Menon, Ravi S., Seiji Ogawa, John P. Strupp, and Kamil Ugurbil. Ocular dominance in human V1 demonstrated by functional magnetic resonance imaging. J. Neurophysiol. 77: 2780–2787, 1997. Very high resolution functional magnetic resonance imaging (fMRI) at a 4 Tesla (T) magnetic field was used to map ocular dominance regions in the human visual cortical layers using the blood oxygen level dependent (BOLD) contrast mechanism. The fMRI response from primary visual cortex (V1) exhibited a distribution of ocular dominance reminiscent of the single-cell recordings of Hubel and Wiesel. Pixels could be grouped into seven categories varying from left-only response to binocular-only response to right-only responses. Nonspecific responses were found in the MRI-visible draining veins as well as in the parenchyma. Although large vessel BOLD signals are easily detectable, regardless of field strength, they demonstrate a fMRI response to photic input that could not be used to distinguish ocular dominance. The difference in BOLD response between a region activated by one eye and that activated by the other is only 2.9% on average. This necessitates the use of a difference paradigm to visualize the regions of ocular dominance accurately. The data show that BOLD-based fMRI is sensitive to neuronal activity in cortical columns when using differential techniques, opening up the possibility of mapping specialized populations of neurons in humans that are not accessible to electrophysiological or other methods of invasive mapping.

INTRODUCTION

In primates, axons from the left and right eyes terminate in monocular laminae of the lateral geniculate body. From this nucleus, geniculo-striate projections to primary visual cortex (V1) continue to reflect either left or right eye input and terminate in layer IVC of V1 where they are arranged in a system of roughly parallel alternating stripes known as ocular dominance columns (ODCs). In cortical layers above and below IVC, cortical neurons vary in the strength of their response to inputs from the two eyes. This response can vary from exclusive dominance by one eye to equal influence of both as one makes a tangential penetration with an electrode through the striate cortex (Hubel and Wiesel 1962). Only in layer IVC do the cells receive innervation from exclusively one eye, and hence the classical periodic columnar pattern is only observed in layer IVC. In nonhuman primates, the organization of ODCs has been studied by histological stains and autoradiography (Hubel and Wiesel 1977; LeVay et al. 1985; Kennedy et al. 1976), by microelectrode recordings (Hubel and Wiesel 1976), real-time optical imaging using voltage-sensitive dyes (Salzberg et al. 1973), and optical imaging of intrinsic signals (Grinvald et al. 1986, 1991; Tso et al. 1990). In humans, the ODCs have been demonstrated as interdigitated stripes of ~1 mm in width by postmortem histochemical staining for cytochrome oxidase in striate cortex by Horton et al. (1984, 1990), but a noninvasive technique for examining human striate cortex organization on the scale of cortical functional subunits has not been available.

The hemodynamic-response mechanism that allows visualization of orientation columns and ODCs in awake monkeys by optical imaging of intrinsic signals demonstrates that corticovascular responses to visual stimuli can be localized to the columnar level in several mammalian species (Grinvald et al. 1986, 1991; Malonke and Grinvald 1996; Tso et al. 1990). The blood oxygen level dependent (BOLD) technique (Ogawa et al. 1990a,b; Turner et al. 1991) on which the vast majority of cortical mapping using functional magnetic resonance imaging (fMRI) is based (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992), is also sensitive to the hemodynamic changes in the local vasculature, which suggests that, in principle, cortical column organization could be mapped noninvasively with the use of fMRI as well. Although the optical data demonstrate that the capillary bed hemodynamic response is sufficiently confined to layer IVC of the cortical column (the ODC), localization of the mapping signal in fMRI with respect to the active cortical area and vascular tree is still quite controversial (Cohen and Bookheimer 1994; Duyn et al. 1994; Frahm et al. 1994; Kim et al. 1994; Kwong 1995; Lai et al. 1993; Menon et al. 1993). At issue here is the belief that BOLD signals coming from large vessels may dominate those coming from the microvasculature, particularly on conventional MRI scanners. This is problematic, because it raises concern that macrovascular changes distal to the actual site of neuronal activity can occur. This would place a fundamental limit on correlation of fMRI activation maps and neuronal activity. Because cells above and below the ODC defined in layer IVC can also respond in varying degrees as mentioned above, the vascular response may not be confined to layer IVC, but might traverse the entire depth of the cortical ribbon. Thus it may be expected, particularly with the resolution used in fMRI, that each pixel would contain variable degrees of left or right eye dominance, and that confinement of the fMRI mapping signal to layer IVC may not be feasible.

When one compares previous optical mapping experiments on awake nonhuman primates (Grinvald et al. 1991;
Malonek and Grinvald 1996) with considerably lower resolution fMRI experiments performed at a magnetic field strength of 4 T (Menon et al. 1995), the temporal response and sign of the optical signal from the capillary beds in V1 of awake monkeys parallels that of the fMRI time course in certain regions of striate cortex in humans. The remarkable similarity of the results obtained from these two techniques, along with other theoretical and experimental evidence for increasing capillary bed BOLD contributions at higher magnetic field strengths (Bandettini et al. 1994; Gati et al. 1997; Menon et al. 1993, 1994; Ogawa et al. 1993; Song et al. 1994) suggest that a component of the fMRI mapping signal arises from microvasculature, at least at the highest magnetic fields available for human research (4 T).

For fMRI studies using clinically available hardware, ~3-mm in-plane resolution and ~5-mm slices are typical because of the limited signal-to-noise ratio (SNR) available in high temporal resolution imaging sequences (Callaghan 1993). Using a high-resolution fMRI pulse-sequence with imaging hardware and parameters optimized at three different field strengths, we have found that the SNR at 4 T is at least three times higher than at the much more commonly available 1.5 T field strength (Gati et al. 1997). This increase is sufficiently large to attempt imaging of ocular dominance in human V1, where ODCs are ~0.8–1 mm on a side for a column and 5–10 mm long in humans (Horton and Hedley-White 1984; Horton et al. 1990). Using a simple visual paradigm in combination with an optimized radio-frequency (RF) coil, head restraint, and the enhanced SNR provided by 4 T, we have been able to demonstrate adjacent image pixels in human V1 that respond predominantly to left or right eye photic input, as well as many that respond only to binocular input.

METHODOLOGICAL

Subjects

Five normal subjects [4 right eye and right hand dominant (3 male, 1 female), 1 left eye and left hand dominant (1 male), ages 25–32] gave informed consent before participating in this study. All had previous fMRI experience. Approval for this protocol was given by the University of Western Ontario Review Board for Health Sciences Research involving human subjects, and radio frequency power deposition guidelines established for clinical scanners by the Food and Drug Administration were adhered to.

Activation tasks

A single round red (635 nm, 300 mcd, Radio Shack ‘‘Jumbo’’) light-emitting diode (LED), placed above the subject’s head and driven by a stimulator (GRASS Instruments, Quincy, MA) at 8 Hz was used for photic stimulation. The LED subtended ~10° of visual field. The subjects were directed to fixate on the position of the LED, which was gated on or off by the scanner, but to generate monocular input, subjects were instructed via a special headset (Resonance Technology, Van Nuys, CA) when to close either the left or the right eyelid gently as the scanning progressed. Binocular stimulation (‘‘B’’ state), sandwiched between periods of darkness (‘‘D’’ state), was used to identify primary visual cortex. Monocular stimulation using the open left eye (‘‘L’’ state) or open right eye (‘‘R’’ state) was used to delineate ocular dominance regions. Each of the states, B, D, L, and R were 15 s in duration.

MRI studies

All MRI experiments were performed on a 4 T whole-body human imager [varian (Palo Alto, CA)/Siemens (Erlangen, Germany)] with a 7.6-cm diameter double-balanced, distributed capacitive transmit/receive RF coil built into the bottom of a rigid Plexiglas head-holder. Subject head motion was restrained with an integrated foam padded vice that pressed against the sides of the head, around the headphones. In some cases, the surface coil was removed and a head coil inserted for anatomic imaging, without disturbing the subject.

Images were usually acquired with parameters (256 complex points/readout window, 256 phase-encoding steps) that yielded a resolution of 547 by 547 µm when using a 14 by 14-mm field of view. To locate the calcarine sulcus at the beginning of each scanning session, we acquired multislice sagittal images with gray-white matter contrast (T1-weighted anatomic images) at 0.5-cm spatial increments centered about the midline using an imaging pulse sequence we have described in detail previously (Kim et al. 1994; Menon et al. 1993; Ogawa et al. 1992). Briefly, 256 centrically ordered phase-encoding steps segmented in 4 blocks of 64 interleaved steps with a magnetization preparation inversion time (TI) of 1.2 s were used for high-resolution FLASH sequence (Haase et al. 1986). For these anatomic images, the echo time (TE) was 5 ms, the repetition time (TR) was 10 s, the slice thickness was 4 mm, and the segment interleave time was 4 s. From these multislice sagittal images the calcarine fissure was easily identified (Menon et al. 1993). Five equally spaced and abutting oblique slices of 4-mm thickness were chosen parallel to the calcarine fissure at the posterior occipital pole. This location and orientation was chosen on the basis of previous MRI myeloarchitectonic analysis of layer IVC in striate cortex (Clark et al. 1992). The chosen orientation allows the columns to run perpendicular to the slice plane. Because the columns are expected to be 5–10 mm in length in humans and 0.8–1.2 mm on a side (Horton et al. 1990), it is expected that they will be perpendicular to the 4-mm-thick slice in at least a few local regions, but not necessarily in the whole slice, given that the calcarine sulcus is rarely straight in human subjects. Anatomic imaging in the same manner as described above was also performed on these five slices.

All fMRI was carried out by the use of serial repetitions of a centered ordered phase-encoded FLASH pulse sequence (TE = 30 ms, TR = 50 ms, slice thickness = 4 mm. Flip Angle ~22°), with an interimage spacing of 2.2 s for a total of 15 s per image. It is worthwhile to note that the fMRI images and the anatomic images are exactly coincident, because they are made with the same imaging sequence and resolution in the same session. We functionally localized primary visual cortex in each subject using a pilot fMRI protocol using binocular photic stimulation while scanning the five slice planes selected above. To identify the maximally activated part of primary visual cortex, three serial sets of the five slices were made with the LED off, and three sets were made while the LED was on for binocular stimulation. In this mapping protocol, the dark and light states each lasted 225 s. Regions of the cortex that responded to binocular stimulation in this multislice paradigm were determined by a t-test as described in the analysis section below. From these multislice maps of binocular activation, we determined the imaging slice location that demonstrated maximum striate cortex activation. Although not as elegant as other fMRI V1 delineation techniques (Sereno et al. 1995; Tootell et al. 1995), this simple paradigm allows rapid identification of activated primary visual cortex, which is essential to set up a single slice study.

The scanning session was then continued (within 5 min) using the slice location that showed maximum activation. To map cortical columns, we obtained 24 serial (in time) fMRI images of this slice in V1 during which time different states involving both binocular and alternating monocular stimuli were presented. In four of five
subjects, the column mapping protocol was repeated twice. The 24 state combination shown in Fig. 1A was used to obtain the data presented in this paper.

**FMRI analysis**

All image analysis was done using Stimulate v5.0 (Strupp 1996) provided by the University of Minnesota, running on a Sun UltraSparc 140. To initially identify primary visual cortex in the pilot multislice scanning protocol, a Student’s t-test was done, on a pixel by pixel basis, to compare the dark and binocularly driven states for each slice. Only pixels with a statistically significant difference between B and D states (P < 0.05) were included. The functional maps were overlaid on the corresponding anatomic slices. The ocular dominance mapping experiment was then performed on the single slice determined most suitable from this analysis.

Once the data from the selected single-slice column mapping study were acquired, a map of the binocular phase of the paradigm was made by cross-correlation of the model time course (Bandettini et al. 1992) shown in Fig. 1B with slightly Gaussian blurred image data. An extremely high correlation value of 0.75 was used. Because a centric phase-encoding scheme was used, the image intensity is dominated by the first few lines of the acquisition, which occur well within the hemodynamic lag time of 5–8 s. Therefore, the reference waveform was shifted by one image to account for the hemodynamic lag in response to visual stimulation as we have demonstrated previously (Menon et al. 1995). The net result is a clean map (“mask”) of the cortical ribbon and vasculature as shown in Fig. 2B in which the pixels that we detect are activated by either or both eyes. The blurring ensures that all layers of the striate cortex are included in the mask. This mask was then used as a template on the original (unfiltered) image data to generate time courses from each 0.55 mm by 0.55 mm by 4 mm voxel that was deemed activated by this procedure. No other image or background thresholding, pixel clustering, or region-of-interest (ROI) limitation was used.

The time courses of the pixels identified above were then binned into seven categories ranging from those that responded solely to left eye visual input, to those that responded to both eyes, to those that responded to right eye input as has been done previously in neurophysiology (Hubel and Wiesel 1962). Binning was accomplished by doing a Student’s t-test for significant differences between right and left eye stimulation periods at the P = 0.05 level. Those pixels that had significant differences were then binned according to the percentage difference between the two monocular conditions. Differences in right minus left response or left minus right response that were <1.5% were not significant at this P value and were considered binocularly responding, those between 1.5 and 4.5% were deemed partially dominated by the appropriate eye, and those exceeding 4.5% were considered monocular. Maps of ocular dominance were made based on these histograms for each subject.

**RESULTS**

An oblique T1-weighted anatomic image parallel to the calcarine fissure, acquired as described above, is shown in Fig. 2A. Overlayed on this image, in Fig. 2B, is the functional map determined for binocular stimulation. This high-resolution functional map of binocular activation was derived from the first four periods of the visual paradigm shown in Fig. 1A using the cross-correlation function in Fig. 1B. The activation was observed to be almost exclusively confined to the occipital pole and to coregister extremely well with the cortical gray matter in the primary visual areas. Areas that appeared yellow in the color scale (>10% change on binocular stimulation) were in regions of cortex with visible venous vasculature.

From such a map, we generated a time series through the whole fMRI data set for each activated pixel, including those overlying visible veins. Typically, this might include 2,500 pixels. These were analyzed sulcus by sulcus, and signals from visible veins (contributing ~1/3 of the activated pixels) were excluded. For example, from the ROI shown in green in Fig. 2B, we extracted the time course shown in Fig. 3, representing temporal data from ~60 activated cortical pixels. This time course showed activity during binocular activation as expected because of the correlation performed, but it also showed well-correlated activity with the paradigm (Fig. 1A) when either eye was stimulated in isolation. Typically, six such regions (3 sulci on each side of the midline) were used in each subject, averaging ~500 pixels per subject in total. For each subject, the pixel time courses were sorted according to the histogram binning procedure described above. The distribution of activation in each subject and the

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**FIG. 1.** Visual paradigm and binocular reference vector. A: the visual paradigm consisted of 24 serial states of darkness (D), binocular stimulation (B), and monocular stimulation of either the left (L) or right (R) eye as shown at top. Each state lasted 15 s during which time 1 image was acquired. B: to identify pixels that responded to photic stimulation in either or both eyes, a cross-correlation of images 1 to 9 was performed with the reference vector shown, shifted by 1 image to account for the hemodynamic lag time.
FIG. 2. Functional magnetic resonance imaging (fMRI) maps of striate cortex to binocular and monocular visual input. 
A: T1-weighted MRI image of subject 1. B: map of pixels that satisfy the cross-correlation criteria shown in Fig. 1B at a correlation value of 0.75. Activation is coded by color [red (1%) → yellow (>20%)]) overlaid on a high-resolution T1-weighted MRI image of the same subject. No significant negative changes were observed. C: map demonstrating pixels responding predominantly to left eye monocular stimulation in reds [red (1%) → yellow (>10%)], whereas those responding primarily to right eye monocular stimulation are shown in blues [blue (1%) → violet (>10%)]. Pixels were chosen on the basis of the ocular dominance histograms shown in Fig. 4. D: expansion of part of C. In A–C the field of view is 14 by 14 cm.

average across all subjects is shown in Fig. 4. The distribution appears quite symmetrical from regions on either side of the midline, precluding hemifield effects.

Maps consisting of pixels corresponding to the two left most bins and the two right most bins of these histograms were made, such as that shown in Fig. 2C and its expansion in Fig. 2D. These are maps of ocular dominance, but the responses are not necessarily confined to layer IVC as discussed earlier. Figure 5 shows the averaged temporal responses of the four left dominant and four right dominant
FIG. 3. Time course of image intensity corresponding to pixels activated during the binocular states. The ROI from which they are extracted is shown in Fig. 2B. Contributions from visible vessels have been excluded. The fractional signal change in this region was 2.48%.

FIG. 4. Histogram of ocular dominance for all 5 subjects and the average across subjects. Positive differences indicate right eye dominance, and negative changes indicate left eye dominance. The bins are 0–1.5% (binocular or no significant difference), 1.6–2.5%, 2.6–3.5%, and 3.5–4.5% (monocular). At a P value of 0.05, differences under 1.5% could not be detected in single pixels. The few pixels whose changes were >4.5% were placed in the 4.5% categories.
FIG. 5. Time course of image intensity corresponding to pixels activated during the monocular states. The average time course of the 4 red pixels (left eye) and the 4 blue pixels (right eye) marked in Fig. 2D are shown. These pixels are chosen on the basis of the ocular dominance histogram for subject 1 in Fig. 4 and have changes $>2.5\%$.

pixels indicated in Fig. 2D. To determine the mean size of the regions demonstrating ocular dominance, we reprocessed the image data with increasingly wider Gaussian filters until pixels that were significantly monocularly activated were blurred together and 50% of the left-right differentiation was lost. This procedure is shown as a function of filter width for two subjects in Fig. 6.

**DISCUSSION**

To assess the significance of the changes measured, we first examine their magnitude relative to the noise. The mean fractional image intensity change of the pixels we characterize as responding during binocular stimulation is $2.7 \pm 0.5\%$ (mean $\pm$ SE; $n = 5$). The mean fractional change in the same regions of cortex during monocular stimulation was similar to the binocular case at $2.9 \pm 0.5\%$ ($n = 5$). We have excluded visible veins from this measurement. In the local draining veins, changes $>20\%$ can be observed. We observe the maximum gray matter changes between binocular and dark stimulus conditions to be $\sim 5\%$ with our slice thickness of 4 mm, and, taking this as the maximum expected parenchymal change, we require the fMRI mapping procedure to be sensitive to changes of $<5\%$ in a single pixel to detect ocular dominance regions. Given the stability of the head and our instrument, the signal-to-noise ratio in the images and our desired confidence levels, differences of $<1.5\%$ between states, are not significant in a single pixel, using FLASH, at the $P = 0.05$ level. Therefore we sort our L-R differences into bins of $0-1.5\%$ (binocular or no significant difference), $1.6-2.5\%$, $2.6-3.5\%$, and $3.5-4.5\%$ (monocular). The difference could be positive or negative depending on which eye is dominant. A positive difference indicated right eye dominance.

One could argue that in any regions where the cortical ribbon is not roughly perpendicular to the slice, a single pixel could contain contributions from both sets of ODCs and the layers that lie above and below them, and that pixel will appear to respond to both eyes to a greater or lesser extent. Because of this partial volume effect, the distribution of ocular preference shown in Fig. 5 may be distorted, but probably randomly so, because our voxel size is smaller than the column cross-section. Nevertheless, measured over five subjects and several thousand pixels, our individual and average distributions bear a strong resemblance to those from single-unit recordings first derived by Hubel and Weisel. It is interesting to note a slight preponderance of right eye dominant pixels, consistent with the eye dominance of our group of subjects. The pixels labeled as being binocular (less than $\pm 1.5\%$ change) should be in layers other than IVC in the striate cortex. However, the pixels showing a preference for one eye could either be in layer IVC (particularly those that seem to respond exclusively to one eye) or in other layers of the cortex. It is likely that the BOLD hemodynamic response from one column “spills over” into adjacent columns to a certain extent (i.e., the local change in deoxyhemoglobin concentration is not perfectly confined to an electrically active column). This is nicely demonstrated by the recent intrinsic optical imaging work of Malonek and Grinvald. Like their technique, our analysis method looks at rela-
FIG. 6. Effects of filtering on ocular dominance response. For pixels such as those shown in Fig. 2D, whose time courses are seen in Fig. 5, the difference between left and right responses was observed as a function of blurring. Half the contrast between eyes is lost at a Gaussian filter full-width at half-maximum (FWHM) of 1.6 pixels (875 μm). Thus, on average, the ocular dominance regions are 875 μm on a side. Third, the ocular dominance regions appear confined to the primary visual cortex. Fourth, we can demonstrate that the temporal states were effectively subtracted, large changes are seen in the draining veins. However, the effective subtraction of the behavior of adjacent pixels of assigned ocular dominance are consistent with that of the stimulus paradigm (Fig. 5). These four observations lend strong support to our identification of the activated regions as regions of ocular dominance and not random noise.

Our data demonstrate that mapping of ocular dominance in humans is possible in a noninvasive manner. The fMRI data show that the hemodynamic response can be used as a direct indicator of neuronal activity in cortical columns, opening up the possibility of mapping specialized populations of neurons in humans that are not accessible to electrophysiological or other methods of invasive mapping. Advances in motion correction, image processing, and MRI hardware should allow more detailed cortical mapping on this scale.

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