Event-related fMRI: Introduction, Statistical Modelling, Design Optimisation and Examples

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Event-related Functional Magnetic Resonance Imaging (efMRI) refers to a technique for detecting the brain's response to brief stimuli or "events". More precisely, efMRI allows detection of the Blood Oxygenation Level Dependent (BOLD) haemodynamic response to neural activity, with a spatial resolution of millimetres and a temporal resolution of hundreds of milliseconds.

Introduction: Advantages of efMRI

The are several important advantages of efMRI over previous "blocked" techniques that have been used in fMRI and Positron Emission Tomography (PET). These include:

1. The opportunity to randomly intermix events of different types, as is standard in psychological and electrophysiological studies. This means that the response to any one event is not systematically influenced by prior events, nor confounded by differences in the subject's cognitive state. Such "state effects" are not trivial: Johnson et al. (1997), for example, showed that the event-related potentials (ERPs) to "old" and "new" words in a memory test differed according to whether the old and new words were blocked or intermixed.

2. Events can be categorised post hoc on the basis of the subject's behaviour. Wagner et al. (1998), for example, categorised words during a simple semantic judgement task according to whether they were later remembered in a surprise memory test.

3. The occurrence of events can themselves be defined by the subject. Kleinschmidt et al (1998), for example, required subjects to indicate spontaneous transitions in their perception of an ambiguous visual stimulus (e.g. the vase-faces illusion).

4. Some events cannot be blocked, such as the occurrence of an "oddball" stimulus that deviates from surrounding context events (Clark et al, in press).

5. Even when stimuli are blocked, treating each as a distinct event provides a potentially more accurate model, particularly when the interstimulus interval is more than a few seconds (Price et al, 1999). Furthermore, it is possible for event (item) effects, block (state) effects, and their interactions, to be modelled separately.

The event-related BOLD response

The precise shape (temporal profile) of the BOLD response to brief stimulation (the "impulse response function") depends on several factors, including blood flow, volume and oxygenation state (Buxton et al, 1998). A canonical form of this response is shown in Figure 1A (solid line). The BOLD signal reaches a peak 4-5s post-stimulation, returns to baseline after approximately 10s, and is followed by an undershoot for another 10s or so (Boynton et al, 1996). In some cases, an initial undershoot is also observed (Malonek & Grinvald, 1996).

While there is considerable similarity of the BOLD response across peripheral areas, such as visual (Boynton et al., 1996), auditory (Josephs et al, 1997) and sensorimotor (Zarahn et al, 1997) cortex, there is some degree of variability across individuals (Aguirre et al, 1998) and across other brain regions (Schacter et al, 1997). This variability concerns mainly the magnitude, latency and duration of the peak response, which show little covariation across individuals or regions (Miezin et al, in press). This variability may relate to differences in vasculature (Lee et al, 1995).

A further question concerns the linearity of the relationship between stimulation and BOLD response. There is good evidence for near-linear additivity of responses to successive, brief stimuli presented at rates up to 1 every 2 seconds (Dale & Buckner, 1997), which is particularly important for modelling (see below). Nonetheless, nonlinearities have been observed as a function of the magnitude and duration of sustained stimulation (Vazquez & Noll, 1998) and at rapid rates of brief stimulation (Friston et al, 1998b). These nonlinearities may reflect saturation of the BOLD signal, habituation of neural activity, or a combination of factors. Nonetheless, in the case of very rapid rates of brief stimulation, a dominant source of nonlinearity appears specific to the BOLD response, because blood flow, as measured with PET, can simultaneously show linear effects (Friston et al., 1998b).

Statistical Modelling: The GLM and SPM

Assuming a linear relationship between stimulation and BOLD response, the continuous signal produced by a specific timecourse of stimulation can be predicted within the General Linear Model (GLM). More specifically, within Statistical Parametric Mapping (SPM99; http://www.fil.ion.ucl.ac.uk/spm/spm99.html; Friston et al., 1995), the predicted signal for repeated, brief stimulation is modelled by convolving a timecourse of delta-functions for each event with a set of basis functions of peristimulus time. The use of multiple basis functions allows the model to capture a range of different response shapes (see above). The resultant signals are then down-sampled every TR (scan repetition time) to produce the covariates of the model ("design matrix"). A least-mean-squares fit of this model to the fMRI timeseries data produces parameter estimates for each basis function, linear combinations of which can be tested against the residual error using t or F tests.

Several choices of basis functions are possible. The most general is a windowed Fourier set of sine and cosine functions, with harmonic periods ranging from the longest conceivable BOLD response (e.g., 32s) up to the Nyquist sampling limit of twice the TR (Josephs et al., 1997; Figure 1C). A more constrained set consists of gamma functions of different lags and widths (Boynton et al., 1996; Dale & Buckner, 1997; Figure 1B), which are smoothly bounded functions of time. An even more "informed" set consists of a canonical response function (Figure 1A, itself a mixture of two gamma functions), and its multivariate Taylor expansion (Friston et al., 1998a) with respect to time ("temporal derivative") and width ("dispersion derivative").

The advantage of the Fourier set is its ability to capture any shape of response; a potential disadvantage is the many degrees of freedom introduced into the model (and entailed in the corresponding F-tests). The advantage of the canonical response set is that t-tests on linear combinations of components can be interpreted in terms of response magnitude, latency or duration (Friston et al., 1998a; Henson et al., 1999c); a disadvantage is that responses that differ markedly from the canonical form (such as latencies beyond the range of ±1s that can be captured by the temporal derivative for example) may not be detected (Henson et al, in press-b). Another issue relates to "Random Effects" analyses, in which the error term is confined to the variability of parameter estimates across subjects. Standard univariate tests can be used, for example, on the estimate for the canonical response; multivariate tests however are required for the multiple estimates of more general basis sets, and such tests are usually less powerful (Henson et al, in press-a).

It is worth considering other methods of efMRI analysis. If the time between events (or Stimulus Onset Asynchrony, SOA) is long relative to the duration of the BOLD response, the overlap between responses can be ignored, and mean signal in each peristimulus scan can be submitted to conventional analyses of variance (Cohen et al., 1997). Unfortunately, such long SOA designs are potentially less sensitive (see below). If the SOA is short, and the order of different event-types is counterbalanced (so that overlap effects are equated), analyses can be restricted to the mean signal in those scans acquired 4-6s after each event (to allow for the delayed peak of the response; Saykin et al., 1999). Furthermore, if "null events" (in which no stimulus is presented) are introduced into a counterbalanced design, "selective averaging" can be used to estimate the signal at each peristimulus timepoint, despite short SOAs (Dale & Buckner, 1997). These approaches can be simulated within SPM by a separate covariate that contains a delta function for each scan at a given peristimulus time (a "finite impulse response" model). Though these approaches might make fewer assumptions about the form of the BOLD response, they are however restricted to designs in which stimuli are synchronised with the scanner and fully counterbalanced. Such restrictions can be problematic when the events are ordered, or defined in time, by the subject's responses (see Introduction).

Another approach is to measure each individual's BOLD response in a region known to be active during a simple sensorimotor task (Zarahn et al., 1997). This measured response can then be convolved with the event onsets to predict the timeseries for that individual in a second task of interest. While this approach caters for individual differences, it does not allow for regional differences within an individual (see above).

Yet another approach is to explicitly parameterise a response function by magnitude, onset delay, width, etc, and perform nonlinear, numerical fitting (Kruggel & von Cramon, 1999). This approach can resolve relative latency differences of as little as 100ms (Miezin et al., in press). The problem with this approach is the computational expense of numerically fitting every voxel in an image.

Timing issues

Providing the scanner sampling does not miss the peak response (Price et al., 1999), sampling rates close to typical TRs (2-4s) do not necessarily impair response detection (i.e. model fits). However, it is possible to achieve a sampling rate higher than the TR by jittering the stimuli with respect to the scanner (Josephs et al., 1997). Such improved temporal sampling (e.g. 0.5-1s) is useful to identify the precise shape of the BOLD response, including response latency for example (Miezin et al., in press)

One caveat with the SPM approach is that the same model is assumed for all voxels. Thus the same signal is predicted for voxels in the first slice acquired as for voxels in the last slice acquired, even though these acquisitions can be several seconds apart (with typical TRs). One solution is to interpolate the data in time. However, such interpolation will alias frequencies above the Nyquist limit, which may be problematic for TRs of more than a few seconds. Another solution is to use a Fourier set, or the temporal derivatives of a more constrained set, that provide some robustness to different acquisition times (Henson et al, 1999a).

Optimising Experimental Designs

The sensitivity of an experimental design is related to the bandpassed energy of the predicted signal (fMRI data in SPM are usually highpass filtered to remove low-frequency noise, and temporally smoothed to swamp high-frequency autocorrelation, Friston et al., submitted). Assuming the noise is independent of experimental design, a more sensitive design will have greater total energy (or "estimated measurable power", Josephs & Henson, 1999). This quantity is also related to the covariance of (a contrast of) the design matrix, with the *efficiency* of estimation being inversely related to the covariance of parameter estimates (Friston et al, 1999).

In the case of a single event-type, any experimental design can be characterised by the minimal SOA, SOA_{min}, and the probability, p, of an event occurring each SOA_{min}. (Friston et al., 1999). In *deterministic* (or fixed SOA) designs, $p=1$. In *stochastic* designs, $0<p<1$, producing a range of different SOAs. The value of p in stochastic designs can be *stationary* (e.g. $p=0.5$), or itself *modulated* over time (i.e., $p=f(t)$). An extreme example of a modulated design is a blocked design, where $p=1$ for the duration of a block, and $p=0$ otherwise.

The most efficient deterministic design for single event-type (versus baseline) obtains when SOA_{min} is close to the dominant period of the BOLD response (approximately 16s). For shorter SOA_{min}, stochastic designs are far more efficient (Dale, 1999). In fact, the most efficient design of all is a blocked design with minimal SOA_{min} and a modulation frequency of approximately 16s (though blocked designs of course have all the limitations outlined in the Introduction). The basic reason for these results is

that the overlap of BOLD responses to events close in time increases the total signal energy, and provided this energy can be moved from low to middle frequencies (by modulating event probability), it can be distinguished from background noise.

With multiple event-types, any experimental design can be characterised by SOA_{min} and a probabilistic stimulus *transition matrix* (Josephs & Henson, 1999). The efficiency of the design then depends on the specific hypothesis (contrast). With randomised designs involving two event-types (Table 1A), the efficiency of the differential effect is maximal for minimal SOA_{min} (Figure 2). However, efficiency to the common effect (versus baseline) is then minimal (equivalent to a deterministic design). When stimulus order is constrained (e.g., transitions between two perceptual states), an alternating design may result (Table 1B), for which the optimal SOA_{min} for a differential effect is approximately 8s. When SOA_{min} is constrained (e.g., the task requires at least 8s between events), then a permuted stimulus ordering (Table 1C) can be optimal for a differential effect. This design is pseudorandomised (randomised to first-order), which may be sufficient as far as the subject is concerned. When the design needs to be sensitive to both the differential and common effects, "null events" can be introduced (Table 1D), when no stimulus is presented (equivalent to a specific stochastic distribution of SOAs). The most efficient estimation of both differential and common effects in this case is with minimal SOA_{min} (Figure 2).

Table 1: Possible transition matrices for two event-types A and B.

Design		A	B	Example Sequence
A. Randomised (first-order)	A	0.5	0.5	ABBBAABABAAAAB....
	B	0.5	0.5	
B. Alternating (first-order)	A	0	1	ABABABABABABAB....
	B	1	0	
C. Permuted (second-order)	AA	0	1	ABBABAABBABABA....
	AB	0.5	0.5	
	BA	0.5	0.5	
	BB	1	0	
D. With "Null events"	A	0.33	0.33	ABB--B-A---AABA--B....
	B	0.33	0.33	

Though minimal SOAs are generally advisable therefore, the above predictions are based on a linear model. While reliable responses have been detected with SOA_{min} as short as 0.5s (Burock et al, 1998), the nonlinear saturation described above will reduce the efficiency of designs with very short SOAs. Indeed the optimal, theoretical SOA in the presence of saturation is approximately 1s (Friston et al., 1999).

Recent Examples

Examples from our laboratory that illustrate the advantages of efMRI listed in the Introduction include:

1. *The intermixing of stimuli*. In a priming study in which first and second presentations of stimuli were randomly intermixed, Henson et al (2000) identified a right fusiform region that showed a decreased response to repetition of familiar stimuli, but an increased response to repetition of unfamiliar stimuli. By modelling an exponential modulation of the response by the parametric lag between first and second presentations of each stimulus, such repetition effects were shown to be transient.

2. *The categorisation of events by the subject's response*. Henson et al (1999b) presented subjects with intermixed old and new words in an episodic recognition memory test. For each word, subjects indicated whether they i) consciously recollected the prior occurrence of a word (R judgements), ii) experienced a feeling of familiarity in the absence of recollection (K judgements), or iii) did not remember prior occurrence of the word (N judgements; Tulving, 1985). Though words were objectively old for both correct R and correct K judgements, several regions showed differential responses as a function of the subjective experience accompanying those words: Left prefrontal regions were more active for R than K judgements, whereas right prefrontal regions were more active for K than R judgements.

3. *The definition of events by the subject's response.* Portas et al (in press) asked subjects to press a key when a 3D percept spontaneously emerged from a 2D stereogram. This key press also produced a tone. When compared with a control event (in which the same tone prompted a key press), which was matched for visual, auditory and simple motor components, several regions, including bilateral posterior thalamus and occipito-temporal regions, showed greater responses associated with the perceptual "pop-out" (in the absence of any visual change).

4. *Oddball paradigms*. Strange et al (submitted) presented subjects with lists of 16 neutral, semantically related words, plus three randomly intermixed oddball words. One oddball was presented in a different font (the perceptual oddball), one was semantically unrelated (the semantic oddball) and one was emotionally aversive (the emotional oddball). All oddball types activated a common network of right prefrontal and bilateral fusiform regions. However, amygdala activation was identified for the emotional oddball only, and left inferior frontal activation was identified for the semantic oddball only.

5. *Item-State interactions*. Chawla et al (1999) asked subjects to view random dots, which transiently changed in colour or in radial motion, under two blocked instructions to attend to either colour or motion. The response in V4 to the same objective colour change was greater during colour-attend than motion-attend blocks. Conversely, the response in V5 to the same objective motion change was greater during motion-attend than colour-attend blocks. This demonstrates how state effects, such as differential attention, can interact with the event-related response.

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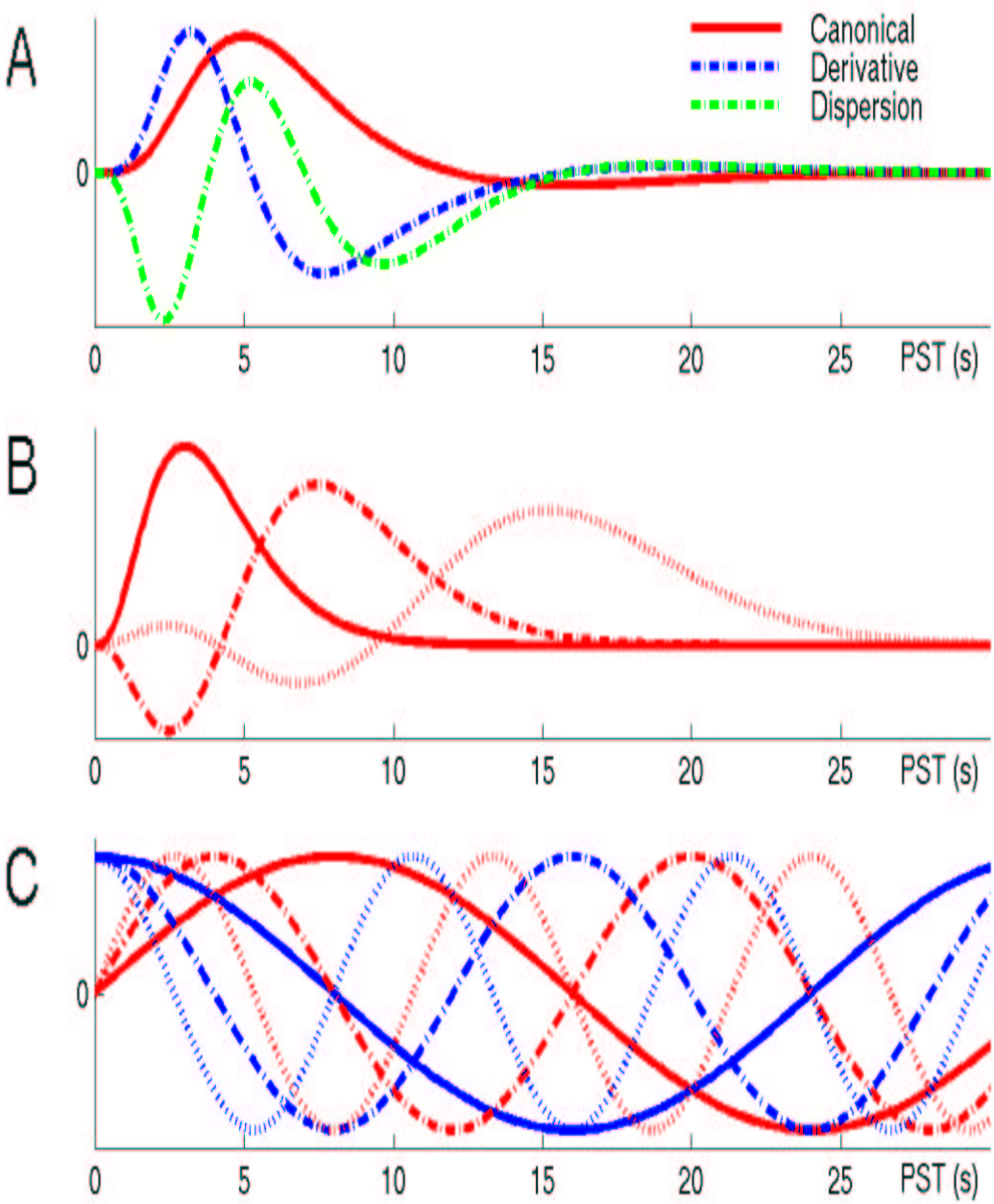

Figure 1. Three types of basis functions: A) Canonical response function and its temporal and dispersion derivatives; B) lagged Gamma functions (serially orthogonalised); C) sine and cosine functions (Fourier set). PST=Peristimulus Time.

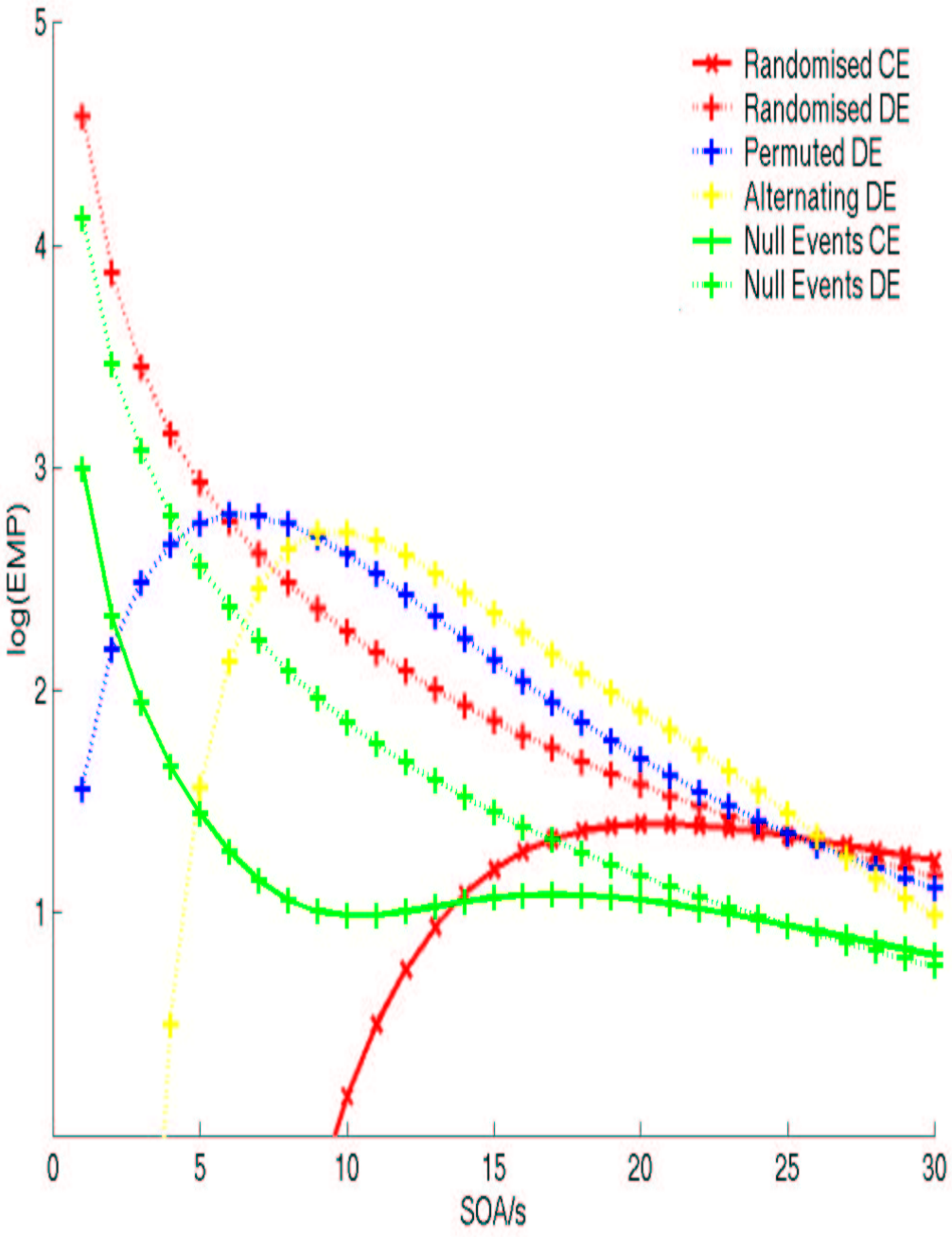

Figure 2. Efficiency (Estimated Measurable Power, EMP) as a function of Stimulus Onset Asynchrony (SOA) and stimulus ordering for transient events of two types. CE=Common Effect; DE=Differential Effect. See text and Table 1 for details.