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Evidence for a Refractory Period in the Hemodynamic Response to Visual Stimuli as Measured by MRI

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We investigated the effects of paired presentations of visual stimuli upon the evoked hemodynamic response of visual cortex measured by magnetic resonance imaging (MRI). Stimuli were identical 500-ms high-contrast checkerboard patterns, presented singly or with an interpair interval (IPI) of 1, 2, 4, or 6 s (onset-to-onset), followed by an intertrial interval of 16–20 s. Images were acquired at 1.5 Tesla using a gradient-echo echoplanar imaging sequence sensitive to blood-oxygenation-level dependent (BOLD) contrast. Single checkerboards evoked a hemodynamic response from visual cortex characterized by a rise at 3 s, peak activation at 5 s, and return to baseline by 10 s. We subtracted subjects' single-stimulus hemodynamic response from their paired-stimulus responses to isolate the contribution of the second stimulus. If the hemodynamic responses were fully additive, the residual should be a time-shifted replica of the single stimulus response. However, the amplitude of the hemodynamic response to the second checkerboard was smaller, and the peak latency was longer, than for the first. Furthermore, the amplitude decrement was dependent upon IPI, such that the response to the second stimulus at 1 s IPI was only 55% of that to a single stimulus, with recovery to 90% at a 6 s IPI. Peak latency was similarly dependent upon IPI with longer latencies observed for shorter IPIs. These results demonstrate an extended refractory period in the hemodynamic response to visual stimuli consistent with that shown previously for neuronal activity measured electrophysiologically.

INTRODUCTION

Magnetic resonance images acquired with pulse sequences sensitive to blood oxygenation level have been used to investigate focal changes in brain activity associated with sensory, motor, and cognitive tasks. Many functional magnetic resonance imaging (fMRI) studies have employed designs in which image intensity changes are evoked by repetitive stimulation maintained over many seconds (Kwong *et al.*, 1992). However, fMRI activations evoked by single brief visual stimuli were observed in an early study by Blamire and colleagues (Blamire *et al.*, 1992), and experimental designs dependent upon averaging of fMRI signal changes evoked by discrete stimulus events have increased in popularity (Dale and Buckner, 1997).

Such event-related experimental designs have the potential to differentiate brain activations associated with subtle psychological processes. However, the utility of this technique depends upon decomposition of the complex hemodynamic response into constituent components evoked by closely spaced physical or psychological events. The average hemodynamic response to a single brief stimulus, as measured by fMRI, follows a relatively typical time course. Little signal change is present 1–2 s after stimulus onset, followed by a rapid rise in signal strength peaking at 5–7 s. A slow return to baseline is complete by about 12 s. Although this approximate form of the hemodynamic response has been well established, there are features that are less commonly observed, such as a short-latency decrease in signal following stimulus onset (Hu *et al.*, 1997) and a undershoot in signal intensity as the response returns to baseline (Friston *et al.*, 1998). Differences have also been observed in peak latency of the response and in its variability across different brain regions (Schacter *et al.*, 1997).

Due to the long lag between stimulus onset and the peak signal, functional imaging studies have typically separated events of interest in time to minimize interactions between successive activations (McCarthy *et al.*, 1997; Rosen *et al.*, 1998; Pollmann *et al.*, 1998). Designs that are more efficient could be realized if individual signal contributions could be recovered from the complex fMRI signal. However, the determination of event-related signal contributions has been problematic. Responses to long-duration stimulus trains cannot be predicted from simple addition of multiple short-duration stimuli (Vazquez and Noll, 1998; Robson *et al.*, 1998; Boynton *et al.*, 1996), suggesting that the characteristics of the hemodynamic response to one stimulus are influenced by preceding stimuli. An ana-

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lytic weighting function to account for these effects has been proposed (Robson *et al.*, 1998).

The most direct test for additivity in the hemodynamic response was conducted by Dale and Buckner (1997), who measured responses in primary visual cortex to single and multiple presentations of high-contrast visual stimuli. Their stimulus was a radial black and white checkerboard at fixation presented for 1 s. On each trial, one stimulus, two stimuli (separated by 2 s), or three stimuli (each separated by 2 s) were presented. To identify the independent signal contributions of the second stimulus, the one-stimulus condition was subtracted from the two-stimulus condition. To identify the contribution of the third stimulus, the two-stimulus condition was subtracted from the three-stimulus condition. Dale and Buckner (1997) reported "roughly linear" additivity in their results, such that the contributions of successive stimuli were similar to that of the first stimulus.

Additivity, if confirmed, would greatly facilitate event-related fMRI studies, since it would allow direct subtraction of signal associated with each event. However, studies using other imaging techniques have found evidence for refractory periods. Cannestra and colleagues (Cannestra *et al.*, 1998) demonstrated, in both rat and human subjects, that a refractory period exists in the hemodynamic response measured using optical imaging techniques. In human subjects, the optical response to a somatosensory stimulus (2 s median nerve stimulation) was reduced by about 20% when another similar stimulus preceded it by 5 s. Electrophysiological studies utilizing paired stimuli also have demonstrated interval-dependent decreases in the amplitude of the evoked potential to the second stimulus of the pair. For some evoked potential components, the refractory period lasts for several seconds. In Allison's (1962) study of paired median nerve stimuli, for example, the late somatosensory potential evoked by the second stimulus did not achieve the amplitude of the first stimulus until an interval of 3–5 s had elapsed.

A study by Friston and colleagues (Friston *et al.*, 1998) indicates that a refractory period is present in the hemodynamic response, as measured by fMRI. In their experiments, a single subject passively listened to nouns, which were presented either at different rates (0.16 to 1.5 Hz) in a blocked design or at 0.03 Hz in an event-related design. By specifying first- and second-order Volterra kernels based on the empirical fMRI time series, the authors generated both linear and nonlinear characterizations of the hemodynamic response. These data were used to simulate the fMRI response to two closely spaced stimuli. The hemodynamic response to the second stimulus in the pair was both reduced in amplitude and increased in latency relative to that of the first stimulus. This suggests that the hemodynamic response as measured by fMRI is not linearly additive at short interstimulus intervals.

To investigate the linear additivity of the fMRI hemodynamic response, we adopted the paired-pulse paradigm long used in electrophysiological studies to examine nonlinear response properties of neuronal populations (e.g., Allison, 1962). Stimuli were identical high-contrast checkerboard patterns presented at fixation for 500 ms. During each 6-min run, checkerboards were presented singly or in pairs separated by intrapair intervals (IPIs) of (onset-to-onset) 1, 2, 4, or 6 s. The intertrial interval between successive single or paired stimuli was 16–20 s to minimize potential refractory effects upon the first stimulus of the pair. This design allowed us to individuate the hemodynamic response to a second stimulus as a function of the elapsed time from a preceding stimulus. If the hemodynamic response is linearly additive, as suggested by Dale and Buckner (1997), then the second stimulus should evoke a time-shifted response identical to that of the first stimulus and independent of the IPI. Alternatively, if there is a refractory period, then the signal change to a second stimulus should be smaller and have increased latency at short IPIs compared to long IPIs.

MATERIALS AND METHODS

Subjects. Sixteen healthy male volunteers were each paid $20.00 to participate in this study. Their average age was 27 years (range 19–41). This study was approved by the Duke University Medical Center Institutional Review Board and each subject provided informed consent. Each subject participated in one of two sets of experimental conditions, as described below.

Stimulus display. The stimulus was a black and white, high-contrast, radial checkerboard pattern, computer back-projected onto a display screen attached to the subject's gurney. Similar checkerboard stimuli have been shown to elicit consistent hemodynamic responses in primary visual cortex (Engel *et al.*, 1997). Between successive stimulus presentations, a fixation cross was displayed on a dark gray field. The subject viewed the display through an angled mirror mounted in the MRI head coil (Fig. 1).

To examine the hemodynamic response characteristics to closely spaced visual stimuli, the checkerboard was presented singly or in pairs separated by an IPI of 1, 2, 4, or 6 s. Successive single or paired stimulus presentations were separated by an intertrial interval that varied between 16 and 20 s. Eight subjects participated in the single, 1 s IPI, and 6 s IPI conditions. Another eight subjects participated in the single, 2 s IPI, and 4 s IPI conditions. The three trial types for each subject were randomly intermixed throughout each 6-min run. Each subject participated in as many

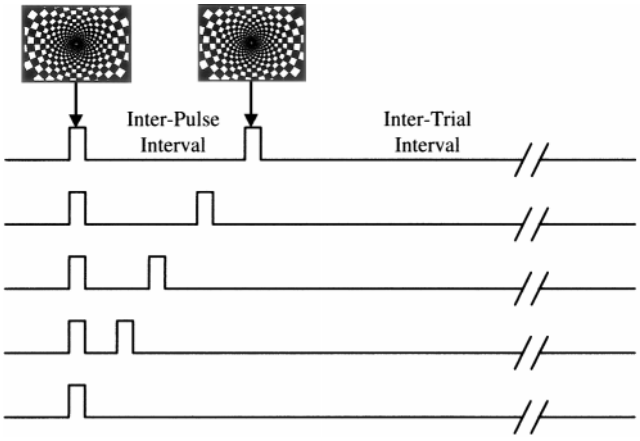

FIG. 1. A schematic illustration of the stimuli presented in the current experiment. On each trial, either one or two stimuli were presented. On two-stimulus trials, the radial checkerboard stimulus was presented for 500 ms, followed by an interpulse interval (onset to onset) of 6, 4, 2, or 1 s (the upper four lines) and a second 500-ms presentation of the stimulus. On one-stimulus trials (the bottom line), only a single stimulus was presented. The intertrial interval was 16–20 s.

experimental runs as time constraints and subject fatigue would allow (mean 9 runs/subject, range 6–11 runs). A vacuum-pack pillow system was used to minimize head motion during the experiment.

Procedure. All scanning was performed on a General Electric 1.5 T scanner equipped with an Advanced Development Workstation for realtime echoplanar imaging. Sagittal T1-weighted localizer images were first collected. The experimenter identified the location of the calcarine sulcus, and two oblique slices (7-mm-thick with no gap) bracketing the calcarine were chosen for study. The functional images were collected using a T2*-weighted gradient-echo, echoplanar imaging sequence [echo time (TE) = 50 msec; repetition time (TR) = 1 s; matrix = 128 × 64; field of view = 40 × 20 cm; in-plane resolution = 3.125 × 3.125 mm]. The functional scans measured changes in BOLD contrast.

For each subject's data, event-related epochs were identified for subsequent analysis. When only a single stimulus was presented, the epoch consisted of the 25 images obtained from 5 s before through 19 s after stimulus onset. When a pair of stimuli was presented, a similar epoch was identified around the onset of the first stimulus in the pair. These epochs were then selectively averaged for each condition, resulting in an averaged epoch for the single stimulus presentation and separate averaged epochs for each IPI.

Voxels activated by the single checkerboard were identified by correlating the time course of each voxel in the averaged single stimulus epoch with an empirically determined hemodynamic response, which was generated from pilot testing of the response to a single checkerboard presentation in three subjects. A region of interest was then defined by first identifying the voxel with the largest activation along the medial calcarine sulcus and then including all contiguous voxels with t values greater than 3.5 ($P < .0002$, uncorrected). If bilateral activation was observed, then the region of interest was defined to include the activation from both hemispheres. In one subject with less activation than the others, contiguous voxels with $t > 2.5$ were used. Even though this approach makes an *a priori* assumption about the shape of the expected response to a single stimulus, it does not introduce bias into the paired-stimulus results. Since the same ROI is tested across multiple IPIs, the particular hemodynamic function used to determine that ROI does not bias the results toward any differences in recovery across the paired-stimulus IPIs.

The signal from each subject's region of interest was measured for the averaged epochs for the single and paired-stimulus presentations. For each subject, the response to a single-stimulus presentation was subtracted from the response to each IPI condition. The residual responses provided a measure of activation evoked by the second checkerboard.

RESULTS

Figure 2 illustrates a typical activation in a single subject for the single-stimulus condition. Activated voxels ($t < 3.5$) are shown superimposed upon an ana-

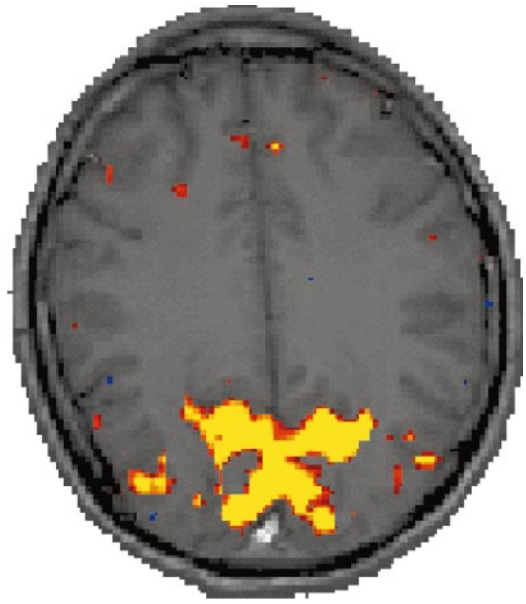

FIG. 2. The pattern of activation observed in a single subject. Overlaid upon a structural T1-weighted image is a statistical map generated by comparing control-trial activation to a predicted hemodynamic response function. Voxels active at a t value of greater than 3.5 (uncorrected $P < .0002$) are indicated on the colored activation overlay. Within each subject, a region of interest was established by identifying the voxel (or voxels, if bilateral) with maximum t value and including all contiguous voxels in that slice with t values greater than 3.5.

tomical image. The large contiguous activation along the midline posterior brain (corresponding to calcarine cortex in this oblique plane) was used as the region of interest for this subject.

Figure 3 shows the mean hemodynamic response (across subjects) for each of the IPIs tested in the current experiment, as compared to the single-stimulus response. The single stimulus evoked a response qualitatively different from that to paired presentations, most notable in the bimodal distributions evident at 4 and 6 s IPIs.

Figure 4 presents the independent contribution of each stimulus presentation obtained by subtracting the single-stimulus response from each paired response and time shifting the residual to align the stimulus onset.

A two-factor ANOVA revealed that the residual hemodynamic response varied as a function of IPI [$F(48, 516) = 1.91$, $P < .001$]. We thus rejected the hypothesis that the hemodynamic response was linearly additive.

To further characterize response changes as a function of IPI, we measured changes in both maximum amplitude of response and latency to peak response. Prior to analysis, the response for each subject for each IPI condition was temporally smoothed with a symmetric moving-average filter. Following this filtering, the point of maximum signal response was identified, and its latency and amplitude recorded. Figure 5 shows the mean amplitude (upper y-axis) and latency to peak of signal (lower y-axis) as a function of IPI.

We then conducted independent regression analyses upon the amplitude and latency measures, treating single-stimulus trials as having an IPI of 16 s (the intertrial interval). The amplitude of the hemodynamic response increased significantly with increasing time since the previous stimulus [$F(1,46) = 8.08$, $P < 0.01$]. At an IPI of 1 s, the response to a second stimulus presentation was about 55% of that to the first stimulus presentation. At an IPI of 6 s, the BOLD response had recovered to about 90% of that of a single-stimulus presentation.

The latency to peak activation was significantly longer following short IPIs than following long IPIs [$F(1, 46) = 7.89$, $P < 0.01$]. The peak latency was about 5.2 s for a single-stimulus presentation. The peak latency had lengthened to about 6.0 s for the second stimulus of the 1-s IPI pair and had recovered to about 5.4 s for the second stimulus of the 6 s IPI.

DISCUSSION

The current study indicates that the hemodynamic response, as measured by fMRI, that is evoked in vi-

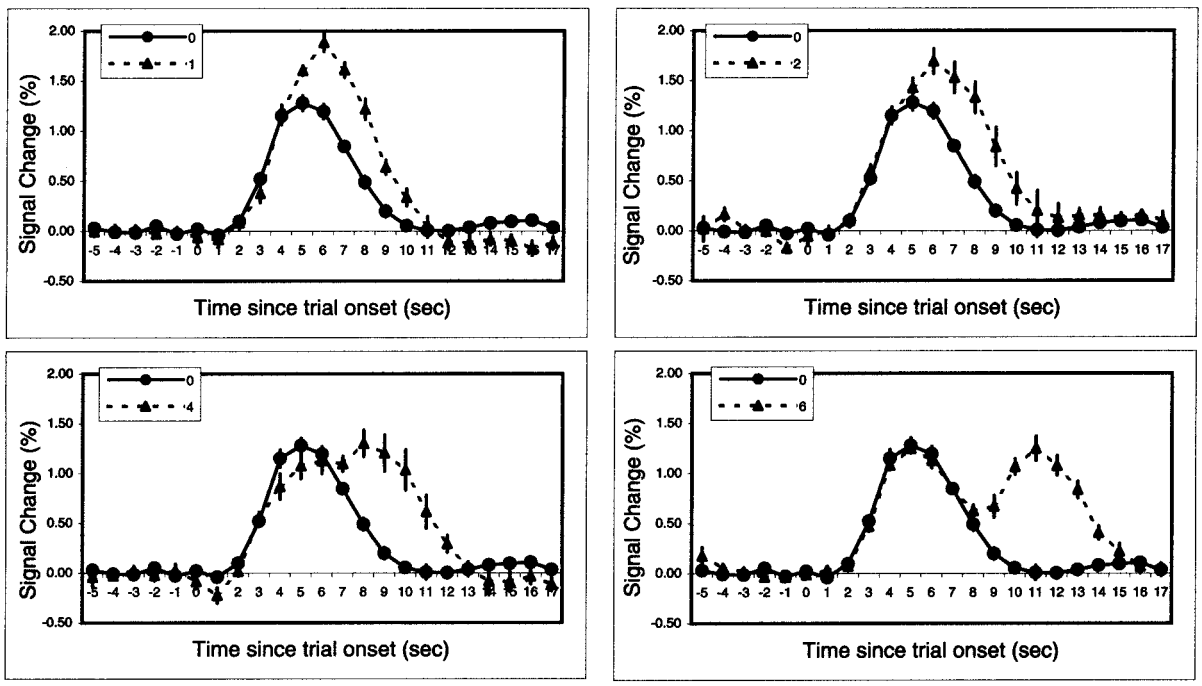

FIG. 3. The hemodynamic response measured for each of the trial types (IPI durations). The top two graphs present results from 1- and 2-s IPIs, while the bottom two present results from 4- and 6-s IPIs. On each x-axis is the time since the beginning of the trial (seconds since presentation of the first stimulus), and on each y-axis is the change in signal observed (percent signal change over baseline). The circles represent the mean signal across subjects when a single stimulus was presented; this curve replicates previous reports of the hemodynamic response for primary visual cortex. The triangles represent the mean signal across subjects when a pair of stimuli were presented. Error bars (standard error of the mean) are presented on all curves; where error bars are not visible, they are contained within the data point symbols.

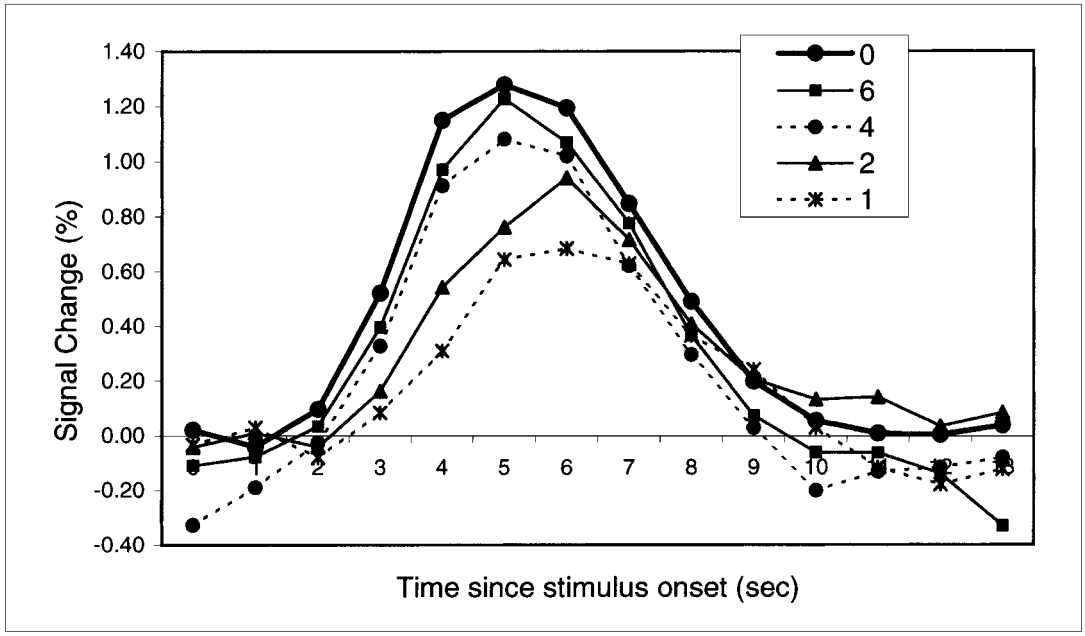

FIG. 4. The changes in the hemodynamic response to a second stimulus as a function of time since the first stimulus. Each line represents one IPI condition (1, 2, 4, or 6 s), with the dark circles indicating the hemodynamic response to a single stimulus presentation (control). On the x-axis is the time since presentation of the second stimulus in seconds, and on the y-axis is the change in hemodynamic response due to the second stimulus (percent signal change over baseline). Thus, this figure provides the same data as described in the legend to Fig. 3, with two changes: (1) the single-stimulus signal (0 s IPI) has been subtracted from each of the paired-stimulus signals, and (2) the resulting waveforms have been temporally aligned to the presentation of the second stimulus. If the hemodynamic response to a second stimulus presentation is linearly additive to that of the first stimulus, then all of the curves should be similar in form and amplitude.

sual cortex by a checkerboard stimulus is not linearly additive. Rather, the response to a second stimulus was both attenuated and slightly delayed, with the degree of attenuation decreasing as the duration of the intervening interval increased. Recovery to approximately 90% of normal amplitude was observed with a 6-s IPI. These results support the idea of a refractory period in the fMRI hemodynamic response that lasts about six seconds from stimulus onset, and are thus consistent with blocked-design studies of nonlinearity in fMRI.

The demonstration of a refractory period in the fMRI hemodynamic response provides empirical validation for recent simulation work indicating that the hemodynamic response to a second stimulus in a pair should be of increased latency and lower amplitude (Friston *et al.*, 1998). We extend this earlier work by showing, in a paired-stimulus design with a larger number of subjects, parametric effects of IPI upon amplitude and latency of response. Furthermore, the current results complement research that shows underadditivity of the hemodynamic response when comparing short-duration stimulus trains to long-duration stimulus trains (Boynton *et al.*, 1996; Robson *et al.*, 1998; Vazquez and Noll, 1998). In these studies, responses to a long-duration stimulus (e.g., 12 s) were overestimated by linear addition of several short-duration stimuli (e.g., four consecutive 3-s stimuli). We find a similar result here for single stimulus presentations separated by discrete IPIs.

However, our finding has methodological implications that are different from those of earlier works. Long-duration stimulus trains are used most commonly in interleaved epoch designs (e.g., ABABAB designs). Since these designs compare activation between two alternating epochs, underadditivity of the BOLD effect with repeated presentations has little effect upon analyses. With event-related experimental designs, in contrast, areas of significant activation are sometimes determined by correlating measured BOLD signal to a predicted waveform. Thus, deviations from linear additivity should be explicitly modeled within event-related analyses.

Dale and Buckner (1997; Buckner, 1998) have argued that event-related fMRI analyses are practical due to linear additivity of the BOLD response. However, close examination of their published figures show a trend toward underadditivity. With presentations of a radial checkerboard separated by 2 s ISI, the residual responses to second and third stimuli were smaller than that to a single stimulus and peaked slightly later. This trend is consistent with the present results that indicate that the response following a 2-s ISI was attenuated by about 30% and delayed by 1 s.

Accurate deconvolution of the fMRI signal to estimate the contributions of individual stimuli does not

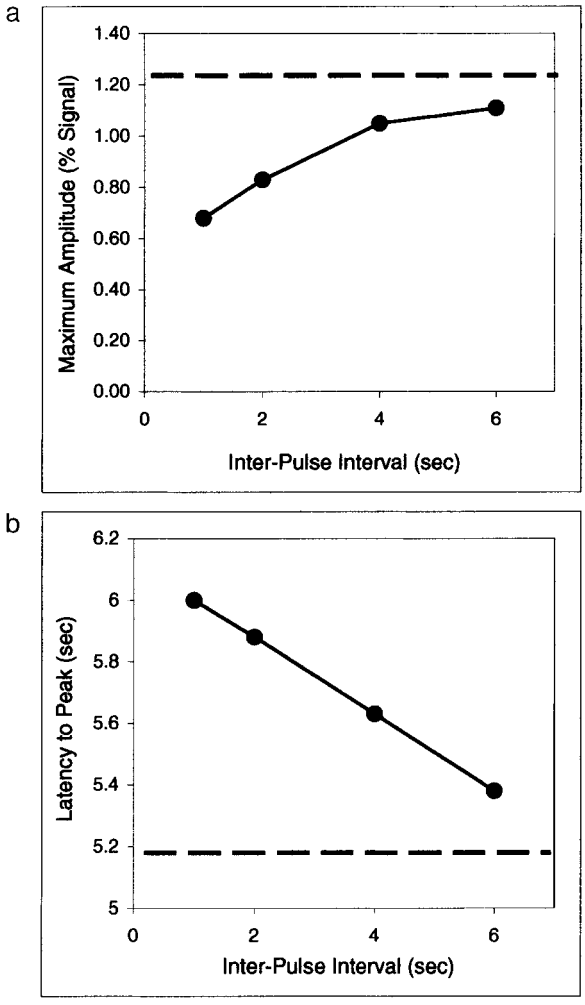

FIG. 5. The effects of IPI upon amplitude (5a) and latency (5b) of the hemodynamic response. For both figures, the mean value on control trials is shown by the dashed lines. As IPI increases, the peak amplitude recovers from 55% of maximum at 1-s IPI to 90% of maximum at 6-s IPI. Similarly, the latency to peak activation is about 1 s longer for the shortest IPI tested (1 s) than for the control trials.

require linear additivity of the hemodynamic response with multiple stimulus presentations. Instead, such deconvolution may be possible by modifying the predicted hemodynamic response function based on the time since a preceding stimulus (Robson *et al.*, 1998). The present study demonstrates that two aspects of the hemodynamic response may change with intervening interval: amplitude and latency (Fig. 5). Other aspects of the response may also change in a nonlinear fashion; for instance, the latency difference in peak amplitude across ISI appeared to be related to rate of rise in the BOLD signal, and not simply to a delay in the onset of that rise. Thus, an improved technique could incorporate changes in these parameters explicitly.

Although the current experiment provides evidence for a refractory period, it has three primary limitations. First, these results cannot distinguish whether the changes in the BOLD signal following stimulus presentation result from neuronal or hemodynamic refractoriness. While, as alluded to in the introduction, extended refractory periods have been observed in evoked potential studies, few direct comparisons have been made between electrophysiological and hemodynamic measures. Cannestra *et al.* (1998) presented somatosensory stimulation to rats (vibrissal deflection) and measured both neuronal responses (evoked potentials) and hemodynamic response (optical imaging of intrinsic signal). No refractory period was observed in the evoked potential data, but a 3-s refractory period was present in the optical imaging data. This decoupling between neuronal and hemodynamic measures of activity suggests that the refractory period observed in the optical imaging data results from vascular responses, rather than from changes in neuronal behavior that presumably would be common across the two measures. If vascular blood outflow from an active area depends on the rate of inflow (Buxton et al., 1998), then the presence of preceding stimuli would serve to reduce the BOLD fMRI response to subsequent stimuli. Nevertheless, the source of the fMRI refractory period reported here cannot be attributed to vascular responsiveness without concurrent demonstrations of fMRI and ERP refractory periods.

Second, the duration of the refractory period may depend upon stimulus duration. In the present study, we presented relatively brief (500 ms) stimuli, as is common in many event-related designs. Longer stimulus durations, however, are often used in cognitive tasks, especially within blocked experimental designs. Given that extended stimulus durations affect the characteristics of the fMRI response (Boynton *et al.*, 1996; Robson *et al.*, 1998; Vazquez and Noll, 1998), it is possible that the duration of the refractory period following a stimulus depends upon the duration of that stimulus. Stimulus-duration effects have been shown in optical imaging of somatosensory cortex in rats, with a shorter refractory period (about 4 s) following shorter-duration stimuli (less than 2.4 s) and a longer refractory period (greater than 7 s) following longer-duration stimuli (Cannestra, 1998). These specific values cannot be extended directly to human fMRI analyses, due to the differences in subject species and in time course of activation (the optical signal rises and falls much more rapidly than that in fMRI). Yet, these results suggest that the duration of refractory periods may be governed by two parameters: interstimulus interval and stimulus duration. More generally, further work is needed to examine whether previous activation of a given voxel (or region), independent of task properties, determines the characteristics of its refractory period, such that amplitude and duration of activation predict subsequent responsiveness.

Finally, the present results describe changes in and near primary visual cortex, but cannot determine whether a similar recovery function is obtained for extrastriate visual areas and for other regions of cortex. Electrophysiological studies have repeatedly shown that refractory periods are different for different components of evoked potentials, with fastest recovery occurring in short-latency potentials presumed to be generated in primary sensory areas, and longer recovery occurring for long-latency potentials presumed generated in other cortical regions (Allison, 1962). If a similar pattern is observed for the hemodynamic response, the duration of the refractory period identified here for striate cortex may be shorter than that obtained in other brain regions.

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REFERENCES

Allison, T. 1962. Recovery functions of somatosensory evoked responses in man. *Electroenceph. Clin. Neurophysiol.* **14:**331–343.

Blamire, A. M., Ogawa, S., Ugurbil, K., Rothman, D., McCarthy, G., Ellerman, J. M., Hyder, F., Rattner, Z., and Shulman, R. G. 1992. Dynamic mapping of the human visual cortex by high-speed magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA* **89:**11069–11073.

Buxton, R. B., Wong, E. C., and Frank, L. R. 1998. Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magn. Reson. Med.* **39:**855–864.

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:**4207–4221.

Buckner, R. L. 1998. Event-related fMRI and the hemodynamic response. *Hum. Brain Map.* **6:**373–377.

Cannestra, A. F., Pouratian, N., Shomer, M. H., and Toga, A. W. 1998. Refractory periods observed by intrinsic signal and fluorescent dye imaging. *J. Neurophysiol.* **80:**1522–1532.

Dale, A. M., and Buckner, R. L. 1997. Selective averaging of rapidly presented individual trials using fMRI. *Hum. Brain Map.* **5:**329–340.

Engel, S. A., Glover, G. H., and Wandell, B. A. 1997. Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cereb. Cortex.* **7:**181–192.

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

Hu, X., Le, T. H., and Ugurbil, K. 1997. Evaluation of the early response in fMRI in individual subjects using short stimulus duration. *Magn. Reson. Med.* **37:**877–884.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., and Turner, R. 1992. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. USA* **89:**5675–5679.

McCarthy, G., Luby, M., Gore, J., and Goldman-Rakic, P. 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. *J. Neurophysiol.* **77:**1630–1634.

Pollmann, S., Wiggins, C. J., Norris, D. G., Cramon, D. Yv., and Schubert, T. 1998. Use of short intertrial intervals in single-trial experiments: A 3T fMRI study. *NeuroImage* **8:**327–339.

Robson, M. D., Dorosz, J. L., and Gore, J. C. 1998. Measurements of the temporal fMRI response of the human auditory cortex to trains of tones. *NeuroImage* **7:**185–198.

Rosen, B. R., Buckner, R. L., and Dale, A. M. 1998. Event-related functional MRI: Past, present and future. *Proc. Natl. Acad. Sci. USA* **95:**773–780.

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

Vazquez, A. L., and Noll, D. C. 1998. Nonlinear aspects of the BOLD response in functional MRI. *NeuroImage* **7:**108–118.