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Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI

Marc A. Burock,[1,2] Randy L. Buckner,[3] Marty G. Woldorff,[4] Bruce R. Rosen[1] and Anders M. Dale[1,CA]

[1]Massachusetts General Hospital, Nuclear Magnetic Resonance Center, Bldg 149, 13th Street, Charlestown, MA 02129; [2]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02129; [3]Washington University, Department of Psychology, St. Louis, MO 63130; [4]University of Texas Health Science Center, Research Imaging Center, San Antonio, TX 78284, USA

[CA]Corresponding Author

PREVIOUS studies have shown that hemodynamic response overlap severely limits the maximum presentation rate with event-related functional MRI (fMRI) using fixed intertrial experimental designs. Here we demonstrate that the use of randomized experimental designs can largely overcome this limitation, thereby allowing for event-related fMRI experiments with extremely rapid presentation rates. In the first experiment, fMRI time courses were simulated using a fixed intertrial interval design with intervals of 16, 3, and 1 s, and using a randomized design having the same mean intertrial intervals. We found that using fixed intertrial interval designs the transient information decreased with decreasing intertrial intervals, whereas using randomized designs the transient information increased with decreasing mean intertrial intervals. In a second experiment, fMRI data were collected from two subjects using a randomized paradigm with visual hemifield stimuli presented randomly every 500 ms. Robust event-related activation maps and hemodynamic response estimates were obtained. These results demonstrate the feasibility of performing event-related fMRI experiments with rapid, randomized paradigms identical to those used in electrophysiological and behavioral studies, thereby expanding the applicability of event-related fMRI to a whole new range of cognitive neurosciences questions and paradigms. *NeuroReport* 9: 3735–3739 © 1998 Lippincott Williams & Wilkins.

Key words: Event-related; fMRI; Hemodynamic response; Overlap; Rapid presentation; visual stimulation

Introduction

Event-related functional MRI (fMRI) procedures allow different trial types to be randomly intermixed for mapping brain function.[1] Such procedures greatly increase the flexibility of fMRI by allowing for trials to occur in unpredictable sequences, for the response to rare event types to be selectively extracted and examined, and for *post-hoc* trial sorting based on subject performance. An open question is how rapidly individual trials can be presented in event-related paradigms and still provide a powerful procedure for fMRI brain mapping. Rapid presentation allows for designs that are exactly matched to typical behavioral and electrophysiological studies. It also allows for improved statistical power, by increasing the number of event-related responses to be averaged per unit of time.

The main limitation in presenting separate events in rapid succession is that the hemodynamic response, which is the basis of blood oxygenation level-dependent (BOLD) contrast fMRI, is delayed in onset and evolves over an extended time period of 10–12 s, even for brief neuronal events.[2] One solution is to space the trials sufficiently far apart so that the hemodynamic responses to sequential events do not overlap.[3,4] This solution is not optimal in that it severely restricts the choice of experimental paradigms for event-related fMRI; it also greatly limits the number of trials available for averaging. On the other hand, if trials are presented at shorter, fixed intertrial intervals, overlap across trials can diminish the ability to detect signal changes.[5,6] It has therefore been argued that the 'optimal' intertrial interval for event-related fMRI experiments is 12–16 s.[5,6] This analysis, however, was based on using fixed intertrial interval experimental paradigms.

Here, we demonstrate that by using randomized experimental designs, it is possible to overcome the overlap problem, even for very rapid mean presentation rates. Accurate, overlap-free estimates of the event-related fMRI response to different trial types are obtained using simple selective averaging methods.[7]

Materials and Methods

Simulations: The simulated BOLD fMRI time course was assumed to be the output of a linear time-invariant system.[7–9] We used an empirically measured hemodynamic response elicited by a 1 s checkerboard as the impulse response function of the model. Stimulus presentation sequences were generated using two different presentation paradigms, fixed and randomized. In the fixed paradigms, stimuli were presented at fixed intertrial intervals of 16, 3 and 0.5 s. In the randomized paradigms, stimulus presentation timing was randomized by randomly interleaving the stimuli of interest with 'non-events.' Non-events are randomized points in time in the stimulus sequence at which there is no stimulus event and which presumably do not evoke a hemodynamic response (e.g. maintaining a fixation point in a visual experiment, see below). For the random design, the randomization interval was chosen such that the mean presentation rate for the events of interest was the same as that for the fixed interval experiment. An estimate of the hemodynamic response for the fastest randomized stimuli was computed by subtracting the event-related average for the non-event trials from that of the average for the event-of-interest trials.[7] (see below for further explanation).

MR methods: Imaging was performed on a 3.0 T General Electric scanner with an echo-planar imaging upgrade (Advanced NMR Systems, Wilmington, MA) and a custom-designed bilateral quadrature surface coil. Visual stimuli were presented to the subject using a PowerMacintosh (Apple Computer) connected to a Sharp 2000 color LCD projector. Images were projected through a collimating lens (Buhl Optical) onto a screen mounted within the magnet bore. For each subject, slices were selected for the functional and anatomical echo-planar acquisitions such that five 7 mm slices were positioned perpendicular to the calcarine cortex. A T1-weighted inversion-recovery echo-planar image was acquired for anatomic alignment (TR = 22 s, TI = 1100 ms, 1.5625 mm in-plane resolution). T2*-weighted functional images were acquired using a gradient echo sequence (TR = 1 s, TE = 50 m, $\alpha = 90°$, 3.125 mm in-plane resolution). Functional images were acquired within runs of 290 timepoints.

Empirical: The event-related stimulus paradigm consisted of three event types: left-hemifield checkerboard, right-hemifield checkerboard, and fixation (i.e., the 'non-event'). The duration of each hemifield trial was 250 ms (one phase change of an 8 Hz counterphased flickering checkerboard), and the randomization intertrial interval was 500 ms. Note that the fixation dot is present at all times, and thus no change in the visual stimulus occurs during the fixation event. The presentation of the events was randomized as described above; at any interval there was an equal probability of presentation among the three event types. In a slight variation on this experimental design, we presented 250 ms full-field, right-hemifield, and fixation trials, with an intertrial interval of 500 ms.

We analysed the data by computing the event-related average for each trial type, where the elements of each average were the 20 s segments of the measured fMRI timecourses time-locked to the onset of their respective event types.[7] We subtracted the event-related average of the fixation events from the left- and right-hemifield event averages to compute estimates of the hemodynamic responses to these stimuli. These estimates were corrected for a small bias due to imperfect randomization.[10,11] Activation maps were calculated using the t-statistic for event-related averages.[7]

Note that in order to simplify the analysis and discussion, the statistical analysis methods used here assume temporally uncorrelated (white) noise, while actual fMRI data are known to be temporally correlated.[12] Although such correlations do not bias the response estimates, they may result in an increased false positive rate.[13] More accurate statistics and response estimates can be obtained by correcting for the observed noise correlations, as described in Ref. 10. Note also that the present analysis assumes a linear time-invariant model for the fMRI signal. Although several studies have provided evidence for the linearity of the hemodynamic response,[7,12] some subtle departures from linearity have also been observed.[7,14] In a separate study investigating the effect of such non-linearities on the hemodynamic response estimates using rapid presentation, randomized event-related designs and analysis, we found that the estimates were largely insensitive to the kinds of long time-scale non-linearities that have been observed.[11]

Results

Simulations: The difference between fixed interval and randomized experimental designs is illustrated in Fig. 1. Figure 1A shows the simulated time course for the fixed interval event-related design, assuming no noise. The intertrial interval was 16 s for the first 144 s block, 3 s for the second 144 s, and 1 s for the final 144 s block. Only small variations are apparent in the signal during the 3 s intertrial interval block, and the response shows no variation at all during the final block. Thus, there is essentially no information during

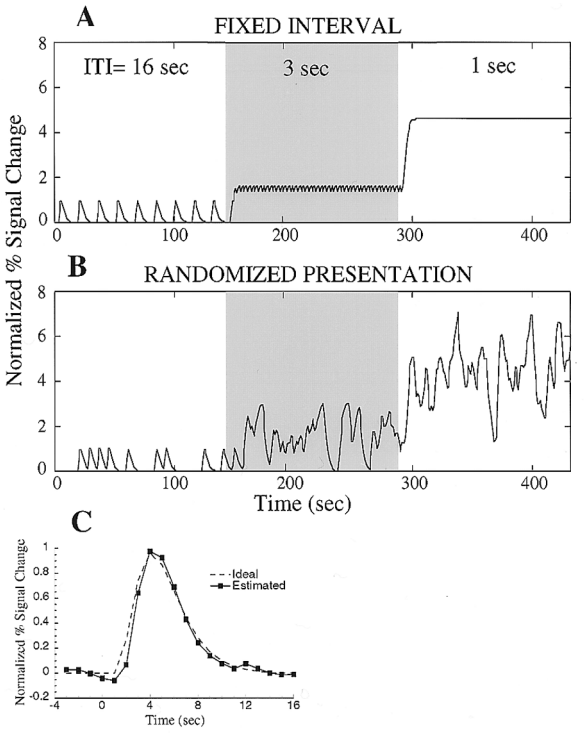

FIG. 1. Simulated time courses for fixed interval and randomized presentation designs assuming a linear hemodynamic response model. (**A**) Results for the fixed interval simulation experiment. The time course is presented in three 144 s blocks: 16 s, 3 s and 1 s intertrial intervals, respectively. There is no overlap during the first block because the settling time of the hemodynamic response is < 16 s. During the second block, the transient information (the variance of the signal) is significantly decreased by overlap, and only a small amplitude sinusoidal signal is observed. For the last 1 s intertrial block the variance in the response goes to zero. (**B**) Results for the randomized design simulation experiment, using the same mean intertrial intervals during each epoch as in (A). In contrast to (A), the transient information in the signal increases as the presentation rate increases. (**C**) Model estimate of the event-related hemodynamic response (solid squares) for 200 s of the randomized design used in the third block of (B), overlaid with the ideal response (dashed).

the 1 s intertrial interval epoch by which to estimate the underlying hemodynamic response. Figure 1B shows the simulated timecourse for the randomized event-related design. The first 144 s block is similar to that of the fixed interval design in that the individual hemodynamic responses are resolvable, but there are clear differences at the faster rates. The variations in the signal around the mean level continue to increase as the randomized mean interval is decreased to 3 s and then 1 s. The estimated hemodynamic response for the fastest rate in the randomized design is shown in Fig. 1C. The estimate is nearly identical to the underlying response except for some slight deviations due to imperfect randomization. It should be noted that for the corresponding fixed interval design no meaningful estimate of the hemodynamic response could be computed.

Empirical: A typical activation map and the estimated hemodynamic response functions are shown in Fig. 2 for one slice in one subject. The clear hemisphere-specific activation is in agreement with activation reported in previous block-paradigm experiments.[15] The averaged hemodynamic responses in Fig. 2B and D were computed over voxels with significance $p < 10^{-7}$. As expected, the hemifield stimuli evoked positive BOLD responses in the contralateral occipital cortex. The transient hemodynamic response to the 250 ms visual stimuli was very similar in general shape to that of the 1 s checkerboard stimuli reported in previous studies.[7] In particular, the hemodynamic response was delayed by ~2 s, peaked at around 4 s for both hemispheres, and returned to baseline around 12 s after stimulus onset. The prestimulus baselines of the event-related responses were relatively flat, indicating that the overlap from adjacent trials had been successfully removed.

Note that although the inter-trial interval was 500 ms in this experiment, the mean interval between subsequent stimulations of a particular part of the visual field (i.e. left or right hemifield) was 1500 ms. In a slight variation on this experiment, we randomized 250 ms trials of full-field, right hemifield, and fixation, with an intertrial interval of 500 ms. In this case, the mean intervals between subsequent stimulations of the right and left visual hemifields were 750 ms and 1500 ms, respectively. Statistical activation maps for full-field *vs* fixation, right hemifield *vs* fixation, and full-field *vs* right hemifield trials are shown in Fig. 3. Note that robust activation of visual cortex contralateral to the stimulus is observed even at this rapid rate.

Discussion

The conventional practice in event-related fMRI experiments is to present trials of the same type at a fixed intertrial interval; however, recent studies have found that such paradigms impose upper limit restrictions on the presentation rate because of decreased statistical power.[5,6] The benefit of random presentation over fixed interval presentation can be easily understood by considering the simulation results in Fig. 1. As the presentation rate increases in the random design, the variance in the signal increases, thereby increasing the transient information and the ability to estimate the underlying hemodynamic response. Conversely, for the fixed interval design, the variance of the signal decreases as the rate increases until there is no transient information in the signal. Meaningful estimation of the hemodynamic response becomes impossible. Additionally, fixed interval event-related designs with trains of identical trials have many of the same confounds as block designs: the subject knows exactly when a

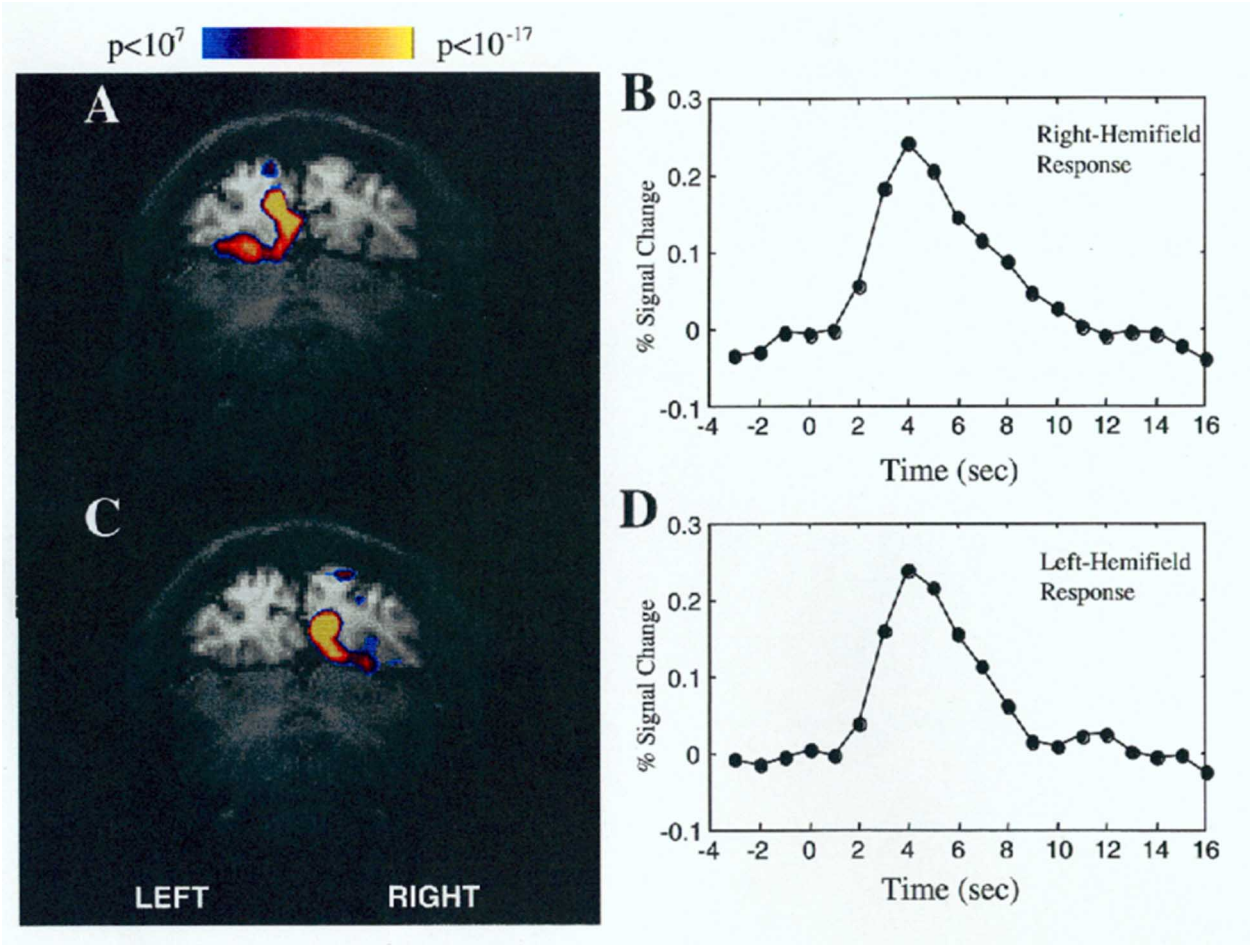

FIG. 2. Statistical parametric maps of event-related visual cortex activation and estimated hemodynamic responses for rapidly presented trials of left and right hemifield stimuli. (**A**,**C**) Statistical activation maps overlaid on echo-planar anatomic images. The images come from a slice through the occipital lobe, perpendicular to the calcarine sulcus. (A) Activation due to 250 ms right hemifield trials. (C) Activation due to 250 ms, left hemifield trials. (**B**,**D**) Averaged hemodynamic response functions computed over the statistically significant regions shown in (A) and (C). For both plots, 3 s of prestimulus baseline are plotted; the flatness of the estimated responses during the prestimulus period illustrates the effectiveness of the overlap removal. It should be noted that the original timecourses from which these responses were estimated resembled the third epoch in Fig. 1B.

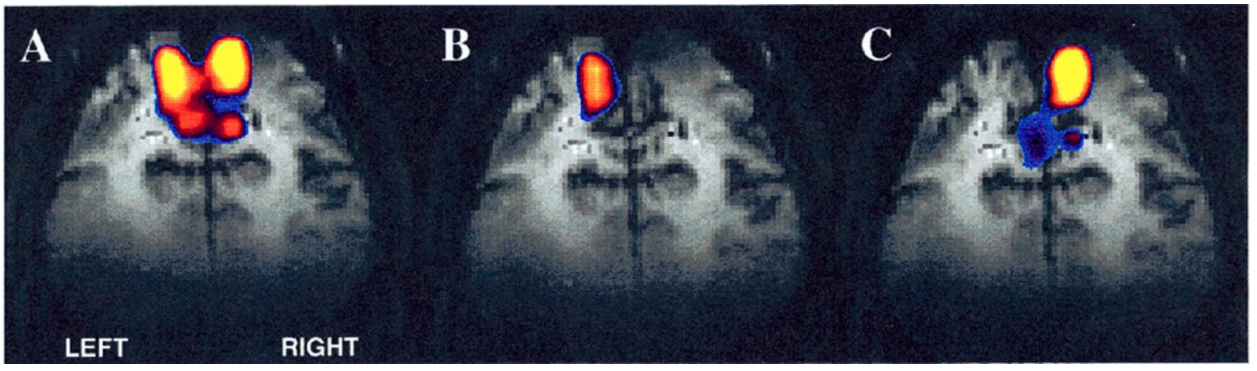

FIG. 3. Statistical parametric maps of event-related visual cortex activation in response to rapidly presented trials of full-field and right hemifield stimuli. (**A**) Activation due to 250 ms full-field trials. (**B**) Activation due to 250 ms right hemifield trials. (**C**) Differential activation due to full-field minus right-hemifield trials.

particular event type is going to occur, complicating interpretations of the cognitive or psychophysical experiment.

In this experiment we produced activation maps from extremely rapid, intermixed event presentations. In particular, differing trials were presented even more rapidly than the sampling rate (TR = 1 s) of our experiment, and we were able to compute estimates of the hemodynamic responses without constraining those estimates to a particular functional form (e.g. a basis set of gamma functions). That is, we did not need to make any *a priori* assumption about the shape of the hemodynamic response. The power of this method stems from the fact that the excitation sequence is uncorrelated with itself. Even though the hemodynamic responses to more than 20 individual trials may be overlapping each other in time, the stochastic nature of the excitation sequence reduces the overlap correction problem to simple averaging and subtraction,[7] which is equivalent to computing the well-defined cross-correlation function.

Previous ERP research has noted the advantages, at fast stimulus rates, of the randomization of stimulus type and intertrial interval as a means of reducing or removing response overlap distortion.[10,16,17] In these studies, as part of an approach that included post-processing deconvolutions, intertrial intervals were 'jittered' over a range of intervals according to a specified probability distribution (typical uniform over a given range). Our method of event and non-event randomization extends the jittering technique to rapid fMRI applicability by implementing a geometric probability mass (discrete-valued) function as the sample interval distribution. Our method can also be implemented with a continuous distribution of intervals, for which case sample intervals would be drawn from an exponential random variable: the continuous time analog of a geometric random variable.

Conclusion

Using a randomized presentation design, we have shown that it is possible to perform event-related fMRI experiments with intertrial intervals as short as 500 ms, and still obtain robust activation maps as well as measurements of the event-related hemodynamic response. Thus, the presentation rate in event-related fMRI experiments need not be limited by the relative sluggishness of the hemodynamic response. Rather, using selective averaging and randomized experimental designs, fMRI can now be used to explore an entire new range of cognitive neuroscience paradigms and questions.

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