brain Mapping, 2008, 29, p329