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Optimal Experimental Design for Event-Related fMRI

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Abstract: An important challenge in the design and analysis of event-related or single-trial functional magnetic resonance imaging (fMRI) experiments is to optimize statistical efficiency, i.e., the accuracy with which the event-related hemodynamic response to different stimuli can be estimated for a given amount of imaging time. Several studies have suggested that using a fixed inter-stimulus-interval (ISI) of at least 15 sec results in optimal statistical efficiency or power and that using shorter ISIs results in a severe loss of power. In contrast, recent studies have demonstrated the feasibility of using ISIs as short as 500 ms while still maintaining considerable efficiency or power. Here, we attempt to resolve this apparent contradiction by a quantitative analysis of the relative efficiency afforded by different event-related experimental designs. This analysis shows that statistical efficiency falls off dramatically as the ISI gets sufficiently short, if the ISI is kept fixed for all trials. However, if the ISI is properly jittered or randomized from trial to trial, the efficiency improves monotonically with decreasing mean ISI. Importantly, the efficiency afforded by such variable ISI designs can be more than 10 times greater than that which can be achieved by fixed ISI designs. These results further demonstrate the feasibility of using identical experimental designs with fMRI and electro-/magnetoencephalography (EEG/MEG) without sacrificing statistical power or efficiency of either technique, thereby facilitating comparison and integration across imaging modalities. *Hum. Brain Mapping 8:109–114, 1999.*

Key words: EEG; MEG; ERP; overlap correction; deconvolution; linear model; systems identification

INTRODUCTION

Event-related experimental designs have become increasingly popular in fMRI research in recent years [Buckner et al., 1996, 1998; Burock et al., 1998; Clark et al., 1998; Dale and Buckner, 1997; Friston et al., 1998; Josephs et al., 1997; McCarthy et al., 1997; Wagner et al., 1998; Zarahn et al., 1997]. In contrast to more traditional blocked designs, where multiple trials of a particular condition are grouped together in blocks, event-related designs allow different trials or stimuli to be presented in arbitrary sequences, thus eliminating potential confounds, such as habituation, anticipation, set, or other strategy effects [Rosen et al., 1998].

A significant challenge in designing and analyzing event-related fMRI experiments is how to optimize the accuracy of the estimated event-related responses. It has been widely argued, based on empirical as well as theoretical evidence, that using ISIs of at least 15 sec is optimal and that using shorter ISIs results in a severe reduction in statistical power [Cox and Bandettini, 1998; Hutton et al., 1998]. However, numerous studies have shown highly reliable event-related fMRI response estimates using ISIs as short as seconds or less [see, e.g., Buckner et al., 1998; Burock et al., 1998; Clark

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et al., 1998; Dale and Buckner, 1997; Wagner et al., 1998]. The explanation for this apparent contradiction is that the expected accuracy (or efficiency) of event-related fMRI response estimates is not fully determined by the mean ISI. In fact, the efficiency critically depends on the entire distribution of ISIs. As shown below, a substantial improvement in efficiency can be achieved by using a variable ISI design, relative to a fixed ISI design with the same mean ISI.

METHODS

Linear model

In the following, we assume a linear time-invariant model for the observed fMRI response [Boynton et al., 1996; Dale and Buckner, 1997; Friston et al., 1994]. According to this model, the response to an arbitrary sequence of stimuli or events is equal to the summation of the responses to each of the individual events. More formally, the fMRI signal $y(t)$ at a particular voxel is given by

$$y(t) = x(t) * h(t) + n(t), \tag{1}$$

where the event sequence $x(t)$ is a sum of time-shifted delta functions, centered at the onset of each event, $h(t)$ is the (unknown) hemodynamic response (HDR) to each individual event, $n(t)$ represents additive noise, and * is the convolution operator. More generally, if there are more than one type of event or condition with different HDRs, equation (1) generalizes to

$$y(t) = x_1(t) * h_1(t) + x_2(t) * h_2(t) + \cdots + x_{N_c}(t) * h_{N_c}(t) + n(t), \tag{2}$$

where N_c is the number of different event types, $x_i(t)$ is the event sequence for event type i, and $h_i(t)$ is the HDR for event type i.

Note that the fMRI signal is not sampled continuously in time, but rather at discrete intervals determined by the repetition rate (TR). Thus if we assume that the hemodynamic response functions have a finite duration (T_{HDR}) and can be represented adequately by a piecewise constant function with a discretization interval of ΔT_{HDR}, the continuous-time equation (2) can be converted into the following discrete-time matrix model for the fMRI signal

$$\mathbf{y} = \mathbf{X}_1\mathbf{h}_1 + \mathbf{X}_2\mathbf{h}_2 + \cdots + \mathbf{X}_{N_c}\mathbf{h}_{N_c} + \mathbf{n}, \tag{3}$$

where $\mathbf{y}$ is a vector of fMRI samples with dimension N_{tp} (the number of discrete time-points or samples), and $\mathbf{h}_i$ is a discrete-time vector representation of the continuous-time hemodynamic response $h_i(t)$ with $N_h = T_{HDR}/\Delta T_{HDR}$ elements. $\mathbf{X}_i$ is known as a stimulus convolution matrix (SCM), a matrix operator representation of the time-discretized convolution with the event sequence $x_i(t)$. The elements of the N_{tp} by N_h matrix $\mathbf{X}_i$ are given by

$$x_{i_{(n,m)}} = \int_{(n-1)TR+(m-1)\Delta T_{HDR}}^{(n-1)TR+m\Delta T_{HDR}} x_i(t)\, \mathrm{d}t, \tag{4}$$

where $x_{i_{(n,m)}}$ is the element at the n$^{\text{th}}$ row and m$^{\text{th}}$ column of $\mathbf{X}_i$, and $x_i(t)$ is again the continuous-time event sequence for event type i. Note that the discretization interval ΔT_{HDR} for the HDR can be shorter than the fMRI sampling interval (TR), thus making it possible to represent the HDRs with a finer temporal resolution than that of the raw fMRI measurements.

Equation (3) can be further consolidated in matrix notation as

$$\mathbf{y} = \mathbf{X}\mathbf{h} + \mathbf{n}, \tag{5}$$

where the design matrix $\mathbf{X} = [\mathbf{X}_1\mathbf{X}_2 \ldots \mathbf{X}_{N_c}]$ is a horizontal concatenation of the SCMs for the individual event types, and $\mathbf{h}$ is the vertical concatenation of the individual HDRs. $\mathbf{X}$ has dimensions N_{tp} by N_{ch}, where $N_{ch} = N_c N_h$ is the total number of hemodynamic parameters to be estimated (i.e., across all event types and lags).

Unbiased estimation

If we assume that the noise process is zero mean and Gaussian with covariance matrix $\mathbf{C_n}$, an efficient unbiased estimate for the HDRs is provided by the maximum likelihood (ML) solution $\hat{\mathbf{h}}_{\mathrm{ML}}$ given by

$$\hat{\mathbf{h}}_{\mathrm{ML}} = (\mathbf{X}^T\mathbf{C}_\mathbf{n}^{-1}\mathbf{X})^{-1}\mathbf{X}^T\mathbf{C}_\mathbf{n}^{-1}\mathbf{y} \tag{6}$$

The ML estimator for a linear model with Gaussian noise is optimal in the sense that it has the smallest variance among all unbiased estimators of the response. Since the noise covariance matrix $\mathbf{C_n}$ may vary considerably across voxels, experimental runs, and subjects, one cannot assume a particular form a priori [Purdon and Weisskoff, 1998]. It is, therefore, desirable to estimate the noise statistics from the same data used to estimate the hemodynamic responses themselves. A promising method for obtaining accurate parameterized estimates of $\mathbf{C_n}$ is by fitting the residual errors

given by $\mathbf{e}_y = \mathbf{y} - \mathbf{X}\hat{\mathbf{h}}_{OLS}$, where $\hat{\mathbf{h}}_{OLS} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{y}$ is the ordinary least-squares estimate of the HDR, as a first-order autoregressive process plus white noise [Burock, 1998; also Burock and Dale submitted]. This noise estimate can then be used to obtain more efficient HDR estimates and to obtain more accurate *p*-values for statistical parametric mapping.

Selective averaging

Note that this linear estimation approach is closely related to the selective averaging method described in Dale and Buckner [1997]. Under the assumption of temporally uncorrelated noise (i.e., $\mathbf{C}_n = \sigma^2\mathbf{I}$), the maximum likelihood estimate in equation (6) reduces to the ordinary least-squares estimate $\hat{\mathbf{h}}_{OLS} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{y}$. This expression can be factored into a "selective summing" term $\mathbf{X}^T\mathbf{y}$, which sums up the recorded fMRI signal at different lags time-locked to every event of a certain type, and an "overlap correction" term $(\mathbf{X}^T\mathbf{X})^{-1}$, which normalizes for the number of events of each type and corrects for potential overlap in the estimated timecourses due to preceding or succeeding events [see, e.g., Hansen, 1983; Woldorff, 1993]. Thus, the method of selective averaging with overlap correction is equivalent to ordinary least-squares estimation. However, although the resulting HDR estimates are unbiased, they are less efficient than the maximum likelihood estimates, given the high degree of temporal correlation of typical fMRI noise [Purdon and Weisskoff, 1998; Burock, 1998].

Hemodynamic basis functions

The methods described thus far make no assumptions about the exact shape or functional form of the HDRs. It should be noted, however, that it is relatively straightforward to incorporate prior knowledge about possible HDR shapes as a bias in the linear estimation framework outlined above. If we assume that the HDRs for all event types and at all locations in the brain are fully contained in an N_p-dimensional linear sub-space L of $\Re^{N_h}$, then, any HDR $\mathbf{h}_i$ can be parameterized uniquely as $\mathbf{h}_i = \mathbf{L}\mathbf{p}_i$, where $\mathbf{L}$ is an N_h-by-N_p-dimensional matrix whose columns form an orthonormal basis for the sub-space L, and where the elements of $\mathbf{p}_i$ (parameters) are the projection of $\mathbf{h}_i$ onto the corresponding basis vectors. Substituting this parameterized expression for $\mathbf{h}_i$ into equations (3), (4) and (5), we get the following expression for the maximum likelihood estimate of $\mathbf{p}$, the vertical concatenation of the parameter vectors $\mathbf{p}_i$ for each event type:

$$\hat{\mathbf{p}}_{ML} = (\mathbf{L}^T\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{X}\mathbf{L})^{-1}\mathbf{L}^T\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{y}. \quad (7)$$

The resulting biased maximum likelihood estimate for the HDRs is given by

$$\hat{\mathbf{h}}_{BML} = \mathbf{L}\hat{\mathbf{p}}_{ML} = \mathbf{L}(\mathbf{L}^T\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{X}\mathbf{L})^{-1}\,\mathbf{L}^T\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{y}. \quad (8)$$

An advantage of such biased estimates is that they are generally more efficient than unbiased ones, especially if the dimensionality N_p of the subspace is much lower than the dimensionality N_h of the embedding space (i.e., fewer unknowns). However, the accuracy of the resulting estimates critically depends on the appropriate bias. Unless the actual event-related response to every event type, in every voxel, in every subject lies entirely within the specified subspace, the resulting estimates will be distorted. Great care should, therefore, be taken to ensure that the choice of basis functions spans the space of all possible HDRs for a given experiment.

Efficiency

As noted above, the maximum likelihood estimator has the smallest variance (or, equivalently, greatest efficiency) among all unbiased estimators of the HDR. The estimator efficiency, which can be seen as a measure of the expected accuracy of the estimator, is typically defined as the reciprocal of estimator variance. More formally, we define the estimator efficiency E as

$$E = \langle \|\mathbf{h} - \hat{\mathbf{h}}\|^2 \rangle^{-1}, \quad (9)$$

where $\langle\cdot\rangle$ denotes the expectation operator. Substituting the maximum likelihood estimator $\hat{\mathbf{h}}_{ML}$ defined in equation (6) into equation (9), we get the following expression for the efficiency of maximally efficient unbiased estimator:

$$E = \langle \|\mathbf{h} - (\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{X})^{-1}\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{y}\|^2 \rangle^{-1}. \quad (10)$$

Further, combining equations (5) and (10) and simplifying, we get

$$E = \langle \|(\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{X})^{-1}\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{n}\|^2 \rangle^{-1}. \quad (11)$$

Finally, recalling that $\mathbf{n}$ is a zero mean Gaussian random variable with covariance matrix $\mathbf{C}_n$, we get the following expression for the efficiency of the unbiased maximum likelihood estimator $\hat{\mathbf{h}}_{ML}$:

$$E = \frac{1}{\mathrm{trace}((\mathbf{X}^T\mathbf{C}_n^{-1}\mathbf{X})^{-1})}. \quad (12)$$

By a similar argument, we find that the efficiency of the *biased* maximum likelihood estimator $\hat{\mathbf{h}}_{\mathrm{BML}}$ is given by

$$E = \frac{1}{\mathrm{trace}(\mathbf{L}(\mathbf{L}^T\mathbf{X}^T\mathbf{C}_\mathbf{n}^{-1}\mathbf{X}\mathbf{L})^{-1}\mathbf{L}^T)}. \quad (13)$$

Observe that the efficiency of the unbiased maximum likelihood estimator depends only on the experimental design, as encoded in the **X** matrix, and the noise covariance, as encoded in the $\mathbf{C}_\mathbf{n}$ matrix. Thus the estimator efficiency is entirely independent of the actual hemodynamic response (this is, in fact, the case for any unbiased estimator). The efficiency of the biased maximum likelihood estimator additionally depends on the assumed HDR subspace, as encoded in the **L** matrix.

Note that the only relevant factors genuinely under the experimenter's control are the sequence and timing of the events (i.e., the **X** matrix), as the noise covariance structure and the HDR subspace are largely governed by the imaging process and the hemodynamic physiology of the subject. An important challenge in event-related fMRI research is thus to determine which experimental designs result in the greatest expected estimation accuracy, given certain constraints such as total imaging time, and minimum interstimulus interval (ISI). The estimator efficiency measure *E* defined above provides an objective criterion for evaluating and optimizing the relative expected accuracy afforded by different experimental designs.

RESULTS AND DISCUSSION

We have previously shown that accurate estimates of the HDRs from different event types can be obtained using event-related fMRI with very rapid presentation, as long as the interstimulus interval is randomized (according to an exponential distribution), rather than kept constant [Burock et al., 1998]. However, others have argued that greater estimation efficiency or statistical power is achieved by using considerably longer ISIs [Cox and Bandettini, 1998; Hutton et al., 1998]. Here, we investigate the effect on estimator efficiency of varying the mean interstimulus interval in fixed and variable ISI designs. Figure 1 shows the efficiency measure *E* for the maximum likelihood HDR estimate for a single-event type or condition as a function of mean ISI, for both variable ISI designs (solid line) and fixed ISI designs (dashed line). For very long mean ISIs (e.g. >20s), variable and fixed ISI designs result in very similar efficiency measures. However, for shorter mean ISIs, the efficiency of variable ISI designs increases dramatically, whereas the efficiency of fixed ISI designs decreases.

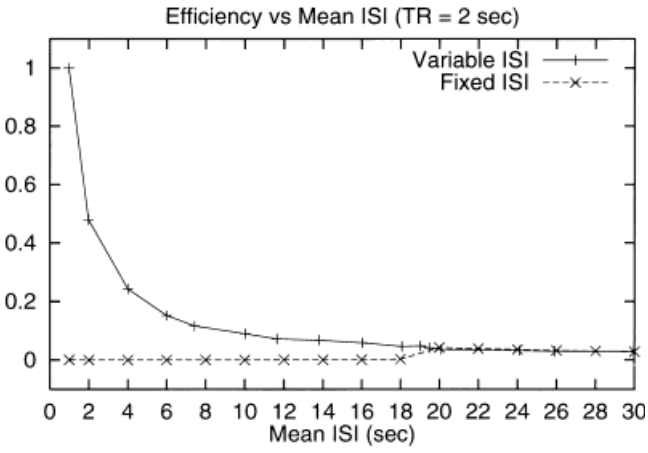

Figure 1.
Relative efficiency of variable and fixed ISI experimental designs is shown as a function of mean ISI. For very long mean ISIs (e.g. >20s), variable and fixed ISI designs result in very similar efficiency measures. For shorter mean ISIs, the efficiency of variable ISI designs increases dramatically, whereas the efficiency of fixed ISI designs decreases. Note that the exact value of the efficiency measure *E* depends on the noise variance at a particular pixel, and thus the relative efficiency measure plotted here is in arbitrary units. The following parameters were used in the simulations: $TR = 2$s, $T_{HDR} = 20$s, $\Delta T_{HDR} = 2$s, $N_{tp} = 128$, $N_c = 1$, $N_h = 10$.

Note that the efficiency of a variable ISI design with a mean ISI of 1 sec is more than 10 times the efficiency of a design with a mean ISI of 20 sec. In other words, one would have to scan >10 times as long (or, alternatively, average 10 times as many subjects) in order to achieve the same estimation accuracy at a mean ISI of 20 sec vs. 1 sec.

It should be noted that since the event sequences in the randomized ISI designs are generated by a stochastic process, the resulting efficiency measures are themselves random variables. This is illustrated in Figure 2, which shows the minimum, maximum, and mean efficiency measure for 10,000 randomly generated designs, assuming four different event types.

As in the one-event-type case shown in Figure 1, the efficiency of variable ISI designs increases with decreasing mean ISI. However, for any particular mean ISI, there is a considerable range of efficiencies. In particular, for long mean ISIs, some of the randomly generated designs result in extremely low efficiency measures. Thus in order to ensure consistently high estimation accuracy for finite-length experiments, one should avoid relying on the asymptotic properties of the stochastic generating process. A significant improve-

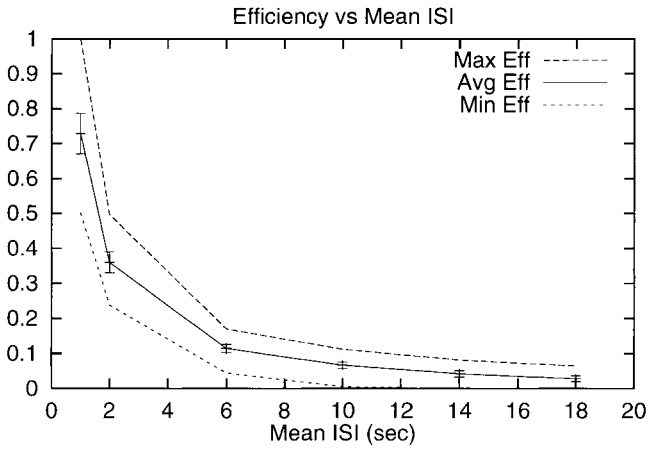

Figure 2.

The minimum, maximum, and mean relative efficiency of 10,000 randomly generated variable ISI designs with four event types are shown as functions of mean ISI (error bars indicate standard deviations). As in the one-event-type case shown in the previous figure, the efficiency of variable ISI designs increases with decreasing mean ISI. However, for any particular mean ISI, a wide range of efficiency measures are observed. This suggests that a considerable improvement in efficiency can be achieved by selecting among multiple, randomly generated experimental designs. The relative efficiency measure is plotted in arbitrary units. The following parameters were used in the simulations: $TR = 2$s, $T_{HDR} = 20$s, $\Delta T_{HDR} = 2$s, $N_{tp} = 256$, $N_c = 4$, $N_h = 10$.

ment typically can be achieved by generating a large number of candidate experimental designs using a stochastic process, and then selecting the one affording the greatest estimator efficiency.

CONCLUSION

We have described a general framework for obtaining efficient estimates of event-related hemodynamic responses using fMRI. In contrast with most existing methods, which assume temporally uncorrelated (white) noise, the current approach allows for an arbitrary temporal covariance structure. Furthermore, efficient unbiased estimates can be obtained for the HDRs with a finer discretization interval (i.e., greater temporal resolution) than the sampling interval (TR) of the fMRI data, provided that the timing of the event sequences is properly randomized. Efficient *biased* estimates of the HDRs can be obtained, in the presence of temporally correlated noise, by restricting the estimated HDRs to a prespecified linear subspace (e.g., defined by a set of basis functions).

Explicit expressions are derived for the relative efficiency of an arbitrary event-related experimental design, for both unbiased and biased estimators. This efficiency measure provides an objective criterion for comparing the relative merits of different estimators and experimental designs. A particularly valuable application of this measure is in the optimization of the timing and sequencing of different events, given specific constraints such as minimum ISI, sampling rate (TR), HDR discretization interval (ΔT_{HDR}), and total imaging time.

The simulation results presented here clearly demonstrate the advantage of using randomized rather than fixed ISI designs in fMRI experiments. Whereas the efficiency of randomized ISI designs increases monotonically with shorter mean ISI, the efficiency of fixed ISI designs falls off dramatically. These simulations, of course, assume that the system can be modeled as linear time-invariant at arbitrarily long or short ISIs. In practice, it is likely that nonlinearities in the underlying neuronal response (due to, e.g., habituation or refractoryness) become pronounced at very short ISIs. Since such non-linear effects are likely to lead to distortions in the estimated HDRs, they may therefore, set a practical limit on the minimal ISIs. This practical lower limit is likely to depend somewhat on the specific sensory or cognitive phenomena of interest, since different brain areas are likely to exhibit different degrees of nonlinear behavior. Such neuronal nonlinearities should, of course, also affect other, more direct correlates of neuronal electrical activity such as EEG and MEG. Thus, it may be possible directly to verify the validity of the assumptions of linearity and time-invariance of the neuronal response by comparing the selectively averaged EEG and/or MEG responses for different ISI ranges for a given experimental design.

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