Regional Differences in the Refractory Period of the Hemodynamic Response: An Event-Related fMRI Study

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INTRODUCTION

Previous research has demonstrated that properties of the event-related functional MRI hemodynamic response (HDR), including its latency and amplitude, depend on the timing of preceding stimuli (Friston et al., 1998; Huettel and McCarthy, 2000; Huettel et al., 2001; Miezin et al., 2000). At intervals of 5–6 s or greater, the hemodynamic responses of multiple stimuli sum in a roughly linear fashion (Buckner et al., 2000; Miezin et al., 2000). However, at shorter intervals (e.g., 1–2 s), there are significant departures from linearity, such that the HDR to the second stimulus in a pair is reduced in amplitude and increased in latency compared to that evoked by a single stimulus (Huettel and McCarthy, 2000). These refractory effects in the event-related HDR occur in both young and elderly subjects (Huettel et al., 2001) and have been demonstrated in auditory (Friston et al., 1998), motor (Miezin et al., 2000), and visual cortices (Huettel and McCarthy, 2000; Huettel et al., 2001). Furthermore, they are consistent with studies using blocked designs that report significant departures from linearity at intervals less than about 6 sec (Boynton et al., 1996; Robson et al., 1998; Vazquez and Noll, 1998).

An important unexplored issue is whether there is regional variation in the form of the hemodynamic refractory period. Electrophysiological studies of the refractory period of evoked potentials have shown that different evoked potential components have different refractory periods with longer latency components generally showing slower recovery (e.g., Allison, 1962). To the extent that different evoked potential components reflect activity in different neuronal populations, we expect that the refractory period of the hemodynamic response in different brain regions might also vary. Huettel and colleagues (2001) reported that there was faster recovery to the second visual checkerboard in a pair in calcarine cortex than in fusiform cortex, even though the single-stimulus HDR was equivalent in both regions. Here we extend investigation of refractory effects in the HDR by investigating changes across
brain regions and, by comparison to earlier studies using checkerboard stimuli, stimulus types.

We employed a visual stimulation task in which faces were presented either singly or in a pair separated by a short interval. Faces were chosen because they, like other complex objects, allow examination of HDR characteristics in both primary visual areas along the calcarine sulcus and in secondary visual areas along the fusiform gyrus. In addition, faces selectively activate middle and anterior regions of the fusiform gyrus (McCarthy et al., 1997b). We measured the hemodynamic response to face stimuli for regions of interest within calcarine and fusiform cortex. By subtracting the response evoked by a single face stimulus from that evoked by a pair of face stimuli (with intervals of either 1 s or 6 s), we identified the independent contribution of the second stimulus to the combined HDR. We compared the resulting refractory effects across the posterior-anterior extent of the anatomical regions investigated.

A secondary goal was to evaluate whether there are systematic differences in HDR latency across brain regions. Electrophysiological studies have identified latency differences in the neuronal responses in different visual regions. For example, Allison and colleagues (1999) demonstrated, using intracranial electrode recordings, that initial responses to faces in ventral face-specific sites occur about 100 ms later than responses in primary visual cortex. It remains to be conclusively established whether latency differences of this magnitude can be identified using fMRI. Previous work has suggested that the effective resolution of fMRI data may be considerably higher than that indicated by the time course of the HDR, which evolves over a period of about 10 s, or by its sampling interval, which typically ranges from 1 to 3 s in fMRI studies (e.g., Menon et al., 1998; Miezin et al., 2000). Initial studies of latency using blocked-design fMRI evaluated differences in signal phase, finding a phase difference of about 1 s between voxels in medial occipital cortex and those in the parietal-temporal-occipital fossa, which corresponds to V5 (McCarthy et al., 1995). Using an event-related design, Huettel and colleagues demonstrated that the hemodynamic response to checkerboard stimuli peaked about 300 ms earlier in calcarine cortex than in fusiform cortex (Huhettel et al., 2001). This result was independently identified in samples of young and elderly subjects, and was evident in single-subject plots of the relative latency of the response in individual voxels. Here we directly tested whether there are latency differences in the HDR across brain regions and whether latency differences between brain regions are stimulus dependent, through comparison with earlier studies using visual checkerboards.

**MATERIALS AND METHODS**

**Subjects.** Ten healthy volunteers (8 male, 2 female) were each paid $20 to participate in this study. Their mean age was 28 years (range 19–38). The Institutional Review Board of the Duke University Medical Center approved this study and each subject provided informed consent.

**Display and procedure.** Single faces or pairs of identical faces separated by different intra-pair intervals (IPIs) were presented to evaluate HDR refractoriness. Faces were presented as black and white photographs at fixation for 500 ms. Visible in each photograph was the person's face and upper torso; all individuals were wearing business dress, and no headgear was present. Each face subtended about 6° by 4° of visual angle. Between successive stimulus presentations, a fixation cross was displayed on a neutral gray background of about the same mean luminance as the face stimuli. The display and all stimuli were projected, via a computer-controlled LCD projector, into the scanner bore onto a screen behind the subject's head. The subject viewed the display through an angled mirror mounted on custom glasses frames.

On each trial, the subject viewed one of three trial types: a single face, the same face presented twice with IPI of 1 s, or the same face presented twice with IPI of 6 s. The IPIs represent the extreme values used in Huettel and McCarthy (2000). Successive single or paired stimulus presentations were separated by a long intertrial interval that varied between 15–19 s to allow complete HDR recovery between stimulus events. The three trial types for each subject were randomly intermixed (6 of each type) throughout each 6-min run. Each subject participated in as many experimental runs as time constraints and subject fatigue allowed (mean 7 runs/subject, range 6–8 runs).

Before the experiment, all subjects were initially tested in a control procedure (15 minutes total duration of blocked presentation of faces against a continuous background of objects) to replicate our earlier findings showing that middle regions of the fusiform gyrus showed more face-specific activation than do posterior regions (McCarthy et al., 1997b). Display and analysis procedures for the control experiment are those described in that earlier work.

**Procedure.** All scanning was performed on a General Electric LX NVi 1.5 T scanner equipped with an Advanced Development Workstation for real-time echoplanar image reconstruction. After collection of sagittal T1-weighted localizer images, we collected a whole-brain set of coronal high-resolution spin-echo structural images [matrix = 256 × 256; field of view = 24 × 24 cm; in-plane resolution = 0.94 × 0.94 mm]. These T1-weighted images were used to select 12 consecutive 5-mm contiguous coronal slices, such that the
most posterior slice chosen was located at the occipital pole.

The functional images were collected using a T2*-weighted gradient-echo, echoplanar imaging sequence [echo time (TE) = 40 ms; repetition time (TR) = 1 s; matrix = 64 × 64; field of view = 24 × 24 cm; in-plane resolution = 3.75 × 3.75 mm]. The functional scans measured changes in BOLD contrast. Epochs for each of the three stimulus conditions were excised from the continuous time series of volumes. For single-stimulus presentations, the epoch consisted of the 25 images obtained from 5 s before through 19 s after stimulus onset. For paired-stimulus presentations, a similar length epoch was identified related to the onset of the first stimulus of the pair. These epochs were then selectively averaged for each condition, resulting in three sets of averaged epochs: single-stimulus, 1 s IPI, and 6 s IPI.

We identified active voxels using the single-stimulus trials only, and then determined HDR timecourses for those voxels across all three trial types. To evaluate whether a voxel was active on single-stimulus trials, we correlated its timecourse with an empirically determined HDR obtained from Huettel and McCarthy (2000). The probability associated with each correlation was calculated and active voxels were defined as those for which the associated t-value was greater than 3.5 (P < 0.002, two-tailed, uncorrected). This value was selected a priori as a conservative estimate of significance. We then identified two sets of anatomical areas using the structural MR images: calcarine cortex and fusiform gyrus. The calcarine cortex regions of interest (ROIs) included V1 and portions of other visual areas. Each anatomical ROI was drawn on a single slice, such that there were 4 calcarine cortex ROIs, 5–20 mm from the occipital pole, and 7 fusiform gyrus ROIs, 25–55 mm from the occipital pole. The voxels used for HDR estimation were those within these anatomical regions that had significant activation to single-stimulus trials.

After identifying active voxels for each ROI, we determined the individual activation timecourses for the single-stimulus trials and for the two types of paired stimulus trials. To identify the HDR evoked by the second face in a pair, the response to a single-stimulus presentation was subtracted from the composite HDR evoked by the pair. The result of this subtraction was then time locked to the onset of the second stimulus. The timecourses for each ROI were then normalized to percent signal change over pre-stimulus baseline levels (1–4 s before stimulus onset) and averaged across subjects.

One limitation of this technique is that we use the same data for choosing active voxels and for identifying the time course of activation in those voxels. It is therefore necessary to control for the possibility that our technique will be biased toward including more-active voxels and therefore overestimating the single-stimulus HDR. An overestimation of the single-stimulus HDR would have the primary effect of introducing artifactual increases in latency for the second stimulus in a pair, since too large of a HDR would be subtracted from the composite waveform. We thus replicated our analyses for a sample of 10 ROIs using one half of the data to identify active voxels and the other half to estimate the single-stimulus HDR. For 9 of the 10 ROIs tested, we found latency increases in the split-data at 1 s IPI. The one ROI without a latency increase was reanalyzed with the other data split and a latency increase at 1 s was observed. These results suggest that our technique does not introduce systematic bias into the time course data. All results below were derived using all data for identifying active voxels and for determining HDR timecourses.

RESULTS

Across subjects, faces evoked activations in three brain regions: medial calcarine (bilaterally), left fusiform gyrus, and right fusiform gyrus. The calcarine cortex activation occurred primarily near the occipital pole, as was expected given that the faces were presented at fixation. The fusiform activation had considerably larger anterior–posterior extent. Consistent activation of these areas was observed in 9 of 10 subjects. The subsequent analyses reported in this section include data from these 9 subjects. Some subjects' activation did not reach our statistical criterion in all slices in all regions, and those slices were excluded from analysis. All 9 subjects analyzed showed right-hemisphere fusiform activation in all 7 slices (63/63 regions), 55 of the 63 left-hemisphere fusiform regions showed significant activation, and 35 of the 36 (4 slices) calcarine regions showed significant activation. Figure 1 shows the pattern of activation in a representative subject.

Amplitude of the HDR. The HDR was defined for each subject's averaged epoch data at each ROI (see procedure above) using spline interpolation of the recorded fMRI signal, upsampled to a resolution of 83 ms (the interval for successive slice acquisitions). Shown in Fig. 2 are the changes in activation, averaged across subjects, in the single- and paired-face conditions across the brain regions investigated: posterior and midfusiform, and posterior and anterior calcarine cortex (timecourses not displayed for all slices). Activation in medial calcarine areas was generally consistent across slices, with a mean signal change over baseline of 0.65%, although there was a trend toward a slight decrease in anterior slices. The patterns of activation in the fusiform gyrus were similar in both hemispheres: the amplitude is largest in posterior slices (>1% signal change), with a decrease to about 0.65% signal change in anterior slices.

To examine recovery of HDR amplitude, we com-
pared amplitude of the single-stimulus response to the amplitude of the residual response to the second stimulus in each IPI condition (details in methods). By dividing the estimated second-stimulus amplitude by the single-stimulus amplitude, we created a measure for amplitude recovery of the HDR (0 indicating no recovery, 1 indicating full recovery). Figure 3 shows the recovery in each of the brain areas tested. For the fusiform gyrus, a three-factor ANOVA examined recovery as a function of IPI (1 or 6 s), slice (7 locations), and hemisphere. Immediately evident is that there is significantly less recovery at 1 s IPI than at 6 s IPI \( F(1,8) = 10.53, P < 0.05 \), with no differences in recovery across hemispheres [main effect: \( F(1,8) = 2.10, P > 0.10 \); all interactions with hemisphere term: \( P > 0.10 \)]. There is a main effect of slice location upon recovery \( F(6,48) = 7.61, P < 0.0001 \), with more anterior regions showing less recovery than posterior regions. Furthermore, there was a significant interaction between slice location and latency since initial stimu-
lus \[ F(6,48) = 2.96, P < 0.05 \], such that recovery was different across slices at 1 s IPI but similar across slices at 6 s IPI.

Recovery of medial calcarine areas, in contrast, did not differ as a function of brain region. At 1 s IPI, there was only 39% recovery, but this amount increased to 76% for the 6 s IPI; this difference was significant [two-factor ANOVA (IPI, slice): \( F(1,8) = 12.74, P < 0.01 \)]. However, there was no differences in recovery across slices \[ F(3,24) = 1.90, P > 0.10 \], nor was there a significant interaction \[ F(3,24) = 0.72, P > 0.10 \].

Latency of the HDR. The latency to peak was defined as the time of the largest value of the spline-interpolated HDR (described in preceding section). Subject ROIs that did not have a positive-amplitude peak between 3 s and 9 s following stimulus onset were excluded from analysis. For the 1 s IPI, one ROI, that from left fusiform cortex 50 mm from the occipital pole, had only two subjects who fit this criterion and was subsequently excluded from analyses. This ROI had the smallest activation amplitude of any tested (<0.10% signal change over baseline), making any ex-

**FIG. 2.** Activation plots for left fusiform (top), calcarine (left), and right fusiform (bottom) brain regions. Each graph provides the hemodynamic responses to single faces (circles), to the second stimulus in 1-s IPI pairs (triangles), and to the second stimulus in 6-s IPI pairs (squares). Plots are shown here for posterior and anterior calcarine and for posterior through anterior fusiform; however, all slices indicated on this figure were measured for calculations on the successive figures. Signal strength (y axis) is presented as a function of time since stimulus onset (x axis). The slice locations in this figure are indicated on a sample brain, with the small numbers indicating millimeter distances from the occipital pole. This sample brain provides a rough indication of the slice locations used in the current study, although the specific anatomy found in any one slice differed across subjects. The inset chart labeled “Mean HDRs” shows the mean hemodynamic response functions measured on single-face trials in calcarine cortex (CC) and fusiform gyrus (FFG), interpolated to 1/12-s resolution, and amplitude normalized. Apparent is the significant latency difference observed, such that the HDR peaked about 400 ms earlier in calcarine cortex.
timate of latency to peak amplitude difficult to interpret. For all remaining slice ROIs, the average latency values across subjects were corrected for slice acquisition order within the TR by time-shifting the data by the offset time for that slice (e.g., 0 ms for slice 1, 500 ms for slice 2, 83 ms for slice 3, etc.). The HDR evoked in calcarine cortex by a single face reached its peak amplitude at a latency of about 5.2 s, whereas the HDR evoked in fusiform cortex reached its peak at a latency of about 5.6 s (see inset of Fig. 2). A \( t \) test (two sample, unequal variance) of latency values in all slices with significant activation revealed that this difference was significant \( t(151) = 5.481; P < 0.0001 \).

Figure 4 presents the refractory effects upon HDR latency for each region tested. For the fusiform gyrus, a three-factor ANOVA examined HDR latency as a function of IPI (single stimulus, 1 s or 6 s), slice (7 locations), and hemisphere. There was a main effect of IPI \( F(2,16) = 10.28, P < 0.01 \), with HDR latency to peak increased by about 0.7 s for the second stimulus in a 1 s IPI pair, relative to the single-stimulus value. However, by 6 s IPI, latency to peak was similar across slices to single-stimulus values (increased by 0.1 s). There was also a main effect of slice location \( F(6,48) = 6.86, P < 0.0001 \), with midfusiform slices generally having shorter latencies. No differences in latency were found across hemispheres (main effect: \( F(1,8) = 0.19, P > 0.10 \)). There were significant interactions between IPI and slice location \( F(12,96) = 2.06, P < 0.05 \) and between hemisphere and slice location \( F(6,48) = 2.62, P < 0.05 \), but visual examination of the results did not suggest any topographic organization to these interactions. In calcarine areas, mean latency was increased by 0.9 s at 1 s IPI, and by 0.4 s at 6 s IPI. Although this difference was numerically large, it was not significant by two-factor ANOVA (IPI and Slice; \( F(2,16) = 2.10, P > 0.10 \)), due to the aberrant data point of the 15mm slice. However, both the main effect of slice \( F(3,24) = 4.31, P < 0.05 \) and the interaction between IPI and slice \( F(6,48) = 5.25, P < 0.001 \) were significant. Given this significant interaction, we interpret the results as suggestive of an overall difference in latency between the IPIs across three of the slices examined, with one slice not evidencing the latency difference.

DISCUSSION

We found that the refractory properties of the fMRI HDR, including its amplitude and latency, vary across visual brain regions. Here, we consider the implications of these findings for design and analysis of event-related fMRI experiments.

Refractory effects in the HDR. Across all brain ar-
eas, we found that the HDR evoked by the second stimulus in a pair was attenuated in amplitude and increased in latency at 1 s IPI. Furthermore, both amplitude and latency of the HDR recovered toward single-stimulus values by 6 s IPI. This general pattern of results replicates that of Huettel and McCarthy (2000), who investigated the refractory period in primary visual areas using checkerboard stimuli. Notably, similar recovery effects were found in the two studies even though they used different stimuli, investigated different brain areas, and were conducted on different scanners. From these findings, we conclude that refractory effects are integral to the fMRI BOLD response.

Recovery effects in primary visual areas were also investigated at similar IPIs in our earlier work (Huettel and McCarthy, 2000), so it is valuable to directly compare the characteristics of the refractory period found in the two experiments. In the earlier study, at 1 s IPI, the HDR was attenuated in peak amplitude by 45% and was increased in latency by 0.8 s; the attenuation at 6 s IPI was 10% and the increase in latency was 0.2 s. Here the amplitude attenuation at 1 s IPI was 60% and the increase in latency was 0.9 s; at 6 s IPI, the values were 25% and about 0.4 s. Thus, between the two studies, there are similar recovery effects upon latency of the HDR, but there is correspondingly less amplitude recovery in the current study. This difference in amount of recovery may be due to the different stimuli used in the two experiments. In the first study, a large black-and-white radial checkerboard stimulus was shown to the subjects, while in the current experiments smaller, lower-contrast face stimuli were employed. Due to its size, brightness, and contrast, it is likely that the checkerboard stimulus more efficiently activates primary visual areas than do the faces. These differences indicate that the amplitude and recovery of the HDR may be stimulus-specific.

These results are consistent with studies using extended stimulus epochs that suggest that the HDR to multiple stimuli cannot be modeled from simple addition of individual stimuli. In many experimental designs, researchers have separated events of interest in time to reduce hemodynamic interactions (McCarthy et al., 1997a; Pollmann et al., 1998; Rosen et al., 1998). When interactions have been explicitly investigated, however, summing the fMRI response to short-duration epochs (e.g., 3 s) overestimated the response to longer epochs (e.g., 12 s), for both visual (Boynton et al., 1996; Vazquez and Noll, 1998) and auditory stimuli (Robson et al., 1998). Similarly, a reduction in effect size has been found in single-trial designs when events

**FIG. 4.** Latency of the hemodynamic response for left fusiform (top left), right fusiform (top right), and calcarine cortex (bottom right) brain regions. For each slice investigated (x axis of graphs), the latency to peak amplitude was defined as the time at which the hemodynamic response function reached its maximal value, as determined by spline interpolation. Each graph indicates the latency to peak increase over single-stimulus values (y axis) for 1-s IPI (triangles) and 6-s IPI conditions (squares). There was a significant increase in latency to the second stimulus in a pair at 1 s IPI, but this difference recovered toward single-stimulus values by 6 s IPI.
Differences in refractory effects across brain regions. The presence of a refractory period, in itself, does not exceptionally complicate event-related fMRI designs. The general shape of the HDR has been modeled using Poisson (Friston et al., 1994) and gamma functions (Boynton et al., 1996), and underlying changes in blood flow and in oxygen extraction have been theoretically described (Buxton and Frank, 1997; Buxton et al., 1998). Analytic weighting functions have been proposed for modifying an idealized HDR function based on the interstimulus interval (Robson et al., 1998). Thus, nonlinearities in the HDRs to successive stimuli may be directly accounted for in model design or may be accounted for as separate conditions within a linear model (Friston et al., 1998). However, differences in the recovery of the HDR across brain regions and across stimuli do complicate event-related approaches to fMRI.

The changes in amplitude of recovery found in different areas of the fusiform gyrus suggest that different brain regions have different refractory periods. At 1 s IPI, regions in posterior fusiform cortex showed about 50–60% recovery to the second stimulus in a pair, while regions in midfusiform cortex showed 10–40%. One possible explanation for the differences across brain areas is that the degree of recovery depends on the amplitude of the initial activation; i.e., areas with greater amplitudes show the greatest recovery, while areas with lesser activation show little recovery. This explanation is at least generally consistent with the results from the fusiform gyrus, in that both the most activation to the single stimulus and the most recovery to the second stimulus (at 1 s IPI) were seen in posterior slices. However, we do not believe that this explanation can account for the specific structure of the data. Consider the data from slices 4 cm from the occipital pole. The signal change to a single stimulus at this slice location is about 0.72%, roughly two-thirds of that found on the most posterior slices (2.5–3 cm, 1.07%). Yet, recovery at both 1 s and 6 s for this slice location was similar to that of more posterior slices.

Another possible explanation for the differences in recovery found across the fusiform gyrus lies in differential processing functions. We tested each subject on a blocked-design control condition, in which faces were presented against a background of objects. Across the nine subjects with significant levels of activation, the control condition verified that the proportion of face-selective voxels was significantly larger in mid-fusiform slices (45, 50, and 55 mm from occipital pole) than in posterior slices (25, 30, and 35 mm from occipital pole) \[F(1,7) = 6.8, P < 0.05\]. This finding is consistent with work using blocked experimental designs that has localized face-selective processing to midfusiform cortex (Kanwisher et al., 1997; McCarthy et al., 1997b). This result suggests that similar regions exhibit both the least recovery, as shown by the experimental condition, and the most selectivity for face stimuli, as shown by the control condition.

Although these results complement earlier investigations of refractory effects in fMRI, two sets of unanswered questions remain. First, investigations of fMRI signal as a function of interstimulus interval cannot distinguish changes in neural response from changes in hemodynamic response, in the absence of concurrent measures of neural activity. Puce and colleagues (1999) investigated changes in event-related potential component amplitude across successive presentations of a single face, using intracranial electrodes located at face-specific sites on the fusiform gyrus. They found a significant decline in N200 amplitude between the first and second presentations of a face, although no additional decline was observed for subsequent presentations. Later face-specific components, such as the N700, showed a consistent decrease as additional faces were presented. These results suggest that, at some sites, part of the HDR refractoriness that we observed may be associated with changes in neuronal activity.

Yet, even if neural activity were exactly equivalent to two successive stimuli, the initiation of a blood flow response to the initial stimulus might affect the response to the second stimulus (e.g., Friston et al., 2000). BOLD fMRI contrast results from the inflow of oxygenated blood following neuronal activity. However, the relation between a neural response and the resulting BOLD context is mediated by more than just cerebral blood flow; changes in cerebral blood volume and in metabolic rate of oxygen are also relevant (Hess et al., 2000; Miller et al., 2001). The perfusion response following a stimulus is greater than required to meet the immediate metabolic demands of local neurons, so that the local blood oxygenation level increases in the seconds following neuronal activity. Therefore, the response to a single stimulus could provide oxygen both for that stimulus and for succeeding stimuli, reducing demand for additional perfusion responses. The strength of refractory effects in a given brain region, under this scenario, could depend on the degree to which successive stimuli activate similar neuronal populations (which in turn trigger similar perfusion responses). Regions highly selective for a given stimulus could more efficiently use the single-stimulus perfusion response, as seen in the present results.

Previous work directly comparing electrophysiological and hemodynamic refractory periods has further suggested that hemodynamic effects may occur in the absence of any differences in cortical evoked potentials. Cannestra and colleagues (Cannestra et al., 1998) examined refractory effects using both hemodynamic (optical imaging) and electrophysiological (evoked poten-
tials) measures. Testing rodent somatosensory, rodent auditory, and human sensorimotor cortices, they found that the hemodynamic response to a second stimulus in a short-1 sI pair was significantly attenuated in amplitude. For stimulus durations of about 2 s or less, the following refractory period lasted about 4 s. Longer stimulus durations evoked progressively longer refractory periods. Evoked potential recordings in the rodent subjects indicated that the second stimulus in a pair evoked similar neuronal responses, as no differences were observed between the successive stimuli. Future extensions of work on refractory periods should therefore combine direct measurement of recovery in the fMRI hemodynamic response with measurement of recovery of selective and nonselective components of evoked potential responses.

Second, these results suggest the existence of, but do not parametrically test, stimulus-specific effects upon refractory period. A large body of work has investigated changes in the fMRI HDR to a single stimulus as a function of stimulus properties, such as duration and intensity (e.g., Hu et al., 1997; Menon et al., 1997). Although refractory period characteristics have not been explicitly tested in fMRI across stimulus durations, several studies have demonstrated nonlinearities in the HDR in long-duration (>3 s) stimuli (Boynton et al., 1996; Robson et al., 1998; Vazquez and Noll, 1998). Furthermore, optical imaging studies in rats have also demonstrated stimulus-duration effects upon refractory periods in somatosensory cortex (Cannestra et al., 1998). Given that the current study, which used face stimuli, shows less recovery at 6 s in calcarine cortex than found by Huet al. and McCarthy (2000), which used checkerboard stimuli, it is necessary to systematically investigate how refractory periods change across different stimulus types and durations. Further studies should be conducted across other regions (e.g., paired-pulse studies of auditory cortex) to extend these conclusions.

Differences in HDR latency across brain regions. The current study revealed significant differences across brain regions in latency of the HDR to a single face stimulus. The HDR peak in calcarine cortex preceded that in fusiform cortex by about 400 ms. These results are similar to those reported by Huet al. and colleagues (Huet et al., 2001), who presented evidence for a HDR shift of about 300 ms between calcarine and fusiform cortex following presentation of single visual checkerboard stimuli. In that study, analysis of latency of a brain region was done for regions of interest in different axial slices, precluding comparison of posterior/anterior regions within the same anatomical region. Here, the results suggest that HDR latency was generally longer in posterior fusiform than in midfusiform cortex, although this conclusion must be tempered by the reduced number of voxels found in more anterior slices, which make latency measures less robust. In summary, our results replicate the general finding of latency differences in the HDR, and they encourage further research into whether HDR latency may vary across regions in a manner consistent with stimulus specificity.

There are two implications for analysis of functional imaging data. First, different brain regions have different HDR latencies, which violates the assumption of impulse-response-based analyses that the characteristics of the HDR are similar across all voxels tested. The current experiment, which measures neural activity solely through evoked hemodynamics, cannot distinguish between differences in the timing of neural activation or differences in vascular properties that mediate the resulting fMRI signal. Regardless of the origin of these differences, a reference HDR derived from one brain region may not be optimal for identifying activations in another region. Second, for a given brain region the latency of the HDR, not just its amplitude, may depend upon the stimulus presented. Amplitude differences in the evoked HDR are central to fMRI analyses, both to determine whether a region is significantly active and to compare the relative strength of activations elicited by different stimuli. We suggest that differences in the timing and shape of the HDR may be similarly informative. Further research should investigate whether ventral extrastriate visual cortex shows similar latency differences in the HDR for other stimulus types that may be functionally localized (e.g., houses/places, letter strings) and whether latency differences are absent for nonselective items (e.g., generic objects).

Conclusion. We investigated characteristics of the HDR evoked by event-related presentation of face stimuli. A refractory period exists in both calcarine and fusiform cortex such that the HDR is significantly attenuated in amplitude and increased in latency to the second stimulus in a pair at 1 s IPI. Significant recovery of both amplitude and latency occurs by 6 s IPI. Furthermore, differences in the characteristics of the refractory period were found for different brain regions. In general, midfusiform regions show reduced amplitude and shorter HDR latency to single stimulus events and longer refractory periods to multiple stimulus events than do posterior fusiform regions. Finally, HDR latency is greater in fusiform cortex compared to calcarine cortex, for face stimuli, replicating earlier work with radial checkerboard stimuli.

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