Linking Hemodynamic and Electrophysiological Measures of Brain Activity: Evidence from Functional MRI and Intracranial Field Potentials

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We investigated the relation between electrophysiological and hemodynamic measures of brain activity through comparison of intracranially recorded event-related local field potentials (ERPs) and blood-oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI). We manipulated the duration of visual checkerboard stimuli across trials and measured stimulus-duration-related changes in ERP and BOLD activity in three brain regions: peri-calcarine cortex, the fusiform gyrus and lateral temporal–occipital (LTO) cortex. ERPs were recorded from patients who had indwelling subdural electrodes as part of presurgical testing, while BOLD responses were measured in similar brain regions in a second set of subjects. Similar BOLD responses were measured in peri-calcarine and fusiform regions, with both showing monotonic but non-linear increases in hemodynamic amplitude with stimulus duration. In sharp contrast, very different ERP responses were observed in these same regions, such that calcarine electrodes exhibited onset potentials, sustained activity over the course of stimulus duration and prominent offset potentials, while fusiform electrodes only exhibited onset potentials that did not vary with stimulus duration. No duration-related ERP or BOLD changes were observed in LTO. Additional analyses revealed no consistent changes in the EEG spectrum across different brain sites that correlated with duration-related changes in the BOLD response. We conclude that the relation between ERPs and fMRI differs across brain regions.

Keywords: BOLD, fMRI, hemodynamic response, visual cortex

Introduction

The noninvasive measurement of localized neuronal activity within the human brain during the performance of sensory, motor and cognitive tasks is a primary goal of modern neuroscience research. Present technologies – such as the recording of event-related electric or magnetic fields from extracranial sensors, or the detection of local changes in blood oxygen levels with functional magnetic resonance imaging (fMRI) – approximate this goal. Each technique, however, has limitations. Analysis of electrical or magnetic recordings from extracranial sensor arrays cannot in principle yield unique solutions for the locations of their neural generators. Rather, those locations are estimated using assumptions based upon the hypothesized number, extent and shape of the generators. While fMRI can provide relatively high-resolution images of the distribution within the brain of changes in blood oxygen-level dependent (BOLD) contrast, how those changes relate to concurrent changes in the spatial extent and magnitude of the precipitating neuronal events is as yet unclear. Indeed, what aspect of neuronal activity – e.g. aggregate neuronal spiking, local field potentials, changes in spontaneous rhythms – is the best predictor of BOLD contrast change has not been established definitively.

The relationship between event-related field potentials (ERPs, or event-related magnetic fields, EMFs) recorded extracranially and BOLD contrast is of particular interest because of their complementary strengths. The location of neural generators based on extracranial recording could be made more precise if the location of BOLD activations could replace, constrain, or seed inverse models (Mangun *et al.*, 1998). The temporal dimension of neuronal activity at a given BOLD activation location would be greatly enhanced if a time course of activity could be derived for that location from extracranially recorded fields.

Several early studies demonstrated a reasonably good spatial correspondence between sites of activation measured by BOLD contrast and ERPs recorded from arrays of intracranial subdural electrodes, which had been placed into the brains of patients to localize active regions of cortex using stimulation and/or ERPs (Puce *et al.*, 1997; Schlosser *et al.*, 1999). However, some studies have revealed discrepant results (McCarthy, 1999). A close correspondence between changes in the magnitude of BOLD contrast and neuronal activity has been supported by studies in which quantitative changes in neuronal firing in monkey V5 in response to changes in motion coherence were compared to quantitative changes in the BOLD response in this same brain region in humans (Rees *et al.*, 2000). However, other comparisons of neuronal firing data to spatial patterns of BOLD activity have been less straightforward. For example, Harel *et al.* (2002) reported that visual stimulation resulted in positive BOLD changes in cat primary cortex and negative BOLD changes in adjacent suprasylvian cortex, despite prior studies indicating that visual stimulation increases neuronal firing rates in both regions.

In a recent study by Logothetis *et al.* (2001), BOLD contrast, multiunit neuronal firing rate and local field potentials were simultaneously measured in the primary visual cortex of macaque monkeys. They found that local field potential activity was significantly correlated with the amplitude of the fMRI BOLD response and that this relation held during manipulation of both the duration and the contrast of a visual stimulus. Multiunit neuronal firing rate was also related to BOLD activity, albeit less closely than the local field potentials. This elegant study has generated considerable interest. Left unanswered, however, is the extent to which the relationship between local neuronal activity and BOLD contrast holds across the typically wide spatial extent of a BOLD activation, or across different brain regions that are activated by the same stimulus. Recent studies have shown that the spatial extent of a BOLD activation can be greatly decreased by mild diffusion weighting, a procedure that de-emphasizes the signal contribution from mobile

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protons in large draining vessels that presumably are not spatially co-localized with the active neurons (Song *et al.*, 1996, 2002). This suggests that typical BOLD activation maps may overestimate the spatial extent of neuronal activation. Other recent studies have reported that refractory effects in the BOLD response differ across different brain regions (Birn *et al.*, 2001; Huettel and McCarthy, 2001), suggesting that the covariation between BOLD and neuronal activity may also differ in different brain regions.

Here we compared variations in the magnitude of local evoked field potentials and BOLD contrast in response to visual stimuli of three different durations. We measured activity changes in three regions: calcarine, fusiform and lateral temporal–occipital (LTO) cortices. Prior studies in >100 patients with subdural electrodes and penetrating multicontact depth electrodes have established that visually evoked ERPs in and near primary visual cortex differ markedly from those evoked in fusiform gyrus and in lateral temporal–occipital cortex (Allison *et al.*, 1999). In particular, ERPs near primary visual cortex are characterized by sustained potentials and large stimulus offset potentials that are uncharacteristic of visually evoked ERPs recorded from other brain regions. We reasoned that if the BOLD response was correlated with local field potentials, then these regional differences in local ERPs should be evident in the magnitude of the BOLD responses evoked in these different regions.

Measurements were taken in two groups. The field potential group consisted of nine patients who had subdural grids and strips of electrodes implanted in visual cortex in preparation for neurosurgery. The fMRI group consisted of 12 neurologically normal young adult subjects, in whom activity was measured using BOLD contrast fMRI at 4 T.

Materials and Methods

Subjects

Twelve young adults (seven females, five males, mean age 21 years) participated in the fMRI study, which was conducted at the Duke-UNC Brain Imaging and Analysis Center. All participants had normal or corrected to normal visual acuity. No subject reported any history of neurological injury or disease.

Intracranial ERP recordings were obtained from nine patients (five females, four males, mean age 31 years) with medically intractable epilepsy who were being evaluated for possible surgery by the Yale Epilepsy Surgery Program. All ERP recordings were conducted at Yale-New Haven hospital. In these patients, strips or grids of stainless steel electrodes (2.2 mm surface diameter) were placed subdurally on the cortical surface. The placement of the strips was determined according to the clinical needs of each subject, and thus electrode locations varied across subjects (see Fig. 2). The location of individual electrodes were derived from T_1-weighted MR images obtained on the day following implantation. Electrode localization procedures are described in detail in earlier work (Allison *et al.*, 1999). This study was one of several sensory and cognitive ERP experiments in which each subject participated, typically 4–8 days following implantation of electrodes.

The imaging protocol used in this experiment was approved by the Institutional Review Board (IRB) of the Duke University Medical Center. The ERP protocol was approved by the IRB of the Yale University School of Medicine. All participants provided informed consent.

Experimental Design

On each trial, a single high-contrast black-and-white radial checkerboard was presented at fixation at one of three durations: 100, 500, or 1500ms. The radial checkerboard had maximum spatial frequency near the fovea (~4 cycles/degree, at 1° from fixation) and spatial frequency increased linearly to its maximum at the edges of the display (~0.25 cycles/degree, at 10° from fixation). The stimulus did not cycle on and off, but remained static over its duration to facilitate ERP recording of onset and offset potentials. In the fMRI experiment, stimuli were projected into the scanner bore onto a screen, which the subject viewed using mirrored goggles. The resulting field of view subtended ~20 × 15° of visual angle. In the ERP experiment, subjects were in a hospital bed and viewed the stimuli on an LCD computer monitor, whose display subtended ~18 × 14° of visual angle.

In both experiments, the interstimulus interval (ISI) was jittered across values that were sufficiently long to preclude refractory effects from preceding trials. The mean ISI for the fMRI experiment was 16s (range 15–17 s) and the mean ISI for the ERP experiment was 6 s (range 5–7 s). All stimuli were presented using the CIGAL display environment (Voyvodic, 1999). All fMRI participants viewed a total of 220 stimuli. Eight ERP participants viewed a total of 126 stimuli over three runs that were separated by rest periods. One ERP participant viewed 84 stimuli over two runs. For both fMRI and ERP studies, the three stimulus durations were randomly ordered within each run.

fMRI Image Acquisition and Analysis

All MR images were acquired using a 4.0 T GE NVI scanner. Following acquisition of a sagittal scout, we identified eight 5 mm thick slices taken parallel to the anterior–posterior commissure line, chosen to encompass calcarine and fusiform cortices. T_1-weighted spin-echo images were acquired at each slice location for identification of anatomically based regions of interest (in-plane resolution = 0.9375 mm^2). For functional imaging, we acquired T_2*-weighted images sensitive to BOLD contrast using a spiral-out gradient-echo pulse sequence (T_R = 500 ms, T_E = 20 ms, flip angle = 20°, in-plane resolution = 3.75 mm^2).

We excised from the continuous fMRI time series peristimulus epochs extending from 10 time points (–5 s) preceding through 24 time points (+12 s) following each stimulus event. We calculated significance values at each voxel by correlating its mean time course, across all stimulus events regardless of duration, to a canonical hemodynamic response. As our experimental hypotheses were based upon activation changes in specified brain regions, we employed a region of interest (ROI) approach. For each subject, we outlined peri-calcarine and fusiform cortices using anatomical landmarks in each subject's T_1-weighted images. We then selected all active voxels ($P < 0.0005$) in one slice within that region. As described in the Results section, every subject also exhibited activity in a more anterior visual region near the lateral temporal–occipital junction. Due to the difficulty of determining anatomical boundaries for V5, we defined the LTO ROIs by identifying the voxel with maximal significance and then selecting all contiguous active voxels.

ERP Data Acquisition and Analysis

The EEG from subdural electrodes was recorded referentially to a mastoid electrode using a 128 channel SA Instruments EEG amplifier system with a 0.01–100 Hz bandpass. The EEG was sampled continuously at 250 Hz/channel using a custom PC-based acquisition system and written to disk. Stimulus codes synchronized to the onset of each checkerboard were incorporated into the data stream to facilitate offline averaging of the visually evoked ERPs. Averages were derived for each stimulus duration and each of the 128 electrodes sampled.

One of the authors (T.A.) localized the position of all posterior electrodes using the MR anatomical images acquired for each subject. Across the nine experimental subjects, we identified a total of 35 calcarine electrodes (8/9 subjects), 17 fusiform electrodes (8/9 subjects) and 22 LTO electrodes (9/9 subjects).

Results

fMRI Data

The presentation of visual checkerboards evoked fMRI activation in the three visual cortical regions of interest (ROI): peri-calcarine cortex, fusiform cortex and an anterior lateral region at the intersection of the lateral temporal and occipital lobes (LTO). Figure 1 presents the patterns of fMRI activity in these

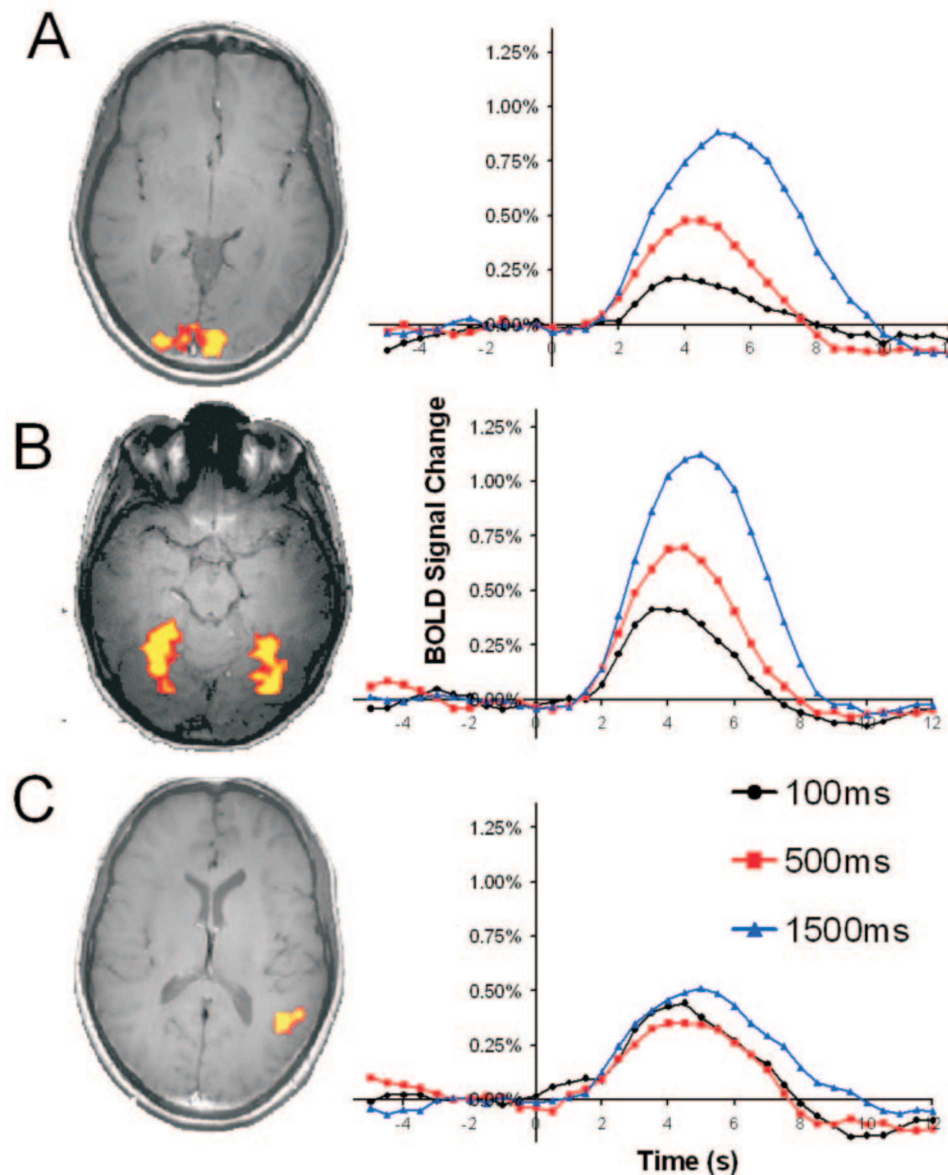

Figure 1. Functional MRI activity in visual cortex. Shown are fMRI results obtained from active voxels within three anatomical regions: (*A*) per-calcarine cortex, (*B*) the fusiform gyrus and (*C*) the lateral junction of the temporal and occipital lobes (LTO). At left are data from a representative subject that illustrate the spatial patterns of activity that were observed, combined across all stimulus durations. The colormaps are scaled according to *t*-value, with red indicating *t*-values of 5.0 ($P < 0.0005$) and yellow indicating *t*-values of 8.0 or greater ($P < 10^{-9}$). At right are shown the time courses obtained within these regions, averaged across the 12 subjects. No activity was observed during the 5 s pre-stimulus baseline. Following stimulus onset, significant hemodynamic responses were found for all regions and durations. For fusiform and peri-calcarine cortices, the amplitude and latency of the hemodynamic response scaled with stimulus duration. In LTO, peak latency but not amplitude depended upon stimulus duration.

anatomical regions for a single representative subject, along with the raw time course for active voxels within each ROI averaged across all subjects.

Significant activity was found, for all subjects, in a bilateral region spanning the upper and lower banks of the calcarine sulcus near the occipital pole. Although visual cortical areas were not functionally mapped in individual subjects, this ROI likely included both primary (V1) and secondary (V2) visual areas and thus is labeled 'peri-calcarine'. Significant activation was observed on the inferior surface of the occipital and temporal lobes. To ensure correspondence between our fMRI and ERP measures, we restricted our inferior ROI to the fusiform gyrus, as identified in each individual's anatomical images. Activation in LTO was found in all subjects. This LTO region has been associated with the processing of motion stimuli and has been considered a human homologue for monkey area V5/MT (McCarthy *et al.*, 1995; Tootell and Taylor, 1995; Rees *et al.*, 2000). No other regions of activation were consistently observed across subjects, and thus further analyses will focus on these three regions of interest.

We next examined the effects of stimulus duration upon the amplitude, area, peak and width of the hemodynamic response. The peak amplitude of the hemodynamic response systematically increased with increasing stimulus duration, as revealed by ANOVA, in both peri-calcarine [$F(2,22) = 62.7$, $P < 0.00001$] and fusiform [$F(2,22) = 42.2$, $P < 0.00001$] cortices.

These results were highly consistent across subjects, with regular peak amplitude rankings (i.e. 100 < 500 < 1500 ms) observed for 11 of 12 subjects in peri-calcarine cortex and 10 of 12 subjects in fusiform cortex. In contrast, activation in LTO was of similar amplitude for all stimulus durations [$F(2,22) = 2.2$, $P > 0.1$]. Likewise area of the hemodynamic response (from 0 to 12.5 s following stimulus presentation) increased with stimulus duration in both-pericalcarine [$F(2,22) = 24.4$, $P < 0.00001$] and fusiform [$F(2,22) = 15.5$, $P < 0.0001$] cortices and there was a small but significant effect of duration upon response area in LTO cortex [$F(2,22) = 3.72$, $P < 0.05$]. This last effect was driven entirely by an increase for the 1500 ms duration compared to the other two groups.

We additionally evaluated the effects of stimulus duration upon the peak latency and offset of the hemodynamic response. Latency to peak amplitude also significantly increased with increasing stimulus duration, for each of peri-calcarine [$F(2,20) = 8.6$, $P < 0.01$], fusiform [$F(2,22) = 5.4$, $P < 0.05$] and LTO cortices [$F(2,22) = 4.4$, $P < 0.05$]. Within peri-calcarine cortex, one subject exhibited no hemodynamic response to the 100 ms stimulus, and that time point was excluded from the latency analysis. Offset of the hemodynamic response was estimated as the first point following the peak that returned to the noise level defined by the standard deviation of the prestimulus baseline. For all three regions, the offset time of the hemodynamic response increased with increasing stimulus latency: calcarine cortex [$F(2,22) = 5.72$, $P = 0.01$], fusiform cortex [$F(2,22) = 4.36$, $P < 0.05$] and LTO cortex [$F(2,22) = 6.14$, $P > 0.01$].

To examine possible functional heterogeneity within the peri-calcarine region, which likely includes voxels within both V1 (medial) and V2 (lateral), we split each ROI into medial and lateral halves and repeated the analyses. No significant differences were found in peak amplitude between the two ROIs for any of the three durations (paired *t*-tests across subjects; all $P > 0.1$), indicating that the choice of ROI location within active peri-calcarine cortex has little effect upon the resulting hemodynamic response. We additionally tested for the presence of functional subregions within fusiform cortex by separating each fusiform ROI into anterior and posterior halves. The fusiform analyses replicated the above results for each half independently, in both overall amplitude and in relative amplitude among the conditions (paired *t*-tests across subjects; all $P > 0.1$). Given the results of these control tests, the entire peri-calcarine and fusiform ROIs were used for all subsequent analyses.

We investigated the linearity of the hemodynamic response with stimulus duration by convolving the response evoked by the shortest duration stimulus (100 ms) with boxcar waveforms corresponding to the other stimulus durations (Boynton *et al.*, 1996). For all three ROIs, responses to longer-duration stimuli were significantly overestimated by linear convolution of shorter-duration stimuli. Summation of multiple 100 ms stimuli overestimated the response to a 500 ms stimulus by a factor of 3.2 for peri-calcarine cortex, 3.6 for fusiform cortex, and 5.8 for LTO cortex (all $P < 0.02$). Summation of 100 ms responses overestimated the response to a 1500 ms stimulus by factors of 4.5, 6.4 and 13.8 across the three ROIs (all $P < 0.001$). And, summation of 500 ms responses overestimated that to a 1500 ms by factors of 1.7, 1.9 and 2.4, respectively (all $P < 0.001$). We concluded that the fMRI hemodynamic response is highly nonlinear with respect to the duration of a static visual stimulus over the intervals tested.

Electrophysiological Data: ERP Analyses

EEG data time-locked to each stimulus were recorded from >1100 electrodes across the nine subjects. The anatomical location of each electrode was determined by post-operative structural MR scanning and electrodes were assigned to regions of interest according to anatomical criteria. A total of 74 electrodes were located within the calcarine ($n = 35$), fusiform ($n = 17$) and LTO ($n = 22$) anatomical ROIs (Fig. 2).

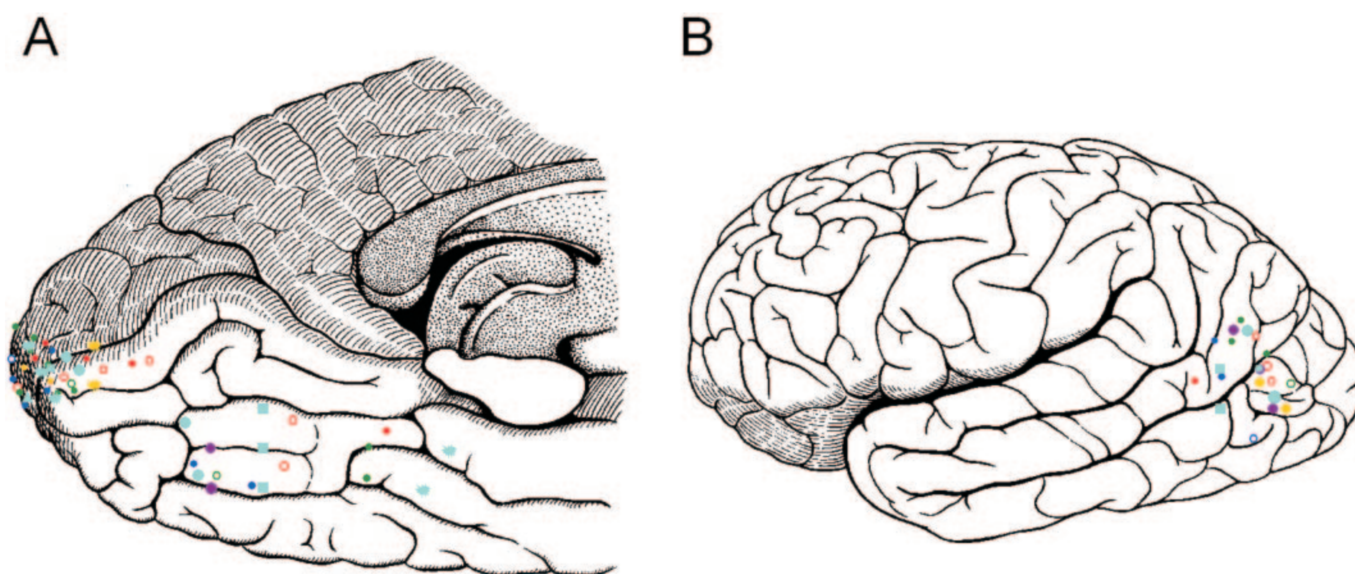

Figure 2. Locations of subdural electrodes. Electrode locations were measured using structural MRI. Only those electrodes determined to reside within the three anatomical regions of interest were included in subsequent analyses. Each symbol type indicates a different subject and each subject could have one or more electrodes in each region. Electrode locations for peri-calcarine and fusiform cortices are shown in (*A*) and electrode locations for LTO cortex are shown in (*B*).

The ERP waveforms recorded from calcarine cortex were highly consistent across electrodes (Fig. 3*a*). The initial ERP component had an onset of ~50 ms and reached peak amplitude at ~110–120 ms with a mean amplitude of 119 μV. Although generally negative, the polarity of the initial component depended upon electrode location, with polarity reversals often evident in consecutive electrodes. Such reversals provide evidence that the electrodes bracketed the component's neural generator. The amplitude and latency of the initial component did not differ as a function of stimulus duration (all $P > 0.05$). Offset potentials were observed at all calcarine electrodes for the 500 and 1500 ms stimulus durations and occurred at ~100 ms after the cessation of each stimulus (Fig. 4). The polarity of the offset potential differed across electrodes, with many electrodes exhibiting offset potentials that were similar in amplitude to the onset potential. Prominent sustained activity was also observed for the longer two stimulus durations, spanning the interval between the onset and offset potentials.

In contrast, activity in fusiform electrodes (Fig. 3*b*) did not differ across stimulus durations, as all three stimulus types evoked an onset potential that peaked around 100 ms, but little or no sustained activity or prominent offset potentials were observed. Unlike the ERPs from calcarine electrodes, which frequently had polarity inversions across adjacent electrodes, the ERPs recorded from the fusiform were consistent in their polarity. The fusiform onset potential was much smaller (mean 50 μV) than that measured in calcarine cortex ($P < 0.00001$).

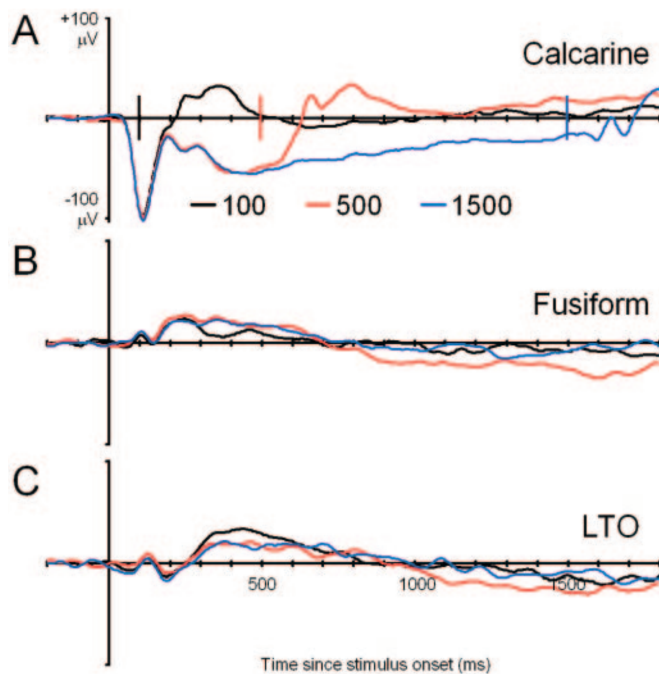

Figure 3. Electrophysiological activity recorded in visual cortical regions. Mean evoked potentials were calculated across all electrodes within each of the three regions of interest, here plotted time-locked to stimulus onset. The *x*-axes span –200 to 1800ms, with each tick mark indicating 100 ms. For clarity, the offset times of the three stimulus durations are shown as colored bars on the upper *x*-axis. The *y*-axes indicate –100 through –100 μV. Within peri-calcarine cortex (*A*), large-amplitude onset potentials were observed, along with duration-dependent sustained activity, and a second transient potential that followed stimulus offset by about 100 ms. Within fusiform (*B*) and LTO (*C*) electrodes, in contrast, much smaller onset potentials were observed. No significant differences in sustained activity were observed.

There were no differences across stimulus durations for LTO electrodes, which exhibited an initial transient response that peaked at ~150 ms and a slower potential that extended from ~300 to 600 ms (Fig. 3*c*). The LTO peak response was likewise much smaller (mean 44 μV) than the calcarine response ($P < 0.00001$) and was not significantly different in amplitude from that observed in fusiform electrodes ($P > 0.1$). Like the fusiform electrodes, the ERP components evoked at the LTO electrodes were consistent in waveshape and polarity.

To assess whether the ERP responses to the three stimulus durations were significantly different, we computed the mean difference between each pair of waveforms (e.g. 100 versus 500 ms) for each subject within 100 ms time bins that extended from 0 to 1700 ms. We evaluated, using *t*-tests at alpha 0.01, whether the distribution of these differences across subjects was significantly different from zero in each time bin. In calcarine cortex, there was strong evidence for sustained differences between the conditions as a function of stimulus duration. The 100 and 500 ms responses significantly differed from each other within each time bin from 200 to 500 ms and from 1500 to 1700 ms, but not at other time bins. The 100 and 1500 ms responses significantly differed at all bins from 100 through 1600 ms and the 500 and 1500 ms significantly differed at all bins from 600 to 1700 ms. However, in fusiform and LTO cortices, there was little statistical support for differences between the durations, with only four bins with significant effects (out of 102 examined) and none with effects corresponding to differential sustained activity or offset potentials.

One limitation of averaging across electrodes is that differences in the polarity of ERP components across electrode sites within the calcarine cortex may obscure duration-related differences. In order to evaluate a polarity-independent measure of ERP activity, we additionally calculated the root mean square (RMS) voltage for each electrode and duration over the 1700 ms interval following the stimulus onset. The RMS voltage provides a measure of the amount of activity independent of its sign, so electrodes with opposite polarity will

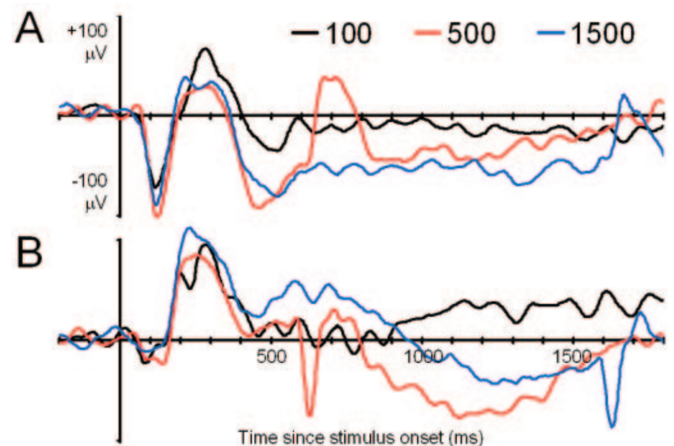

Figure 4. Large amplitude, polarity-reversed offset potentials in calcarine cortex. Shown here are two consecutive electrodes from a strip running along the calcarine sulcus in a single subject. Visible are the very large (50–100 μV) offset potentials following termination of the 500 and 1500 ms stimuli. Note that the potentials have opposite polarity, suggesting that they bracket a common source. Such polarity reversals can obscure large amplitude potentials when averaging across electrodes.

contribute to the total RMS rather than canceling each other out. Though performed primarily for the calcarine electrodes, which did vary in the polarity of the initial components, this analysis was conducted across all electrode sites. The 1700 ms interval was chosen to allow the resolution of offset potentials for the longest stimuli. Mean RMS was significantly higher in calcarine cortex electrodes than in fusiform or LTO electrodes [$F(2,71) = 18.4$, $P < 0.00001$], as shown in Figure 5. In calcarine cortex, RMS power was significantly lower for 100 ms stimuli than for 500 or 1500 ms stimuli ($P < 0.00001$), which were not significantly different from each other ($P > 0.1$). No effects of duration were observed in either fusiform or LTO. These analyses strengthen the above conclusions by indicating that total ERP power increases with stimulus duration in calcarine cortex, but not in the other regions.

Electrophysiological Data: Spectral Analyses

Our primary analyses presented above focused upon ERPs that were time-locked to stimulus onset and averaged. As signal averaging de-emphasizes the contributions of local neuronal fields that are not precisely synchronized with stimulus presentation, we were concerned about overlooking some aspect of neuronal activity present in the individual trials (but 'averaged out' by signal averaging) that might be systematically related to stimulus duration. We therefore conducted additional analyses that focused upon single trials.

The first analysis investigated changes in the EEG power spectrum associated with stimulus presentation. Power spectra were calculated for a 2100 ms pre-stimulus interval and for a 2100 ms post-stimulus interval beginning at stimulus onset. In the period before stimulus presentation, there were no significant differences in the power spectra across stimulus durations for any of the three ROIs (Fig. 6*a*). In the interval following stimulus onset, there were clear duration-related differences in the spectra obtained from electrodes in calcarine and fusiform cortices (Fig. 6*b*). In calcarine cortex, there were significant increases ($P < 0.01$) in power for the 1500 ms stimuli compared to each of the shorter duration stimuli at frequencies of 20–45 Hz (gamma range). In fusiform cortex, there were significant decreases ($P < 0.01$) in power at frequencies of 5–11 Hz and from 15–17 Hz, for the 1500 ms duration compared to the other stimulus durations. No significant differences in the raw spectrum were observed in LTO electrodes, although there was a suggestion of decreased power at low frequencies.

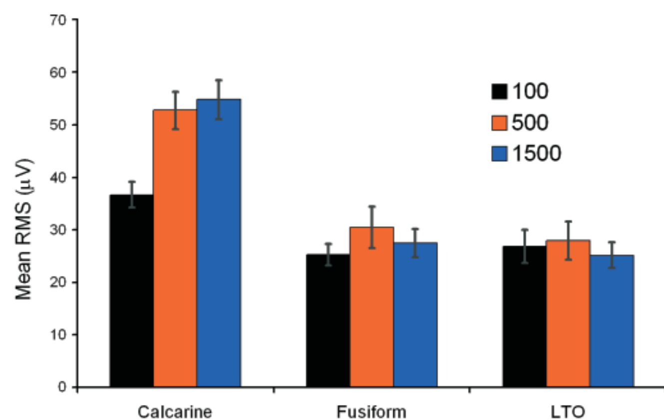

Figure 5. Mean RMS power across stimulus durations. For each region of interest, the mean RMS value across subjects was calculated for the interval between 0 and 1700 ms. Significantly greater RMS power was observed for calcarine cortex than for fusiform or LTO cortices, which did not significantly differ from each other or differ across durations. Within calcarine cortex, RMS values were greater for the 500 and 1500 ms stimulus durations than for the 100 ms stimulus duration. These results provide strong evidence for the increased electrophysiological activity present in calcarine cortex.

These results were replicated by a discriminant analysis, whose robustness was ensured by a jackknife procedure (Efron, 1982), which found that the spectrum that maximally distinguished between stimulus durations had increased power at high frequencies (~40 Hz) for calcarine cortex and decreased power at low frequencies (<20 Hz) for fusiform cortex. Interestingly, there was decreased activity at ~10 Hz for all three brain regions; as this decrease was significant in the discriminant analysis, but not when examining the raw spectra, it merits further study. We concluded that duration-related changes in spontaneous EEG activity are present in both calcarine and fusiform cortex, although the specific frequency bands affected, and thus the likely neural generators, are different for the two brain regions.

Discussion

The relationship between changes in the magnitudes of ERPs and the fMRI BOLD responses as a function of the duration of a visual checkerboard stimulus was inconsistent across the three visual regions examined. In peri-calcarine cortex, the evoked hemodynamic responses increased in both amplitude and latency across the three stimulus durations tested, although the increase in amplitude was not a linear function of duration. In this same region, large amplitude transient ERPs were recorded, followed by sustained potential shifts that lasted throughout the duration of the stimulus and which culminated in prominent offset potentials. The positive relationship between the sustained potentials and the increases in BOLD is consistent with the findings of Logothetis *et al.* (2001) that demonstrated a strong relationship between BOLD measures and local field potentials in monkey visual cortex.

Covariation between the magnitude of local ERPs and BOLD responses also occurred in the LTO region, although here the relationship was quite different from peri-calcarine cortex. There were no significant differences in the amplitude of the BOLD response as a function of stimulus duration, nor were there consistent differences in the amplitude of the ERPs. In this region, the ERPs did not exhibit either sustained potentials or prominent offset potentials. Compared to the peri-calcarine region, both the ERPs and the fMRI BOLD responses were small in amplitude.

No covariation was obtained, however, between the magnitude of local ERPs and the BOLD response within the fusiform gyrus. Here the evoked hemodynamic responses were on average more than twice as large as those measured in the LTO and ~5% larger than those measured in the peri-calcarine region. Like those in the peri-calcarine, the hemodynamic responses in the fusiform increased in both amplitude and latency with increasing stimulus duration. But while the fMRI BOLD responses in the fusiform were similar to those measured in the peri-calcarine, the ERPs were more similar to those measured in the LTO. That is, they showed neither consistent sustained activity nor a prominent offset potential.

One difference between our ERP and fMRI measures is that they were collected in different groups of subjects, due to the

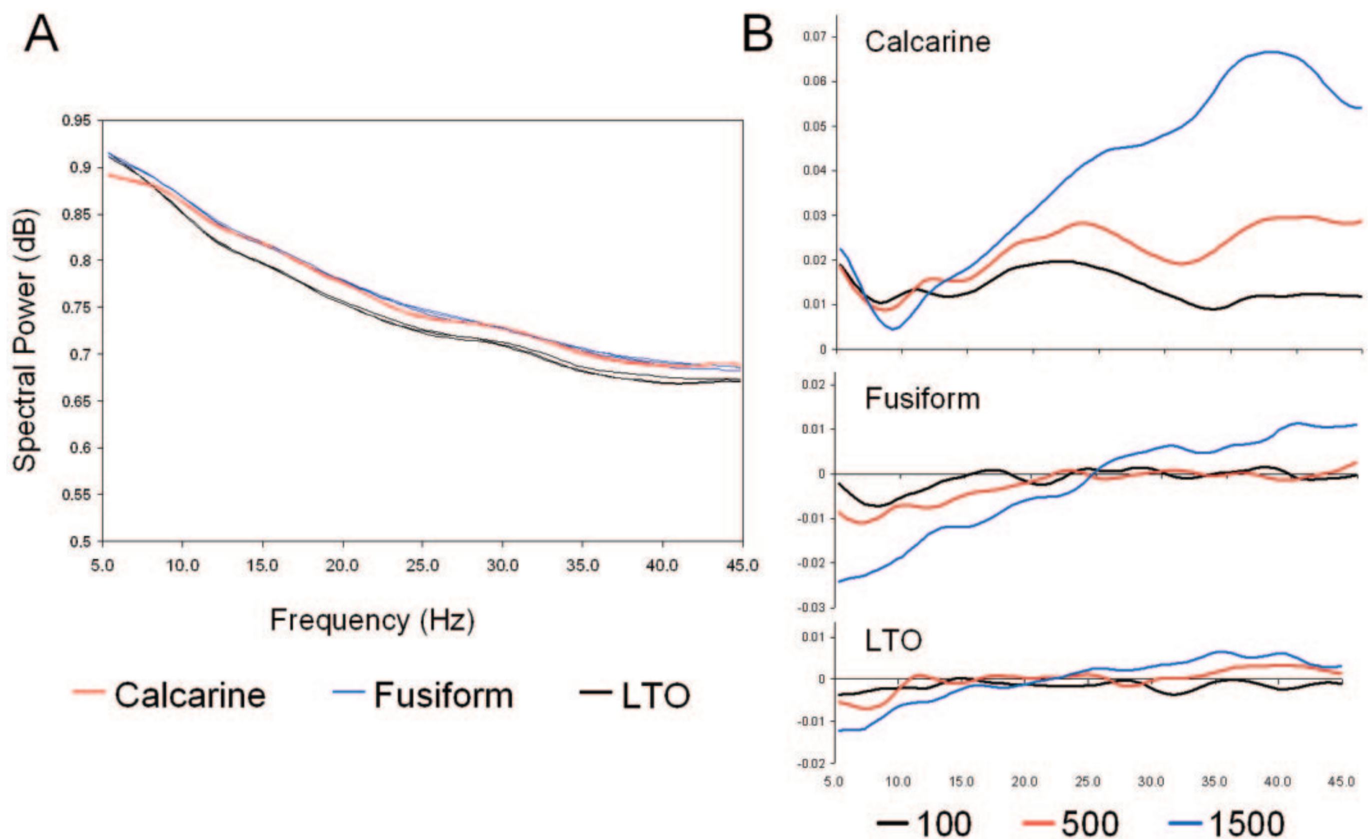

Figure 6. Analysis of power spectra of electrophysiological data. For each region of interest, raw power spectra were measured over 2100 ms intervals before stimulus onset (pre-stimulus) and after stimulus onset (post-stimulus). In the pre-stimulus period (*A*), there were no significant differences as a function of stimulus duration within any of the three regions of interest. Following stimulus presentation, there were significant differences in calcarine and fusiform electrodes, although the frequencies that exhibited duration-dependent effects were different between the regions. Shown in (*B*) are subtraction spectra that indicate the change in power at each frequency associated with stimulus presentation. Within calcarine electrodes, there were significant increases in power with stimulus duration at 20–45 Hz. In fusiform electrodes, there were significant decreases in power at 5–11 and 15–17 Hz. No significant differences were observed in LTO electrodes.

obvious restrictions of intracranial electrode recording in humans to clinical patients. We attempted to minimize procedural differences between the groups, so that both groups of subjects viewed similar checkerboard stimuli that spanned similar visual extents. The interstimulus interval was reduced in the ERP group so that more trials could be obtained, but a sufficiently long interstimulus interval was chosen to make refractory effects from preceding trials unlikely. The subject groups also differed in their composition. The ERP patients all had focal epilepsy, although none of the subjects included in this study had suspected seizure foci in visual cortex, nor was any epileptiform activity observed in any of the included electrodes. Also, antiepileptic medications were usually tapered or stopped following the initial surgery for electrode implantation.

Despite these differences, it is unlikely that the differences between the subject groups had a meaningful effect upon the experimental results. When compared directly, intracranial ERP data and fMRI data have been found to have good spatial correspondence, despite the substantial variation in disease state, site of epileptic focus and medication across studies (Puce *et al.*, 1995, 1997; Schlosser *et al.*, 1999). Similarly, within the present study we found activity in similar regions using the two measures. However, the current results demonstrate differences across regions in the effects of stimulus duration upon the measures. Therefore, the effects of differential medication status or experimental procedures would have to be specific to particular brain regions (i.e. leading to a reduction in fusiform gyrus activity, while not affecting activity in primary visual cortex). We therefore consider group differences to be an unlikely explanation for the observed inter-region differences in the ERP-fMRI relation.

Another possible explanation for the discrepancy between the ERP and fMRI BOLD responses is the relative spatial extent of their underlying activities. As discussed in the introduction, the spatial extent of the BOLD response may exceed that of the neuronal activity that precipitated it. For example, a large draining vessel may reflect task-related changes in BOLD contrast even though it is distant from the neuronal activity that precipitated the BOLD response. An electrode placed directly outside of this large vessel may show little or no neuronal activity despite being well within a region of high BOLD contrast. An additional complication is that, due to volume conduction, averaged ERPs reflect the sums of the neuronal activity from both nearby and distant generators. Because the amplitude of the extracellular potential fields decrease rapidly with distance from their neuronal generators, ERPs will be dominated by the contributions of nearby generators. However, if nearby generators are weak or absent, ERPs may nevertheless be recorded that reflect activity that has been

volume conducted from more distant active neuronal populations. The large amplitudes, sharp spatial gradients and polarity reversals of the ERPs recorded in calcarine cortex suggest the presence of nearby neuronal generators. However, the smaller ERP amplitudes and more shallow spatial gradients recorded in both the fusiform and LTO in response to this static checkerboard are less indicative of a nearby generator, raising the possibility that the electrodes located in these regions were more distant from the active neuronal populations than those in the calcarine region. Thus, the fact that both BOLD contrast and ERPs can reflect activity at some distance from the actual active neurons may be a key fact in explaining the pattern of results reported here.

As ERP components reflect the activities of populations of neurons that are time-locked to the stimulus, we reasoned that local changes in EEG activity associated with the stimulus, but not phase-locked sufficiently with stimulus onset to be reflected in the average ERP, might be present and might covary with BOLD magnitude changes. Prior comparisons of the magnetoencelphalogram (MEG) and fMRI data have indicated that areas exhibiting changes in cortical synchronization also show evoked hemodynamic responses (Singh *et al.*, 2002). We therefore examined changes in the EEG spectrum from the pre-stimulus to the post-stimulus epoch on a single trial basis. In calcarine regions, we found an increase in both alpha and gamma band activity with increasing stimulus duration. In the fusiform, however, a decrease in alpha activity was noted with increasing stimulus duration, and no changes in the EEG spectrum were found in LTO. Thus, no consistent relationship was found between duration-related changes in the EEG spectrum and BOLD magnitude changes across the three regions sampled. Additional data driven analyses using independent component analysis were performed on the single trial post-stimulus epochs to search for systematic differences between brain regions that might correlate with increasing stimulus duration. These analyses reaffirmed the average ERP differences observed between calcarine electrodes and those located in both fusiform gyrus and LTO without revealing additional duration-related changes at fusiform and LTO sites.

Summated field potentials – such as represented in the ERPs and local spontaneous EEG activity – may not be the best measure of neuronal activity to compare to changes in BOLD activation. Indeed, a good case could be made that local multi-unit activity should be the best correlate of local metabolic requirements and thus of BOLD, as Attwell and Laughlin (2001) indicated that action potentials account for 47% of ATP consumption in the nervous system. Direct investigation of the relationship between multiunit activity and BOLD by Logothetis *et al.* (2001), however, suggests that multiunit activity may not be the best predictor of BOLD activation.

Although not the focus of the present investigation, our finding of region-variable nonlinearities in the fMRI hemodynamic response is consistent with recent studies demonstrating refractory effects of both duration and interstimulus interval within individual regions (Boynton *et al.*, 1996; Friston *et al.*, 1998; Robson *et al.*, 1998; Glover, 1999; Huettel and McCarthy, 2000; Liu and Gao, 2000) and across regions (Birn *et al.*, 2001; Huettel and McCarthy, 2001). We extended these results here by showing systematic differences in linearity across brain regions; in peri-calcarine and fusiform cortices there were monotonic, but nonlinear, increases with duration, while in LTO duration had no effect upon BOLD. Birn *et al.* (2001) reported an analogous result in a motor task, such that BOLD amplitude increased with duration in primary motor cortex but not in supplementary motor cortex. One possible explanation for this similarity is that both supplementary motor cortex and LTO are associated with transient processing unrelated to the stimulus duration, namely preparation for a motor act and responding to visual onset, respectively. Under this hypothesis, the pattern of neuronal activity within these areas would be independent of stimulus duration, consistent with our ERP findings from LTO and the resulting nonlinearities thus would have a neuronal and not hemodynamic origin. We note that although Birn and colleagues also reported data from a visual duration task, they used a flickering counterphase checkerboard as a stimulus, which would evoke multiple onset responses and thus is not comparable to the present study.

Notes

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