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Rapid Communication

The BOLD fMRI refractory effect is specific to stimulus attributes: evidence from a visual motion paradigm

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Functional magnetic resonance imaging (fMRI) studies have demonstrated that the blood oxygenation level-dependent (BOLD) hemodynamic response (HDR) to a stimulus is reduced by the previous presentation of a similar stimulus. We investigated the dependence of this refractory effect upon stimulus characteristics using a novel adaptation paradigm while scanning subjects using fMRI at 4 T. The stimuli were composed of horizontal stripes that scrolled up, scrolled down, or remained static, randomly presented for 1-s duration with stimulus-onset asynchronies (SOAs) of 2–7 s. We identified regions of interest (ROI) in lateral temporal–occipital cortex that were activated by motion stimuli, regardless of direction or SOA. We found strong evidence for direction specificity in motion-sensitive lateral temporal–occipital (LTO) cortex. For stimuli whose direction of motion reprised that of the previous stimulus (e.g., up preceded by up), the fMRI response was attenuated at short SOAs (2–4 s) compared to long SOAs (5–7 s). However, for stimuli whose direction of motion was opposite that of the previous stimulus (e.g., up preceded by down), little or no refractory effect was observed. Additionally, examination of activity in pericalcarine cortex indicated a similar pattern. We conclude that the fMRI refractory effect predominantly reflects local stimulus-specific neuronal or neurovascular adaptation and is unlikely to be a nonspecific response of large vessels that support broad functional regions.

Keywords: fMRI; Blood oxygenation; Refractory; Motion; Adaptation; Vascular

Over the past decade, functional magnetic resonance imaging (fMRI) has become the dominant method for studying the organization of the human brain in vivo. Using blood oxygenation level-dependent (BOLD) contrast, fMRI data can be acquired with spatial resolution on the order of millimeters and temporal resolution on the order of seconds. An important experimental advance has been the growing use of fast event-related paradigms, in which successive events of interests are separated by only a few seconds. Under the assumption that the BOLD hemodynamic response (HDR) reflects a linear transformation of neuronal activity (Boynton et al., 1996), the composite hemodynamic response to several events presented in rapid succession should reflect the linear summation of the responses to the individual events. The idea of linearity has been extremely influential and forms the basis for most fMRI analysis strategies, at least at interstimulus intervals (ISIs) under 12 s or so.

However, a number of laboratories have demonstrated that when two identical stimuli are presented in rapid succession (i.e., at an interval of 6 s or less), the fMRI HDR to the second stimulus is attenuated compared to that of a single stimulus presented in isolation (Dale and Buckner, 1997; Friston et al., 1998; Huettel and McCarthy, 2000). Likewise, when a series of stimuli are presented in rapid succession, the fMRI response adapts over time, so that the response to a long-duration series is less than would be expected based upon the response to a short-duration series (Boynton et al., 1996; Robson et al., 1998; Vazquez and Noll, 1998). Taken together, these results indicate that the fMRI BOLD response has a refractory period that lasts at least 6 s following initial activity, with greater attenuation at shorter interstimulus intervals.

The mechanism underlying fMRI BOLD refractory effects remains unknown. One possibility is that refractory effects are caused by adaptation of local neuronal populations (or of the local vasculature that directly supports a functional region), so that they will be present for stimuli that evoke similar neuronal activity but absent for stimuli that evoke different neuronal activity (Grill-Spector and Malach, 2001). Another possibility is that refractory effects could be a nonspecific response of large vessels that support broad functional regions. Thus, they could be present for stimuli that evoke different neuronal activity, as long as the active neurons

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were within a larger functional area (e.g., one that supports multiple stimulus attributes). These two possibilities are not distinguishable in most studies of refractory effects, because those studies have typically repeated identical stimuli. However, they can be deconfounded by manipulating whether stimulus attributes repeat or change over successive trials (Boynton and Finney, 2003; Grill-Spector and Malach, 2001; Soon et al., 2003).

To investigate whether the fMRI refractory effect depends upon adaptation to stimulus attributes, we presented visual gratings that moved either upward or downward within a rapid event-related design. We chose simple motion stimuli because they can differ in direction but share all other physical properties and because motion-selective areas (MT/V5) in lateral temporal–occipital (LTO) cortex are not contiguous with primary visual regions, so these regions can be easily distinguished. We hypothesized that if the fMRI refractory effect is due (at least in part) to underlying refractory effects in local neuronal responses, then there should be larger refractory effects for stimuli that share attributes (i.e., same direction of motion) than for stimuli that have different attributes (i.e., different direction of motion). Conversely, similar refractory effects regardless of stimulus attributes would suggest that the BOLD fMRI signal operates on a spatial scale coarser than that of directional processing.

Materials and methods

Subjects

The fMRI sample consisted of 11 young adults (seven female, four male; mean age: 25 years). All had normal or corrected-to-normal visual acuity, and none reported any history of neurological injury or illness. Data from an additional three subjects were excluded due to poor behavioral performance (described below), and two additional subjects were excluded due to excessive head motion. The study was conducted under the guidelines of the institutional review board of Duke University Medical Center, and all subjects provided informed consent for their participation.

Experimental task

Subjects fixated on a small cross at the center of the display (total field of view: 20° × 16°). Surrounding the fixation cross was a pattern of horizontal white bars (spatial frequency: one cycle/6°). Each white bar was overlaid with higher frequency black bands (spatial frequency: one cycle/0.6°) to increase visible contrast. Static black bars covered 2° around the vertical and horizontal meridians. Stimuli were presented using the CIGAL environment (Voyvodic, 1999) and were viewed by subjects using LCD goggles (Resonance Technologies, Inc.).

There were three types of experimental trials: upward motion, downward motion, and static. On motion trials, the stimulus scrolled upward or downward for 1 s at a rate of 12°/s, ending at the starting point in the cycle, while on static trials, the stimulus did not change (i.e., static trials were indistinguishable from the intertrial interval). The static trials were equivalent to what have been called "nostim" or "null" trials in other fast-rate studies and were included to aid in estimation and removal of overlapping responses from adjacent trials in the stimulus sequence. The three trial types (moving up, moving down, static) were presented equally often in a randomized order, with stimulus-onset asynchronies (SOAs) randomized between trials in 1-s increments from 2 to 7 s. Subjects participated in an average of 8.8 experimental runs, each 5 min in duration, for a total of approximately 180 stimuli of each trial type (distributed across the SOAs). To ensure attention to the display, subjects pressed a button to the infrequent and random appearance of a white 1° border which surrounded the stimulus display for 84 ms. All subjects included in the analyses had detection rates of 95% or greater. Three excluded subjects had detection rates of 64%, 50%, and 30%.

FMRI parameters

Functional images were acquired on a 4T GE NVi scanner (Waukesha, WI) using a BOLD-sensitive spiral-in gradient-echo pulse sequence (TR, 1000 ms; TE, 40 ms), which allows high temporal resolution and ameliorates susceptibility artifacts (Glover and Law, 2001; Guo and Song, 2003). For each subject, 23 axial slices with voxel size of 3.75 × 3.75 × 3.8 mm were selected parallel to the line connecting the anterior and posterior commissures, based on initial sagittal structural scanning. For identification of anatomical locations, the same imaging volume was sampled using T_1-weighted SPGR images with 0.9375-mm in-plane resolution and 1.9-mm through-plane resolution. Functional images were corrected for subject motion and time of slice acquisition within a volume (SPM99; Wellcome Department of Cognitive Neurology, London).

FMRI Analyses

We identified voxels in LTO cortex sensitive to motion stimuli using an iterative correlation analysis. More specifically, for each voxel in each subject, we first determined the net effect of motion stimuli on the HDR by subtracting the mean HDR across all static trials from the mean HDR across all motion trials. By determining the correlation between this net response and a canonical HDR derived from visual cortex (Huettel and McCarthy, 2000), we identified a region of interest (ROI) in pericalcarine cortex, from which we estimated a subject-specific HDR (Aguirre et al., 1998). We used a relatively loose correlation ($P < 0.01$) at this initial stage to minimize biasing effects of the choice of initial HDR. We next repeated the correlation analysis using each subject's individual HDR. From the resulting activation map ($P < 0.001$), functionally defined ROIs for each subject were identified in LTO and pericalcarine cortices. The LTO activation (and resulting ROI) was bilateral in 9 of 11 subjects and restricted to the right hemisphere in the remaining two subjects. A second functional ROI was defined by selecting contiguous active voxels within the medial occipital lobe along the calcarine sulcus; this ROI was selected without regard to the initial pericalcarine ROI.

We categorized each motion trial into one of two groups. On congruent trials, a motion stimulus followed another with a similar direction of motion (i.e., up preceded by up, down preceded by down). On incongruent trials, a motion stimulus followed another with the opposite direction (i.e., up preceded by down, down preceded by up). For each of these categories at each SOA, we determined the net effect of stimulus motion by subtracting the HDR to the corresponding static trial; for example, the HDR to static trials preceded by up trials at a certain SOA was subtracted from the HDR to up trials preceded by up trials at that same SOA. Because the specified preceding HDRs were identical in these cases, their overlap would also be identical, thus allowing this subtractive procedure to eliminate the independent contribution of

the preceding trial (Buckner et al., 1998; Burock et al., 1998; Woldorff, 1993), so that direct comparison could be made between the responses to the current stimulus across the different SOAs.

Results

The presentation of a brief motion stimulus reliably evoked activity in LTO and pericalcarine cortices. Within LTO cortex, there were more active voxels in the right hemisphere than the left hemisphere across subjects [$t(10) = 3.42$, $P < 0.01$]. Within both regions, we observed a standard BOLD hemodynamic response with a peak mean percentage signal change over baseline of about 0.5% at 4 s following stimulus onset.

Fig. 1 shows the mean response in the LTO and pericalcarine ROIs across SOA durations for all stimuli regardless of whether direction of motion differed from that of the previous stimulus. As expected, there was a refractory effect of prior stimulus presentation, such that the BOLD hemodynamic response increased with increasing SOA, for both regions of interest. The magnitude of the refractory effect, defined as the reduction in mean amplitude at time points 3–5 between minimal and maximal SOAs, was approximately 40% in LTO and 60% in pericalcarine cortex. For LTO, the specific refractory effect values for SOAs 2–6 s (compared to SOA 7s) were 37%, 46%, 41%, 19%, and 31%. For pericalcarine cortex, the refractory effects for SOAs 2–6 s (compared to SOA 7 s) were 59%, 33%, 26%, 16%, and 16%.

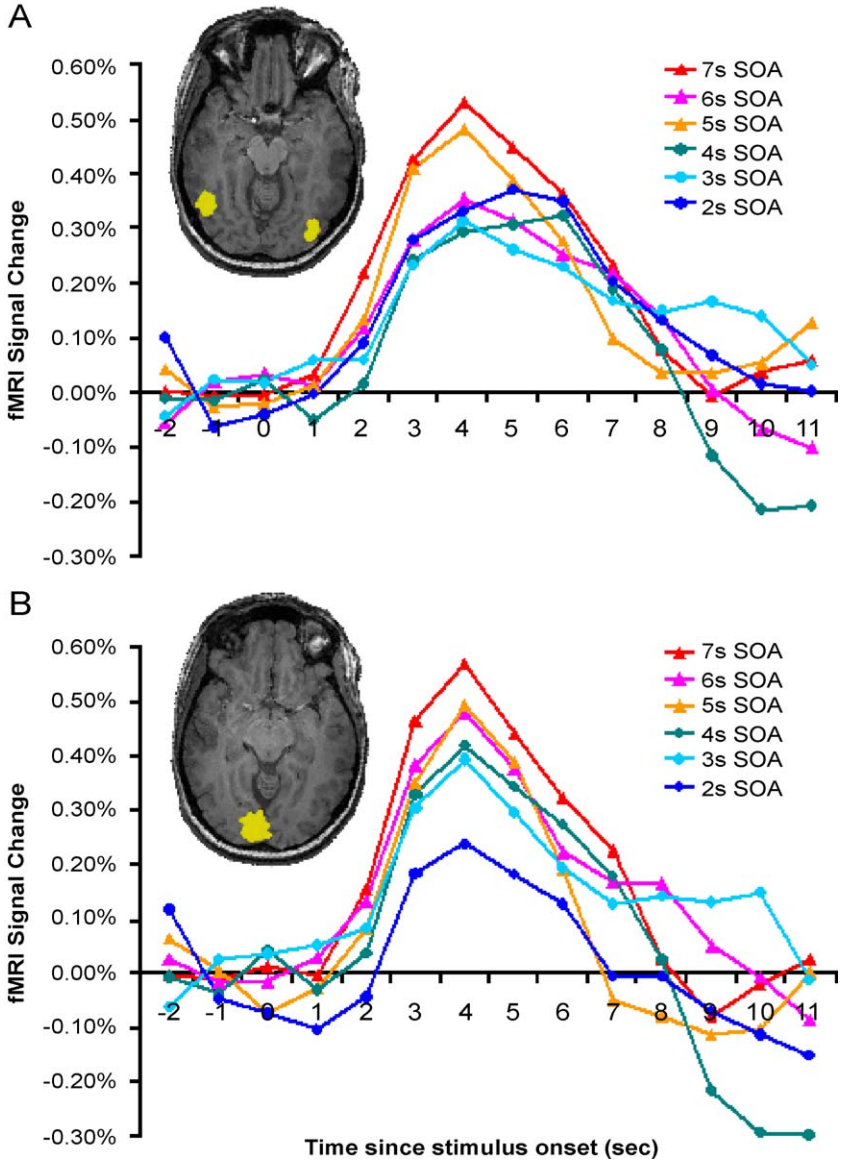

Fig. 1. FMRI refractory effects in lateral temporal–occipital (LTO) and pericalcarine cortices. Plotted is the mean fMRI BOLD response to a 1-s presentation of moving bars as a function of the time since the preceding stimulus or stimulus-onset asynchrony (SOA). Within both LTO (A) and pericalcarine (B) regions, the fMRI response increases significantly with increasing time since the previous stimulus. This attenuation at short SOAs demonstrates the refractory effect in the fMRI BOLD hemodynamic response.

Direction specificity of the refractory effect

We next evaluated whether refractory effects were present in each ROI for each motion-congruency condition using a repeated-measures ANOVA with factors of SOA (six levels: 2, 3, 4, 5, 6, 7 s SOAs) and time point of the hemodynamic response around its peak (three levels: 3, 4, 5 s following onset). It is important to recognize that the same physical stimuli were compared across all analyses, the only differences being the direction of motion and the relative timing of the preceding stimulus.

In LTO cortex, BOLD amplitude decreased at short SOAs in the congruent condition [$F(5,50) = 3.00$; $P < 0.05$] but was not different across SOAs in the incongruent condition [$F(5,50) = 0.84$; $P > 0.10$]. We also examined the interaction between these factors by including an additional factor of congruency (two levels: congruent, incongruent) in the ANOVA. We found a significant congruency × SOA interaction [$F(5,50) = 2.43$; $P < 0.05$], indicating that congruency has a significant effect upon the magnitude of this amplitude reduction.

Likewise, in the pericalcarine cortex, BOLD amplitude decreased at short SOAs in the congruent condition [$F(5,50) = 2.84$; $P < 0.05$], but was unchanged across SOAs in the incongruent condition [$F(5,50) = 0.72$; $P > 0.10$]. There was also a significant congruency × SOA interaction in the combined ANOVA [$F(5,50) = 6.04$; $P< 0.01$]. These results mean that, for both regions, the BOLD fMRI refractory effect is present for congruent trials but not for incongruent trials.

Fig. 2 shows the effects of stimulus congruency for both brain regions investigated. For clarity, we have collapsed the data into "short SOA" conditions (i.e., 2–4 s) and "long SOA" conditions (i.e., 5–7 s). Visible is the considerable attenuation of the response in the congruent condition. To ensure that this representation did not affect the analyses, we repeated the above ANOVAs using only two levels of SOA (short and long) in each analysis. As before, significant refractory effects were found in the congruent conditions for both LTO [$F(1,10) = 8.24$; $P < 0.05$] and pericalcarine cortices [$F(1,10) = 6.74$; $P < 0.05$], but no refractory effects were present in the incongruent conditions for either region ($P > 0.10$). Combined ANOVAs that included the congruent and incongruent conditions revealed that the congruency × SOA interaction was significant for both the LTO [$F(1,10) = 5.11$; $P < 0.05$] and pericalcarine [$F(1,10) = 9.79$; $P < 0.05$] regions.

We additionally compared the magnitude of attenuation across subjects for each ROI. In the LTO ROI, the mean hemodynamic response at short SOAs was attenuated by more than 40% in the congruent condition, and this effect was significant across subjects [$t(10) = 2.87$; $P < 0.05$]. The attenuation in the incongruent case was only 12% and was not significant [$t(10) = 1.54$; $P > 0.10$]. In

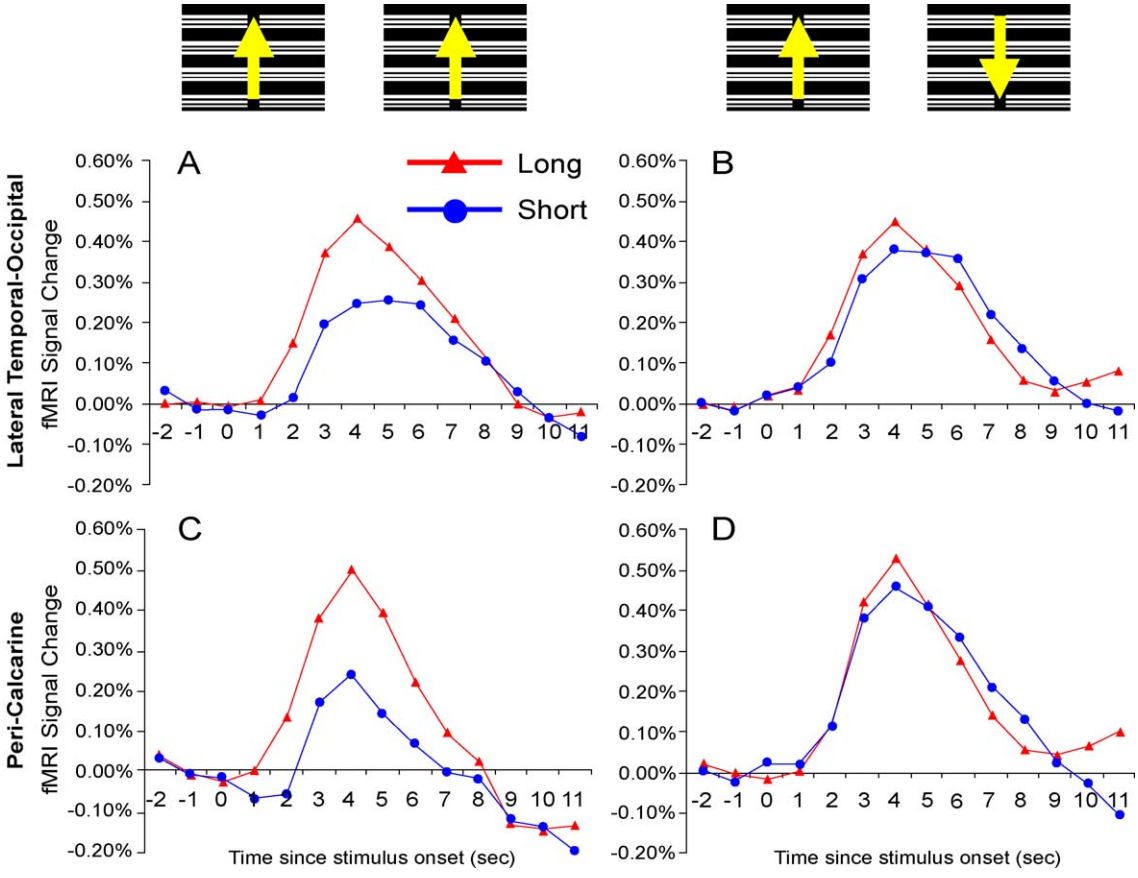

Fig. 2. Dependence of the fMRI refractory effect upon stimulus attributes. Shown are the mean fMRI BOLD responses to motion stimuli as a function of whether the direction of motion was the same as (left column) or changed from (right column) that of the previous stimulus. When the direction of motion repeated, the amplitude of the fMRI response was significantly smaller at short SOAs (2–4 s) than at long SOAs (5–7 s), for both LTO (A) and pericalcarine cortices (C). However, when the direction of motion changed, there were no significant refractory effects for either region (B, D). These results demonstrate that the fMRI refractory effect depends upon repetition of particular stimulus attributes, not merely upon repetition of the same general stimulus class.

pericalcarine cortex, there was significant attenuation in the congruent condition of more than 55% [$t(10) = 2.60$; $P < 0.05$] but again only a much smaller (8%), nonsignificant attenuation in the incongruent condition [$t(10) = 0.58$; $P > 0.10$]. Thus, at interstimulus intervals of 2–4 s, there were very large refractory effects in the congruent condition but no significant refractory effects in the incongruent condition.

Discussion

Our results provided support for three specific conclusions. First, the BOLD fMRI response exhibits a refractory effect to repeated presentation of motion stimuli, consistent with results using other stimulus types. Second, the refractory effect was present for congruent motion stimuli but was largely absent for incongruent motion stimuli, even at short stimulus durations. Third, similar direction specificity was found in both LTO and pericalcarine cortices. We consider the implications of each of these results in turn.

Attribute-specific refractory effects

In this experiment, we identified refractory effects in the BOLD fMRI response using a novel experimental paradigm and stimulus modality. Previous studies have investigated the nonlinearity of the BOLD response using two primary approaches. In the duration-based approach, researchers evaluate whether the fMRI response to a long-duration stimulus is equivalent to the linear combination of multiple short-duration responses (Birn et al., 2001; Boynton et al., 1996; Huettel et al., 2004; Robson et al., 1998; Vazquez and Noll, 1998). In the paired-pulse approach adapted from electrophysiology, researchers present two or more discrete stimuli in rapid succession, measuring whether the response to the second stimulus in a pair changes as a function of the intrapair interval (Boynton and Finney, 2003; Buckner et al., 2000; Dale and Buckner, 1997; Friston et al., 1998; Huettel and McCarthy, 2000, 2001; Huettel et al., 2001; Soon et al., 2003).

While these previous approaches have provided important information about refractory effects, they are not ideal designs for other research questions. For example, the paired-pulse approach uses long intertrial intervals to ensure full recovery of the fMRI response between successive pairs, resulting in a relatively low density of stimuli per unit time and limited statistical power. More efficient rapid event-related designs present stimuli with short but jittered interstimulus intervals (Birn et al., 2002; Burock et al., 1998; Liu et al., 2001; Miezin et al., 2000; Woldorff, 1993). The current results demonstrate that fMRI refractory effects can be observed using a rapid event-related paradigm, even when events are spaced as closely as a few seconds apart. We note that examination of the gross response to each stimulus revealed a substantial overlap from the previous trial, as expected based upon the short intervals used. However, as has been demonstrated previously, removal of the previous-trial response using subtraction resulted in clean hemodynamic responses (Buckner et al., 1998; Burock et al., 1998; Woldorff, 1993). However, fast-rate designs can potentially introduce effects of earlier stimuli in the sequence. For example, in the present study, the response to 6-s SOA stimuli was somewhat less than that to the 5-s SOA stimuli in both regions. Subsequent analysis of the random stimulus sequence revealed that the 6-s SOA stimuli had been randomly preceded by shorter SOAs, on average, than any other condition. Additional work will be necessary to quantify the effects of multiple preceding stimuli upon refractory effects.

Despite substantial interest in the fMRI refractory effect both for improvement of experimental analyses and for potential localization of function, there is a paucity of studies that have investigated the attribute specificity of this effect. A recent study by Soon et al. (2003) using a paired-pulse design investigated refractory effects in visual cortical regions to the presentation of either repeated or different faces. They found significant refractory effects in calcarine and fusiform cortices, with activity in both regions reduced at 3-s SOA compared to 6-s SOA, consistent with earlier results (Huettel and McCarthy, 2001). They further found that activity in midfusiform cortex, which is generally most face-selective, had a greater reduction when the same face was repeated than when different faces were presented. However, within calcarine cortex and posterior fusiform cortex, face congruency did not influence the refractory effect.

In another recent fMRI study, Boynton and Finney (2003) presented static gratings of either similar or different orientation in a paired-pulse design. Although refractory effects were found in all visual regions, the responses in primary visual cortex (V1) and in secondary visual area (V2) were not affected by the congruency of the orientations, while in higher visual cortical areas (V3, V4v) there were orientation-specific effects. These results stand in contrast with those of an earlier report that found that changing the orientation of a stimulus in a blocked design resulted in an increase in fMRI signal in V1 proportional to the angle of change (Tootell et al., 1998).

Combined with the results from the present study, these studies suggest that stimulus attributes can influence the fMRI refractory effect, such that repeating a stimulus attribute results in reduced activity compared to changing that attribute. Yet, several issues remain unsettled, notably whether attribute-selective effects exist in primary visual cortical regions and whether the refractory effect can be essentially eliminated, even at short intervals, under appropriate conditions. We discuss these issues in the following section.

Implications for fMRI studies of cortical organization

The relative contributions of electrophysiological and vascular components to the fMRI refractory effect remain poorly understood, and both may contribute to the fMRI data (Boynton and Finney, 2003). Electrophysiological studies have clearly demonstrated that refractory effects influence the amplitude of local field potentials associated with neuronal activity (Allison, 1962; Naatanen and Picton, 1987; Nelson and Lassman, 1973; Woods et al., 1980) and can themselves be heavily influenced by attention (Woldorff and Hillyard, 1991). However, electrophysiologically measured refractory periods are generally short, often less than a second, with longer latency components having more extended refractory effects (Allison, 1962; Naatanen and Picton, 1987; Nelson and Lassman, 1973; Woods et al., 1980). For example, intracranial electrode recordings in human inferior occipital cortex indicate that the refractory period to the presentation of brief color stimuli is only a few hundred milliseconds in duration (Allison et al., 1993). In contrast, the fMRI refractory effect resolves over a duration of about 6 s for all stimulus types tested so far (Boynton et al., 1996; Huettel and McCarthy, 2000; Huettel et al., 2001; Robson et al., 1998; Soon et al., 2003; Vazquez and Noll, 1998). This discrepancy suggests that electrophysiological refractory effects alone cannot fully explain the fMRI refractory effect. Future

studies employing both electrophysiological and hemodynamic measures, using identical paradigms and contrasts, seem likely to be particularly useful for helping to delineate the source of these attribute specificity effects.

One approach that holds promise for addressing this issue is the use of stimulus adaptation paradigms (Grill-Spector and Malach, 2001), such as used in the present study for stimulus attributes. As previously implemented, after repeatedly presenting a stimulus to induce adaptation of the fMRI response, a slightly different stimulus can be presented and the recovery from adaptation measured. Large recovery in a brain region indicates that the region is sensitive to the manipulated attribute, while continued adaptation indicates insensitivity. A fundamental assumption of adaptation approaches is that the vascular response to which fMRI is sensitive is measured at a coarser scale than the true functional organization of cortex, meaning that the same pattern of observed hemodynamic activity could reflect any number of patterns of neuronal activity.

Our results support the use of adaptation paradigms, in that we found that congruent stimuli evoked a smaller fMRI response than incongruent stimuli. Yet, such congruency effects were found not only in motion-selective cortex, but in pericalcarine cortex as well. The latter result differs from those of Soon et al. (2003) and Boynton and Finney (2003) but is consistent with the results of Tootell et al. (1998). Of particular interest is the discrepancy between the current results and those of Boynton and Finney, who used line gratings with different orientations. While V1 neurons known as simple cells are sensitive for line orientation but not direction of motion, neurons known as complex cells respond preferentially to stimuli moving in one direction or another (Hubel and Wiesel, 1959), through integration of information from multiple simple cells. We speculate that should the fMRI refractory effect result from changes in the coupling between neuronal activity and the vascular response, this coupling could be driven primarily by such integrative cells, as their activity may be most predictive of the future metabolic demands of a brain region.

We finally note that our results have implications for the vascular source of the fMRI refractory effect. Even at short SOAs of 2–4 s, at which refractory effects are typically robustly observed, the fMRI BOLD response to incongruent stimuli was not significantly different from its maximal value. While the lack of a significant effect for this condition does not necessarily imply that no such effect, even one of a small magnitude, exists, it does suggest that the refractory effect may be largely independent of large vessel contributions (i.e., veins draining from regions that span multiple attribute values). That is, if large veins experience vascular refractoriness, then the refractory effect should likely have been present for both the congruent and incongruent stimuli. Instead, the BOLD refractory effect may depend upon properties of the local microvasculature, thus perhaps providing potentially better localization of function than the standard BOLD effect. The use of diffusion-weighted fMRI pulse sequences to isolate signal from different vascular compartments, in conjunction with adaptation designs like that used in the present study, will allow finer spatial characterization of vascular compartments and will prove important for future studies of refractory effects.

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