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Separating Processes within a Trial in Event-Related Functional MRI

I. The Method

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Many behavioral paradigms involve temporally overlapping sensory, cognitive, and motor components within a single trial. The complex interplay among these factors makes it desirable to separate the components of the total response without assumptions about shape of the underlying hemodynamic response. We present a method that does this. Four conditions were studied in four subjects to validate the method. Two conditions involved rapid event-related studies, one with a low-contrast (5%) flickering checkerboard and another with a high-contrast (95%) checkerboard. In the third condition, the same high-contrast checkerboard was presented with widely spaced trials. Finally, multicomponent trials were formed from temporally adjacent low-contrast and high-contrast stimuli. These trials were presented as a rapid event-related study. Low-contrast stimuli presented in isolation (partial trials) made it possible to uniquely estimate both the low-contrast and high-contrast responses. These estimated responses matched those measured in the first three conditions, thereby validating the method. Nonlinear interactions between adjacent low-contrast and high-contrast responses were shown to be significant but weak in two of the four subjects.

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INTRODUCTION

The ability of blood oxygenation level-dependent (BOLD) weighted functional MRI (FMRI) (Ogawa *et al.*, 1990; Kwong *et al.*, 1992) to resolve individual components of responses to an experimental paradigm has steadily improved. Early FMRI studies were restricted to block designs, which measure the time-averaged response to many successive stimuli. Several investigators found, however, that the response to brief stimuli could be measured (Blamire *et al.*, 1992; Savoy *et al.*, 1995; Boynton *et al.*, 1996; Konishi *et al.*, 1996). This response is characterized by a delay lasting roughly 2 s followed by a slow, unimodal response that largely decays in approximately 20 s. Buckner *et al.* (1996) showed that this hemodynamic response to individual stimuli could be reliably detected by averaging the responses to multiple, identical stimuli spaced at intervals of 20 s. This method of widely spaced event-related FMRI made it possible to randomize the presentation of stimuli in a more behaviorally appropriate way.

Unfortunately, this event-related technique reduces the available signal, since fewer events are presented per unit time. Moreover, it limits the type of behavioral paradigms that can be implemented. Two developments resolved these issues. First, Boynton *et al.* (1996) showed that the hemodynamic response in V1 could be modeled as the response of a linear system to a neuronal input and that the kernel of the linear system could be modeled by a gamma function. Second, Dale and Buckner (1997) showed that the responses sum in an approximately linear fashion and that the responses to rapidly presented stimuli could therefore be extracted from the data if the stimulus presentation interval is randomly varied. These results led to the development of rapid event-related FMRI, which models the individual responses to discrete stimuli presented at varying intervals. The intervals can be as short as 1 s (Dale, 1999).

Initial rapid event-related techniques estimated a single response on each trial of a behavioral paradigm (Dale and Buckner, 1997). Many behavioral paradigms, however, involve a series of overlapping sensory, cognitive, and motor processes. For example, in a match-to-sample paradigm that is widely used throughout neuroscience, a subject is shown a sample object, a delay is introduced, and then a test object is presented. The subject's task is to determine whether the test object is the same as the sample object. Different cognitive processes are involved during the temporal evolution of a single trial: encoding the sample information, maintaining that information during the

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delay interval, and matching that information to the test stimulus. Different brain regions may emphasize each process. It is therefore important to separate the signals during the different task intervals. Moreover, information is carried not only by the existence of a hemodynamic response, but also by its shape. For example, areas that encode the sample stimulus should show a relatively transient response while areas that maintain that information over the duration of the delay period should show a more sustained response. Therefore, it is important to estimate these responses without making any prior assumptions about their shape.

Current event-related techniques (Courtney *et al.*, 1997; Zarahn *et al.*, 1997) attempt to separate component responses within a trial by modeling each component with a regressor based on a mathematical model of the hemodynamic response. Several mathematical models have been proposed (Boynton *et al.*, 1996; Clark *et al.*, 1997; Dale and Buckner, 1997; Zarahn *et al.*, 1997; Aguirre *et al.*, 1998; Friston *et al.*, 1998). Since the shape of the hemodynamic response is known to vary across subjects and across regions of the brain (Lee *et al.*, 1995; Buckner *et al.*, 1996; Kim *et al.*, 1997; Schacter *et al.*, 1997; Buckner *et al.*, 1998), the magnitude of activation computed by these methods depends on the accuracy with which they model the hemodynamic response. This is not a problem if the observed BOLD response matches the expectations of the model. However, any deviation from the expected form of the response reduces the estimated magnitude of the response, and large deviations can lead to missed activations. Moreover, if deviations from the model are more pronounced for certain conditions in an experiment (e.g., because those conditions produce changes in the shape of the response that are not accurately modeled), then the magnitude of the response for these conditions will be underestimated, producing a biased analysis that incorrectly characterizes the effect of task variables on the BOLD response.

We show here that successive hemodynamic responses can be estimated without making shape assumptions by mixing *compound* trials with *partial* trials. We define compound trials as trials that elicit two or more distinct responses with starting points separated by fixed intervals. Partial trials elicit only an initial subset of these responses. The interval between successive trials of either type is randomly varied. The time courses of the responses to each component of the compound trial can then be estimated using a linear model. We call such studies *compound event-related* studies. In this paper, we present the method and evaluate it in a study of four subjects. Methods for analyzing the resulting time courses are presented in a companion paper (Ollinger *et al.*, 2001).

METHODS

Estimation of Time Courses

The first step in the analysis is to estimate each point of each BOLD response. If the trials are widely spaced, this is equivalent to simply averaging across trials. In the more general case of rapidly presented trials (Buckner *et al.*, 1996), the general linear model (Friston *et al.*, 1995; Petersson *et al.*, 2000) can be used. This approach models the data at each point as the sum of one or more effects. For a given voxel, this leads to the expression for the data at time i of $y_i = a_{i,0}b_0 + a_{i,1}b_1 + \ldots + a_{i,M-1}b_{M-1} + \epsilon_i$, where b_m is mth variable to be estimated, $a_{i,m}$ is a weight that relates it to the data at time i, ϵ_i is random noise, and M is the number of modeled effects. The sample times i correspond to the acquisition of single volumes at intervals given by the repetition time (TR). This equation is usually written in matrix form as $Y = \boldsymbol{A}\boldsymbol{b} + \underline{\epsilon}$, where Y is the observed data, $\boldsymbol{b}$ is a vector of effects being modeled, $\underline{\epsilon}$ is a vector of noise samples, and $\boldsymbol{A}$ is the *design matrix* of coefficients relating the modeled parameters to the observed data. Time courses can be estimated by appropriately defining the design matrix and then inverting the model using the relationship $\hat{\boldsymbol{b}} = (\boldsymbol{A}^T\boldsymbol{A})^{-1}\boldsymbol{A}^T\boldsymbol{Y}$ (Beck and Arnold, 1977). As illustrated in Fig. 1, this is done by placing a one in the row corresponding to the time at which each image is acquired and in the column corresponding to the appropriate point of the hemodynamic response. Inverting the model yields estimates of the time course at each point. In mathematical terms, this method uses a basis set consisting of delayed delta functions, one for each point in the BOLD response. This basis set spans the space of all possible responses and is therefore insensitive to changes in the shape of the response. It only assumes that the same BOLD response is measured for each trial of the same type. The model can be solved if the portion of the design matrix corresponding to the estimated time courses (the effects of interest) has full rank, i.e., if no column of the design matrix can be expressed as the weighted sum of any other set of columns.

Linear models are applied to compound trials as shown in Fig. 2. In this example, each trial consists of the sequential presentation of two stimuli. For the sake of exposition, we assume that this is a match-to-sample paradigm where the compound trials consist of a sample stimulus followed two TRs later by the test stimulus. The hemodynamic response to these stimuli is given by $h(t)$. The trial is repeated every nine TRs. Averaging across trials yields an estimate of the average BOLD time course $y(t)$. An equation can be written that relates each measurement of this average to the sum of the hemodynamic responses occurring at that

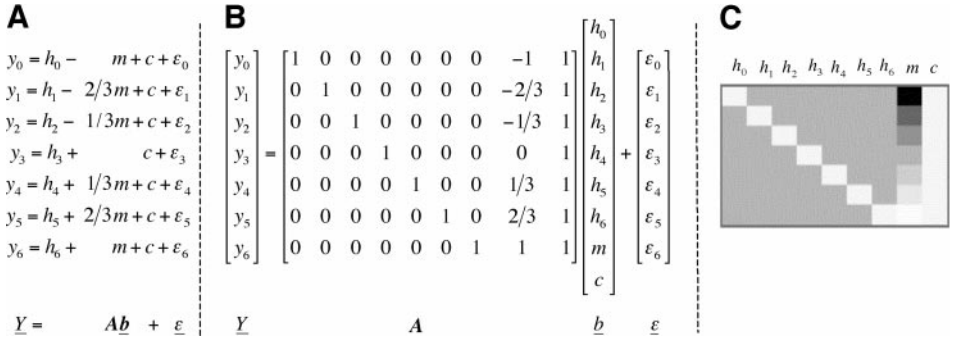

FIG. 1. Three representations of the linear model for a mock experiment with a single stimulus followed by the acquisition of a time series of data consisting of seven points. The model includes the hemodynamic response and a linear trend. (A) Basic equations relating the observed data y at point i to the hemodynamic response (h), a linear trend (slope m and intercept c), and the noise (ϵ). The matrix form of this equation is shown at the bottom of A. This matrix representation is expanded in B to show the definition of the design matrix. Since the dimensions of the design matrix are usually large (with hundreds to thousands of rows), it is represented pictorially in C, where each matrix element is represented by a rectangular block of pixels whose magnitude is represented by a gray level. The columns of this image represent the effects in the model while the rows represent volumes of measured data.

time. As shown in Fig. 2A, this approach yields nine equations and 14 unknowns, so a unique estimate of the time courses cannot be found.

The number of equations can be increased as shown in Fig. 2B. Here, the sample stimulus is presented every seven TRs, but the test stimulus is omitted after alternate samples to form partial trials. The measured time course can be averaged again, this time over each pair of compound trials and partial trials. This approach yields 14 equations and 14 unknowns, so the time courses can be uniquely estimated. In general, the time courses can be separated if there are enough independent equations to uniquely estimate each point in each time course.

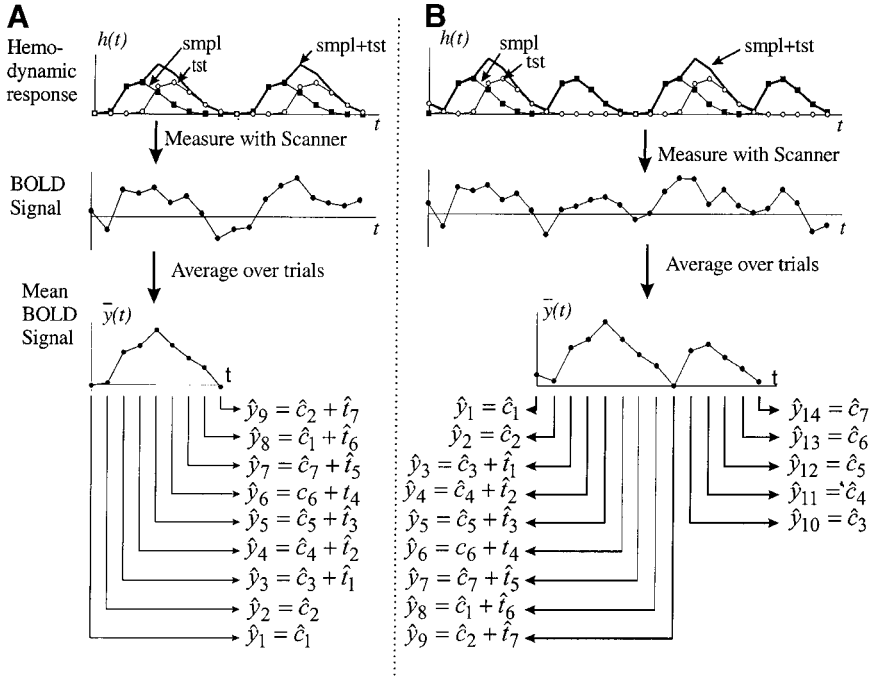

FIG. 2. Diagram showing the analysis of data from a match-to-sample study without partial trials (A) and a study with partial trials (B). The top row shows the underlying hemodynamic response $h(t)$, where t is time, the second row shows the measured BOLD response, and the third row shows the average BOLD response to a single trial $\bar{y}(t)$. Each trial consists of two stimuli, the sample (smpl) and the test (tst). The sample stimulus is presented at seven TR intervals. In A, every presentation of the sample is followed two TRs later by the presentation of test stimulus. This yields data representing nine unique combinations of the sample and test responses, i.e., 9 equations and 14 unknowns. Therefore, the time courses cannot be uniquely estimated. In B, partial trials are created by omitting the test stimulus after every other presentation of the sample. This yields five additional unique combinations of the sample and test responses, i.e., 14 equations and 14 unknowns. Therefore, the time courses can be uniquely estimated.

Two modifications to this simple paradigm are required in practice. First, behavioral and statistical power considerations make it desirable to space the compound trials closely together. Therefore, we present the trials rapidly so that the responses to successive compound trials overlap. This requires that we vary the intertrial interval in order to estimate the time courses (Dale and Buckner, 1997). Second, the partial trials are randomly interspersed among the compound trials. It is critically important that subjects are unable to predict whether a trial is going to be a compound or partial trial. Mixing the partial and compound trials increases the likelihood that most of the cognitive processes during a partial trial are the same as the cognitive processes during the first component of a compound trial.

The method can be summarized as follows. The experimental paradigm must consist of two types of trials: compound trials where all hemodynamic responses occur at fixed intervals with respect to each other and partial trials in which only the initial subset of responses occur. The intertrial intervals among all trial types should be varied over a range of values for behavioral and statistical reasons. Partial trials are inserted randomly in the paradigm. The optimum fraction of partial trials and the optimum range of intertrial intervals are determined from statistical considerations as discussed below.

The baseline of the estimated BOLD responses depends on the details of how the experimental paradigm is coded into the design matrix. If the entire design matrix has full rank and the regressors for the effects of interest are nonnegative, the baseline is represented by the intercept term of the linear trend. The estimated time courses represent departures from this baseline and therefore have a mean starting value of zero. Intuitively, the baseline represents the control state of the experiment, i.e., the state of the brain when none of the transient effects in the model is present. For example, if a fixation crosshair is present at all times except during task presentations, the baseline represents the mean, non-BOLD signal plus whatever BOLD response the fixation point elicits.

The interpretation of the baseline changes if there is a single dependency among the columns in the design matrix. This usually occurs when the sum across a subset of the columns representing the effects of interest is equal to the sum across a subset of the columns representing mean values. In this case, the design matrix does not have full rank but the model can still be uniquely inverted if a constraint is added. This is done by adding a constant to the effects of interest at each row such that their sum is zero. The baseline now becomes the mean of the BOLD signal (rather than the "resting" state), so each estimated time course has a nonzero starting point.

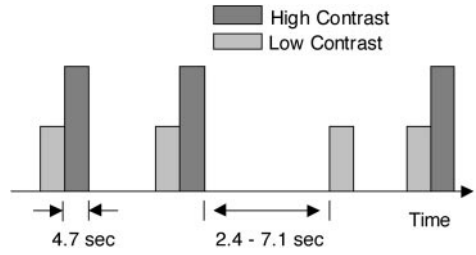

FIG. 3. The mixed trial paradigm. In compound trials, low-contrast (5% contrast ratio) and high-contrast (95% contrast ratio) stimuli were presented in consecutive, 7.1 s intervals. Twenty-five percent of the trials were partial trials in which only the low-contrast stimulus was presented. The interval between trials was randomly varied among 2.4, 4.7, and 7.1 s (one, two, and three TRs).

Experimental Methods

Four subjects were studied to characterize the method.

Subjects

Subjects were recruited from the Washington University community in return for payment. All were right-handed, had normal or corrected-to-normal vision, and reported no history of significant neurological problems. Subjects provided informed consent in accordance with the guidelines set by the Washington University Human Studies Committee.

Stimuli

Five-hertz flickering checkerboards were presented bilaterally (the checkerboards were 40° "wedges" presented at an eccentricity of 3 to 7°) at two contrast levels. The low-contrast stimulus had a 5% contrast and the high-contrast stimulus had a 95% contrast. Stimuli were presented for durations of 4.72 s (two TRs, where the TR is 2.36 s). The stimuli were presented in four distinct experimental designs to each subject. In the first, the high-contrast stimulus was presented in a widely spaced event-related paradigm with ITIs of 14.2 s. In the second design, the high-contrast stimuli were presented in a rapidly presented ER paradigm with the ITIs uniformly distributed across intervals of 2.4, 4.7, and 7.1 s. These ITIs correspond to stimulus-onset asynchronies of 7.1, 9.4, and 11.8 s. The third design had the same timing as the second but used the low-contrast stimulus rather than the high-contrast stimulus. The fourth design was a compound event-related design consisting of 75% compound trials and 25% partial trials as shown in Fig. 3. The compound trials consisted of a low-contrast stimulus for 4.7 s followed immediately by a high-contrast stimulus lasting 4.7 s. The partial trials consisted of only the low-contrast stimulus. The ITIs were uniformly distributed with values of 2.4, 4.7, and 7.1 s. Scans of the four designs were randomly intermixed.

Stimuli were presented using a Power Macintosh computer and an LCD projector (Sharp, Model XGE850), which projected stimuli on a screen placed at the head of the bore. The screen was viewed through a mirror attached to the head coil.

Image Acquisition

FMRI scans were collected on a Siemens 1.5-Tesla Vision system, using an asymmetric spin-echo echo-planar sequence sensitive to BOLD contrast [TR = 2.36 s, readout delay (for BOLD weighting) of 50 ms, flip angle = 90°] (Ogawa *et al.*, 1990). During each scan, 128 volumes of 16 contiguous 8-mm axial slices were acquired at a 3.75 × 3.75-mm in-plane resolution, allowing complete brain coverage at a high signal-to-noise ratio (Conturo *et al.*, 1996). Functional images were acquired parallel to the AC–PC plane in each subject after prescribing slice position based on automatic measurements of rotation, translation, and tilt of the initial images to an average (n = 12) MP-RAGE anatomical image (target) representation of the atlas of Talairach and Tournoux (1988). Structural images were acquired using a sagittal MP-RAGE sequence, optimized for contrast-to-noise ratio and resolution (Epstein *et al.*, 1994) (repetition time TR = 9.7 ms, echo time TE = 4 ms, flip angle = 12°, inversion time TI = 300 ms).

Nonlinearities

If the brain were a linear system, two presentations of the same stimulus with the second presentation delayed by δ sampling intervals would elicit a response at sample k of $y_k = h_k + h_{k-\delta}$, where h is the response to a single stimulus presented in isolation. If the brain were nonlinear, the response would be different by an amount that depends on other stimuli that have been presented in the recent past. If we assume that this dependence is zero for responses that have largely decayed (which we will assume to have occurred in 20 s), we can write the response of a nonlinear system with two concurrent responses as $y_k = h_k + h_{k-\delta} + g_{k,k-\delta}$, where $g_{k,k-\delta}$ is the effect of the first stimulus, presented at time $k - \delta$ on the response to the second stimulus presented at time k. We refer to these terms, $g_{k,k-\delta}$, as interaction terms. If we assume that the BOLD response decays after eight TRs (18.9 s), there would be 64 possible interactions between two hemodynamic responses and 512 interactions among three responses. These interaction terms can be estimated with a linear model. We hypothesize that these terms should account for a statistically significant portion of the variance if there is a significant degree of nonlinearity in the hemodynamic response.

We tested this hypothesis by including these interaction terms in the design matrix and then using the extra sum of squares principle to compute an F statistic over activated voxels in V1. The large number of possible interaction terms led us to use a two-stage approach. First, we combined the data from the widely spaced high-contrast design and the rapidly presented high-contrast design and then tested the significance of the interaction terms in the region drawn over V1. Significance ($P < 0.5$) would imply the presence of interactions among overlapping high-contrast responses. If these interaction terms were not significant ($P > 0.05$), we assumed that interactions among the low-contrast responses would also be nonsignificant. We then jointly analyzed the data from all four designs with interaction terms included for overlapping low-contrast and high-contrast responses. Again, an F test was used to test for interactions among the low- and high-contrast responses.

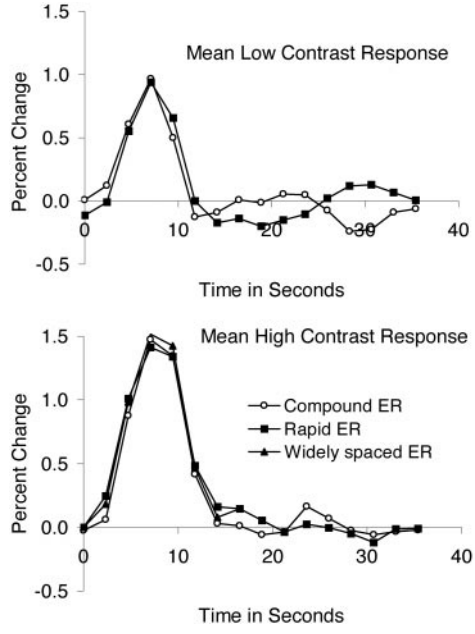

FIG. 4. Mean time courses for responses to low-contrast stimuli (top) and high-contrast stimuli (bottom) as estimated from rapid event-related designs, a compound event-related design, and a widely spaced event-related design.

RESULTS

Time Courses

For each subject, regions of interest were formed from the voxels activated along the calcarine sulcus. Estimated time courses averaged across subjects are shown in Fig. 4. The time courses measured with the compound event-related design match those measured with rapid event-related designs for both the low-contrast and high-contrast stimuli. This concordance is noteworthy given that the high-contrast response is always measured as a sum with the low-contrast response for the condition involving compound trials. It

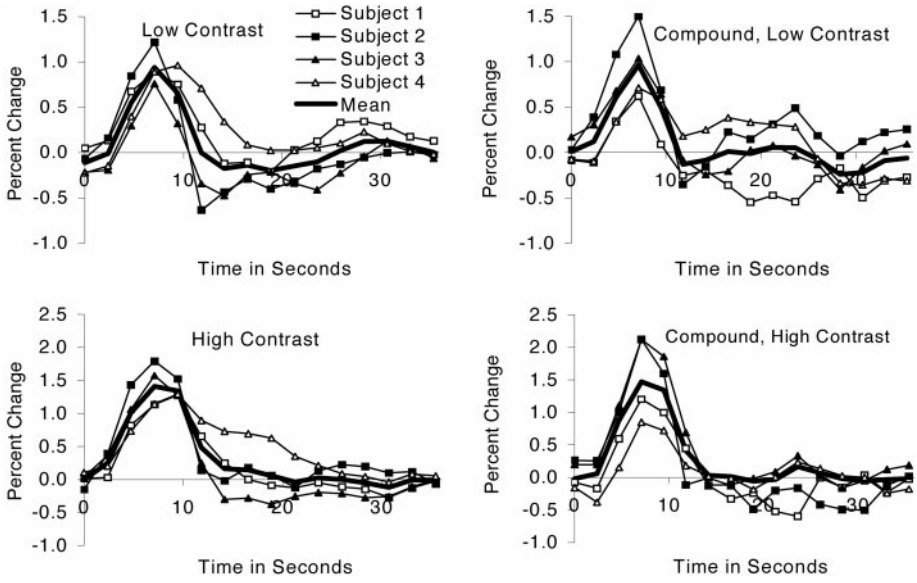

FIG. 5. Low-contrast and high-contrast time courses for all subjects. The means across subjects are shown by thick lines.

is also of interest that the time courses estimated with widely spaced trials match well those estimated with closely spaced trials. Figure 5 shows that the time courses vary significantly both across subjects and between the compound and single-component experiments within a subject. It is striking that the mean time courses converge to the same shape with only four subjects. This is consistent with other results in our laboratory (Miezin *et al.*, 2000). Notice also the absence of noise spikes in the estimated time courses. The correlation among the time points discussed in Ollinger *et al.* (2001) causes this "smooth" noise. As one would expect, this correlated noise averages out across subjects.

Nonlinearity

The interaction terms used to model nonlinearities between overlapping high-contrast responses were not significant at the $P = 0.05$ level as shown in Table 1. This lack of significance led us to assume that there were also no appreciable nonlinear interactions among low-contrast responses. Using this assumption, we combined all of the data from a given subject into a single model to test the significance of interactions between the low-contrast and high-contrast components of the compound trials. The interaction terms were significant for two subjects, s2 and s4, with P values of 0.033 and 0.028. These two subjects had the least typical time courses and the lowest z scores. These results suggest that nonlinearities are present, at least in some individuals. Two facts suggest that they are not an important confound in the presence of much more highly significant activations. First, although significant, the nonlinear terms were modest in magnitude; and second, for the high-contrast stimulus, the time courses that were estimated from widely spaced trials closely match those estimated from rapidly presented and compound trials as shown in Fig. 4.

DISCUSSION

This study demonstrates that the hemodynamic responses to contiguous stimuli can be accurately separated without making assumptions about the shape of the response. The time courses for both the low- and high-contrast checkerboards estimated from the compound design closely matched those estimated from the rapidly presented design. This correspondence is par-

TABLE 1

F Statistics Averaged over V1 and Their Corresponding *P* Values for the Analysis of Nonlinearities

	High-contrast/high-contrast interaction		Low-contrast/high-contrast interaction	
	F	*P* value	*F*	*P* value
Subject 1	$F(16,672) = 1.23$	0.238	$F(33,1343) = 1.03$	0.428
Subject 2	$F(16,440) = 1.28$	0.208	$F(31,1229) = 1.53$	0.033
Subject 3	$F(16,672) = 1.19$	0.267	$F(34,1806) = 1.28$	0.134
Subject 4	$F(16,672) = 1.04$	0.411	$F(34,1902) = 1.52$	0.028

Note. *F* statistics were computed using the extra sum of squares principal to test whether the interaction terms accounted for a significant fraction of the variance. The high-contrast/high-contrast interaction used the data from both high-contrast experiments to test interactions between successive high-contrast responses. The low-contrast/high-contrast interaction used all of the data to test interactions between overlapping low-contrast and high-contrast responses.

ticularly impressive for the high-contrast checkerboard, since for the compound trials the high-contrast checkerboard only occurred adjacent in time to the low-contrast checkerboard. This technique should therefore be valuable in separating task-related or cognitive processes that occur in different time intervals, such as separating the response to an attentional cue from the subsequent modulation produced by that cue in a test stimulus. More generally, this technique can separate processes involved in task preparation from those involved in task execution.

The correspondence of the time courses for the high-contrast checkerboards between the rapidly presented and compound trial studies also implies that any nonlinear low-contrast/high-contrast interactions on compound trials were small in magnitude. The statistical analysis indicated that this effect was weak but significant ($P < 0.05$) in two of the four subjects. Furthermore, the estimated time course for the high-contrast checkerboard was very similar whether the trials were widely or closely spaced, which indicates that any nonlinear interactions were small in magnitude. No subject showed significant high-contrast/high-contrast interactions in the high-contrast study, where ITIs ranged from 2.4 to 7.1 s (one to three TRs).

Miezin *et al.* (2000) have shown that closely spaced event-related designs yield magnitudes roughly 17% lower than widely spaced designs. This study, however, used a flickering checkerboard with a 95% contrast ratio for all trials, while the low-contrast trials used here had a contrast ratio of only 5%. Therefore, the weakness of low-contrast/high-contrast interactions in the present study suggests that the degree of nonlinearity is dependent on the intensity of the stimulus. The absence of high-contrast/high-contrast interactions in the present study may reflect a different factor. The current study used a uniform distribution of ITIs (2.4–7.1 s), while the Miezin *et al.* study used an exponential distribution that emphasized shorter ITIs. It is possible that nonlinearities may be produced when a series of trials involving short ITIs (e.g., <3 s) allows several hemodynamic responses to accumulate.

The analysis presented here differs from that of Buckner *et al.* (1998) in that the fixation task is not explicitly coded. In that work, the stimulus paradigm was required to be counterbalanced such that each ordering of sequential tasks was repeated an equal number of times. The time course could then be extracted by taking the difference of the task and fixation time courses. This constraint cannot be met by multicomponent trials and indeed is not necessary in general. We assume that the subject is always engaged in a "control task" when not performing the experimental task. Activations due to this control task are therefore part of the baseline signal, which is implicitly estimated as part of the mean, and the activations are modeled as departures from this baseline. Therefore, the control task never appears explicitly in the design matrix. This approach can be extended to experiments with more than one control task by blocking the control tasks, modeling these control states as a block effect, and then defining activations as departures from the appropriate control state. It is still necessary, however, to model one control state as a baseline state to obtain an invertable design matrix.

In summary, the proposed method can be used to separate the hemodynamic responses to neural events that occur in a fixed sequence within a compound trial without making any assumptions about the shape of the hemodynamic response. The only restriction is that the experimental paradigm includes partial trials that are cognitively equivalent to the initial stage of the compound trials. This result is significant for two reasons. First, the shape of the BOLD response is known to vary across the brain and across subjects, so shape assumptions confound these variations with variations in the response magnitude. This biases the relative importance of different responses. Second, these variations are sometimes related to the underlying pattern of neuronal activity. Analyses that account for variations in shape may lead to different conclusions about the function of an area than analyses that assume a shape (Shulman *et al.*, 1999; Corbetta *et al.*, 2000).

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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.

Beck, J. V., and Arnold, K. J. 1977. *Parameter Estimation in Engineering and Science.* Wiley, New York.

Blamire, A. M., Ogawa, S., Ugurbil, K., Rothman, D., *et al.* 1992. Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **89:** 11069–11073.

Boynton, G. M., Engel, S. A., Glover, G. H., and Heeger, D. J. 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci.* **16**(13): 4207–4221.

Buckner, R. L., Bandettini, P. A., O'Craven, K. M., Savoy, R. L., *et al.* 1996. Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging [see comments]. *Proc. Natl. Acad. Sci. USA* **93**(25): 14878–14883.

Buckner, R. L., Goodman, J., Burock, M., Rotte, M., *et al.* 1998. Functional–anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. *Neuron* **20**(2): 285–296.

Clark, V. P., Maisog, J. M., and Haxby, J. V. 1997. FMRI studies of face memory using random stimulus sequences. *NeuroImage* **5:** S50.

Conturo, T. E., McKinstry, R. C., Akbudak, E., Snyder, A. Z., *et al.* 1996. Sensitivity optimization and experimental design in functional magnetic resonance imaging. *Soc. Neurosci. Abstr.* **22:** 7.

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., *et al.* 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat. Neurosci.* **3**(3): 292–297.

Courtney, S. M., Untergeider, L. G., Keil, K., and Haxby, J. V. 1997. Transient and sustained activity in a distributed neural system for human working memory. *Nature* **386:** 608–611.

Dale, A. M. 1999. Optimal experimental design for event-related fMRI. *Hum. Brain Mapp.* **8**(2–3): 109–114.

Dale, A. M., and Buckner, R. L. 1997. Selective averaging of rapidly presented individual trial using fMRI. *Hum. Brain Mapp.* **5:** 1–12.

Epstein, F. H., Mugler, J. P. I., and Brookeman, J. R. 1994. Optimization of parameter values for complex pulse sequences by simulated annealing: application to 3D MP-RAGE imaging of the brain. *Magn. Reson. Med.* **31:** 164–177.

Friston, K., Holmes, A., Worsley, K., Poline, J., *et al.* 1995. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2:** 189–210.

Friston, K. J., Josephs, O., Rees, G., and Turner, R. 1998. Nonlinear event-related responses in fMRI. *Magn. Reson. Med.* **39**(1): 41–52.

Kim, S. G., Richter, W., and Ugurbil, K. 1997. Limitations of temporal resolution in functional MRI. *Magn. Reson. Med.* **37**(4): 631–636.

Konishi, S., Yoneyama, R., Itagaki, H., Uchida, I., *et al.* 1996. Transient brain activity used in magnetic resonance imaging to detect functional areas. *NeuroReport* **8**(1): 19–23.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., *et al.* 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. USA* **89:** 5675–5679.

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**(6): 745–754.

Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., *et al.* 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.

Ogawa, S., Lee, T. M., Kay, A. R., and Tank, D. W. 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc. Natl. Acad. Sci. USA* **87:** 9868–9872.

Ollinger, J. M., Shulman, G. L., and Corbetta, M. 2001. Separating processes within a trial in event-related functional MRI. II. Analysis. *NeuroImage* **13:** 218–229.

Petersson, K. M., Nichols, T. E., Poline, J. B., and Holmes, A. P. 2000. Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. *Phil. Trans. R. Soc. London* **354:** 1261–1281.

Savoy, R. L., Bandettini, P. A., O'Craven, K. M., Kwong, K. K., *et al.* 1995. Pushing the temporal resolution of fMRI: Studies of very brief visual stimuli, onset variability and asynchrony, and stimulus-correlated changes in noise. *Proc. Soc. Magn. Reson. Third Sci. Meeting Exhibition* **2:** 450.

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

Shulman, G. L., Ollinger, J. M., Akbudak, E., Conturo, T. E., *et al.* 1999. Areas involved in encoding and applying directional expectations to moving objects. *J. Neurosci.* **19**(21): 9480–9496.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotaxic Atlas of the Human Brain.* Thieme Medical Publishers, New York.

Zarahn, E., Aguirre, G., and D'Esposito, M. 1997. A trial-based experimental design for fMRI. *NeuroImage* **6:** 122–138.