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Functional MRI mapping neuronal inhibition and excitation at columnar level in human visual cortex

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Abstract

The capability of non-invasively mapping neuronal excitation and inhibition at the columnar level in human is vital in revealing fundamental mechanisms of brain functions. Here, we show that it is feasible to simultaneously map inhibited and excited ocular dominance columns (ODCs) in human primary visual cortex by combining high-resolution fMRI with the mechanism of binocular inhibitory interaction induced by paired monocular stimuli separated by a desired time delay. This method is based on spatial differentiation of fMRI signal responses between inhibited and excited ODCs that can be controlled by paired monocular stimuli. The feasibility and reproducibility for mapping both inhibited and excited ODCs have been examined. The results conclude that fMRI is capable of non-invasively mapping both excitatory and inhibitory neuronal processing at the columnar level in the human brain. This capability should be essential in studying the neural circuitry and brain function at the level of elementary cortical processing unit.

Keywords

fMRI mapping; Ocular dominance column; Human brain; Paired stimulus paradigm; Binocular interaction; Inter-stimulus interval

Introduction

Cortical inhibitory interaction at the columnar level has functional significance in many basic brain functions including general principles of cortical circuitry and local neural processing, and particular mechanism and architecture underlying the processing of complex sensory input (Sillito et al. 1995; Das and Gilbert 1999; Eysel 1999). For instance, combining optical imaging and electrophysiological techniques has revealed that long-range horizontal connections in primary visual cortex (V1) modulate both excitatory and inhibitory synaptic interactions between iso-orientation columns (Weliky et al. 1995) and that these horizontal connections are widely assumed to be present to support contour integration (Mitchison and Crick 1982). The short-range inhibition between neighboring columns with different orientation preferences, on the other hand, is engaged in providing contextual information about the visual scene (Das and Gilbert 1999) or may be closely related to cross-orientation inhibition (Vidyasagar et al. 1996) and sharpening the orientation column tuning response (Lund et al. 2003). Recent publications also suggest that mutual inhibition between the two monocular neuron populations in human V1, presumably left-eye ocular dominance columns (ODCs) and right-eye ODCs, plays a key role in binocular rivalry (Haynes et al. 2005; Wunderlich et al. 2005). Hence, the capability of non-invasively mapping neuronal excitation and inhibition at the columnar level is vital in revealing fundamental mechanisms of brain functions.

It is, however, a challenging task to non-invasively map columnar excitation and inhibition. The techniques of neuron recording and optical imaging, though with very high spatial resolution up to the cellular level, have very limited field of view and involve invasive surgeries. Among all non-invasive neuroimaging modalities, blood oxygenation level-dependent (BOLD)-based functional magnetic resonance imaging (fMRI), with its superb spatial resolution and large field of view, is most widely used (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992). To date, the capability of fMRI for mapping brain activation in compartmentalization such as the human visual cortex on the scale of several centimeters (Engel et al. 1994; Sereno et al. 1995) and brain sub-organizations such as lateral geniculate nucleus on the scale of a few millimeters (Chen et al. 1998, 1999; Chen and Zhu 2001) has been well documented. Recently, fMRI mapping columnar activities in the dimension of 1 mm or smaller has also been demonstrated in the human visual cortex (Menon et al. 1997; Menon and Goodyear 1999; Cheng et al. 2001; Goodyear and Menon 2001; Goodyear et al. 2002; Yacoub et al. 2007). However, the feasibility of simultaneously imaging both neuronal excitatory and inhibitory activities at the columnar level has not been explored. In this work, we have designed and tested a novel method allowing non-invasively mapping neuronal excitatory and inhibitory activities in the human ODCs using high-resolution fMRI.

Rationale

We have found that binocular inhibition between the two ODC neuron populations in the human visual cortex can be effectively elicited by sequentially stimulating the two eyes (Zhu et al. 2001). The selective stimulation of one eye can substantially inhibit the activity induced by subsequent stimulation of the other eye if the delay between the paired monocular stimuli is as short as 30–90 ms (defined as the maximal inhibition condition); this inhibition progressively disappears when the delay exceeds 300–400 ms (defined as the minimal inhibition condition) (Zhu et al. 2001). The degree of inhibition at different inter-stimulus intervals (ISIs) reflects the dynamics of the binocular inhibitory interaction between the left- and right-eye ODCs. Since, for each eye ODC group, the BOLD responses under the maximal and minimal inhibition conditions are significantly different, the excited and inhibited ODCs can in principle be distinguished by this difference using high-resolution fMRI in conjunction with an appropriately designed paired stimulus paradigm that consists of a pair of monocular stimuli separated by an ISI (Ogawa et al. 2000; Zhang and Chen 2006; Zhang et al. 2005).

Specifically, a similar magnitude of BOLD response is expected for the activated pixels covering both left- and right-eye ODCs under the minimal inhibition condition at a long ISI (~300 ms). In contrast, magnitudes of BOLD responses in the two ODC groups become distinguishable under the maximal inhibition condition at a short ISI (30–90 ms): i.e., the BOLD response will be significantly inhibited in one-eye ODC group experiencing the second stimulus, yet remaining the same in the other eye ODC group experiencing the first stimulus. As a result, the spatial separation of the inhibited and excited ODCs depends on the degree of reduction in the BOLD responses between the maximal inhibition condition and the minimal inhibition condition.

The feasibility of mapping neuronal inhibition and excitation at human ODCs using this fMRI method was examined from two aspects in this study. Qualitatively, the morphological features of mapped ODCs in terms of the column appearance, size and orientation were compared to the literature findings about human ODC from postmortem experiments (Hitchcock and Hickey 1980). Second, the reproducibility of ODC maps generated at the same condition was quantified and statistically evaluated for all subjects.

Materials and methods

Three healthy subjects participated in this study. For each subject, multiple fMRI study sessions were conducted for optimizing ISIs of maximal and minimal inhibition conditions and creating ODC maps. The subjects provided informed consent, which was approved by the Institutional Review Board of the University of Minnesota.

All fMRI experiments were performed on a 7T 90-cm bore magnet (MagneX Scientific, UK) interfaced with a Varian INOVA console (Varian Inc., Palo Alto, CA). A dual ^1H radiofrequency (RF) coil configuration consisting of a half-volume 14-cm quadrature surface coil for exciting the water proton spins and a 6-cm quadrature surface coil for receiving MRI signal was used. This dual-coil configuration allowed for sufficient RF field homogeneity in the visual cortex for RF transmission while preserving the advantage of higher SNR provided by the small reception coil (Adriany et al. 2001). Subjects' head motion was strictly restrained with the use of a bite-bar system.

In each fMRI session, a conventional T_1 -weighted Turboflash (Haase 1990) anatomical image adjacent to the interhemispheric fissure in the sagittal orientation was firstly acquired with the acquisition parameters of field of view (FOV) = $12.8 \times 12.8 \text{ cm}^2$, 256×256 image matrix size, in-plane resolution = $0.5 \times 0.5 \text{ mm}^2$, slice thickness = 3 mm, inversion recovery time (TI) = 1.5 s, echo time (TE) = 5 ms, repetition time (TR) = 2.56 s. Based on this sagittal image, one oblique image slice parallel and adjacent to the straight course of the calcarine fissure was chosen for the fMRI study. With this slice prescription, the mapped ODCs are expected to run orthogonal to the interhemispheric fissure line in an alternating pattern (Cheng et al. 2001). On this selected oblique slice, high-resolution multi-segmentation gradient echo planar images (GE-EPI) were acquired with the acquisition parameters of FOV = $12.8 \times 12.8 \text{ cm}^2$, 256×256 image matrix size, in-plane resolution = $0.5 \times 0.5 \text{ mm}^2$, slice thickness = 3 mm, TE = 28.8 ms, TR for each imaging segment = 550 ms and 16 segments for each image (equivalent to 8.8 s/image acquisition); low-resolution GE-EPI were acquired with the parameters of FOV = $12.8 \times 12.8 \text{ cm}^2$, 64×64 image matrix size, in-plane resolution = $2 \times 2 \text{ mm}^2$, slice thickness = 3 mm, TE = 30 ms, TR = 1000 ms. Also, on the selected imaging slice, a region of interest (ROI) in an anatomically well-defined region inside V1 was chosen for each individual subject. The ROI, as demonstrated in Fig. 1, met three requirements: (i) its location should correspond to the straight part of the calcarine fissure shown in the sagittal anatomical image; (ii) it has a relatively flat and wide appearance of gray matter without obvious veins, which can be visualized by the dark holes on a high-resolution GE-EPI image as illustrated in Fig. 1; and

(iii) it is located at the proximity of the interhemispheric line in the selected oblique slice to ensure that it is exclusively a section inside V1.

The visual stimulation presented as short light flashes (17-ms duration per flash) was generated by a pair of LED goggles (Grass Instruments, Quincy, MA). The visual stimuli consisted of a pair of monocular stimuli to the left and right eyes separated by an ISI corresponding to either the maximal inhibition condition or the minimal inhibition condition, respectively. The ISIs that induced maximal and minimal inhibition conditions were optimized for each individual subject based on low-resolution GE-EPI fMRI data. The details of optimizing maximal and minimal inhibition conditions can be found in our previous studies (Ogawa et al. 2000; Zhang and Chen 2006; Zhang et al. 2005). Briefly, a block design was used in the low-resolution fMRI study. Each fMRI run consisted of six stimulation blocks (10 images per block) separated by seven resting blocks (40 images per block) in an interleaving manner. During each stimulation period, paired monocular stimuli with the same ISI were repeatedly presented. Six different ISIs of 0, 40, 70, 200, 300 and 400 ms applied in six stimulation blocks were chosen and arranged in a pseudo-random order in each run. During the resting period, the subjects were in uniform darkness. Six fMRI runs were acquired in each session. The maximal inhibition condition was determined by the ISI at which the largest reduction in the BOLD signal was induced. The ISI at the maximal inhibition condition was defined as ISI_{short} , which was ~40 ms for two subjects and 70 ms for one subject. Likewise, the minimal inhibition condition was determined by the ISI at which the smallest BOLD reduction was observed. The ISI at the minimal inhibition condition was defined as ISI_{long} and was 300 ms for all subjects. The BOLD amplitude at ISI_{short} was significantly reduced to 60–85% of the BOLD amplitude at ISI_{long} for the three subjects. These results were consistent with our previous report (Zhu et al. 2001).

High-resolution fMRI experiments also used a block design. Each fMRI run consisted of two stimulation blocks (8 images each) sandwiched by three resting blocks (8 images each). During the stimulation period, paired monocular stimuli with the same ISI were repeatedly presented to the subjects. ISI_{long} and ISI_{short} were applied in a randomized order to eliminate habituation effect in each run. During the resting period, the subjects were in uniform darkness. Eight to ten runs were acquired in each fMRI session to ensure enough signal-to-noise ratio (SNR).

Data analysis was performed using Stimulate software package (Stimulate, Center for Magnetic Resonance Research, University of Minnesota) (Strupp 1996) and Matlab (The Mathworks Inc., Natick, MA, USA). The activation map for the maximal and minimal inhibition conditions was separately generated using the period cross-correlation method with a box-car function as the reference and a correlation coefficient (cc) >0.4 (equivalent to P value <0.001) as the statistical threshold (Bandettini et al. 1993; Xiong et al. 1995). The hemodynamic delay was accounted for by skipping the first imaging volume after the onset and the offset of a stimulation period. Pixels containing large vessels were excluded by using a mask, of which the values are the ratio between standard deviation and mean of MR signal constructed from a time series acquired at the resting period. High standard deviation versus mean ratio was taken to signify the presence of large vessels (Chen et al. 1999; Glover 1999).

A suppression ratio (SR, defined as the ratio of the BOLD amplitude in the maximal inhibition condition versus that in the minimal inhibition condition) was calculated for each activated ROI pixel. When the SR of a pixel was smaller than a certain threshold (defined as SR_{Th}), that pixel was designated to the inhibited ODC group; on the other hand, if the SR of a pixel was not smaller than unity, that pixel was designated to the excited ODC group. The value of SR_{Th} was determined for each individual subject based on the averaged SR value (SR_{avg}) from all the activated pixels in ROI. SR_{avg} has two contributing components: the pixels from the inhibited ODCs and the pixels from the excited ODCs. In principle, the averaged SR for the

pixels of the inhibited ODCs is SR_{Th} and that for the pixels of the excited ODCs is 1. Assuming that the two ODC groups have approximately the same number of neurons (Cheng et al. 2001), SR_{avg} can thus be given by the following equation:

$$\begin{aligned} SR_{avg} &= 50\% \cdot SR_{inhibited} + 50\% \cdot SR_{excited} \\ &= 0.5 \cdot SR_{Th} + 0.5 \end{aligned} \quad (1)$$

As a result, SR_{Th} can be calculated as $SR_{Th} = (SR_{avg} - 0.5)/0.5$.

To normalize all subjects, SR was one-to-one mapped to an *ODC Index (ODCI)* for each activated pixel according to the following equation:

$$\begin{aligned} ODCI &= SR - SR_{Th} + 1 \quad \text{if } SR \leq SR_{Th} \\ &1 + \frac{SR - SR_{Th}}{1 - SR_{Th}} \quad \text{if } SR_{Th} < SR < 1 \\ &SR + 1 \quad \text{if } SR \geq 1 \end{aligned} \quad (2)$$

Using this equation, any activated pixel with an *ODCI* value smaller than 1 (corresponding to the SR value smaller than SR_{Th}) was designated as belonging to inhibited ODC; any activated pixel with an *ODCI* value larger than 2 (corresponding to the SR value larger than 1) was designated as belonging to excited ODC. The ODC map was generated based on the *ODCI* value for all the activated pixels in ROI. The pixels from the inhibited ODCs were shown in red, and the pixels from excited ODCs were shown in yellow. Any activated pixel with an *ODCI* value between 1 and 2, which was linearly interpolated from a SR value between SR_{Th} and 1, can still reflect the degree of inhibition (smaller *ODCI* means stronger inhibition) and therefore was displayed using a graded color coding. For example, pixels that were relatively inhibited were shown in more reddish colors, while pixels that are relatively excited were shown in more yellowish colors (See “Results”). All fMRI ODC maps were presented vertically in which the top part of the map corresponded to the posterior V1.

To validate the notion that ODC maps generated using the proposed fMRI method are reproducible, fMRI data acquired within the same session were divided into two halves. Each half of data contains 4–5 fMRI runs with the same total number of maximal inhibition and minimal inhibition tasks. An ODC map was separately created based on each half of fMRI data. An overlap map was generated from all reproducible pixels (i.e. pixels that are either both inhibitory or both excitatory in the two separate maps).

Results

One ODC map generated using the proposed fMRI method in one subject was shown in Fig. 1. In this ODC map, alternating ODC-like strips or patches between the inhibited (red color) and excited (yellow color) ODCs are clearly observed in the map, and most of the ODCs identified are approximately orthogonal to the interhemispheric fissure as expected based on the slice prescription. Consistent with the histological finding, the inter-columnar distance in the ODC map was estimated between 0.5 and 1.5 mm (Horton and Hedley-Whyte 1984). All these morphological features can be observed in ODC maps from all subjects shown in other figures in this article.

Interestingly, in all ODC maps (see Figs. 3, 4 and 5), activated pixels in ROIs are clustered into two populations: an inhibited population (in red color) and an excited population (in yellow color). Most of partially inhibited pixels (colored as graded orange in the color bar) are located at boundaries between adjacent ODCs due to the partial volume effect and/or relatively weaker ocular dominance strength at the boundary. This notion can be verified in Fig. 2, which shows

the histograms of *ODCI* from all activated pixels inside ROI from one representative subject (Fig. 2a) and from the average of all three subjects (Fig. 2b). Clearly, the dominant portion of all activated pixels belongs to either inhibited population (*ODCI*<1) or excited population (*ODCI*>2). This unique distribution is in remarkable contrast to the distribution of random noise. Consistent bi-modal distribution of activated ROI pixels in all subjects strongly indicates that the structures in ODC maps are organized populations instead of random fluctuating noise. The fact that all activated ROI pixels are clustered into an inhibited population and an excited population when subjects are stimulated by a paradigm inducing binocular inhibition, as well as the fact that these organized structures located in V1 contain the morphology that is conform to human ODC provide the supportive evidence that the mapped structures are indeed ODCs.

For the purpose of examining the reliability of mapping ODC using the proposed method, the reproducibility of ODC maps was investigated. Panels (b) and (c) in Figs. 3, 4 and 5 are ODC maps generated from each half of high-resolution fMRI data acquired in the same sessions, respectively, for all three subjects (lower panels are blurred versions of the corresponding upper panels to facilitate visualization of continuous ODC structures). Panel (d) is the overlap of reproducible pixels in maps (b) and (c). Panel (a) is the ODC maps generated by combining both halves of data in panels (b) and (c). Qualitatively, ODC maps in panels (b) and (c) preserve all the ODC-like features and resemble each other in terms of their column orientation, position and width. Although less activated pixels remain in the overlap map, the major ODC structures persistently show up in maps.

Quantitatively, mapping reproducibility was evaluated from three perspectives: the reproducibility of the distribution pattern of *ODCI*, the reproducibility rate of inhibited and excited pixels and the reproducibility of *ODCI* values.

For all activated pixels in both ODC maps separately generated from each half of data, distributions of *ODCI* from inhibitory pixel group (*ODCI*<1.5) and excitatory pixel group (*ODCI*>1.5) were separately fit to a Gaussian function, respectively. The means and variances of the distributions were compared between the two halves (listed in Table 1). The results indicate that, for all subjects, both means and variances are highly reproducible for both the inhibited and excited populations between two halves of data, suggesting that inhibited and excited pixels obtained from two halves of data have almost identical *ODCI* distributions in the same subject though the mean value varied across subjects.

As a second step, we counted the portion of overlapped pixels in panel (d) and calculated the reproducibility rate of all common activated pixels in ODC maps generated from two halves of fMRI data. The reproducibility rates are 75, 66 and 65% for three subjects in Figs. 3, 4 and 5, respectively. Statistically, the reproducibility rate is significantly higher than the reproducibility rate expected from random noise ($P = 0.03$, $n = 3$, two-tailed paired *t*-test comparing to the number of 50%) even for such a small sample size. These results are also in line with the numbers reported in the literature regarding the reproducibility rate of ODC mapping using high-resolution fMRI (0.63 for Cheng et al. 2001; 0.75 for Goodyear and Menon 2001).

Third, *ODCI* of activated pixels obtained from one half of data was correlated to *ODCI* of the corresponding pixels obtained from the other half of data for all activated ROI pixels, as shown in Fig. 6a. For all subjects, significant correlations were found between *ODCI*s of the corresponding pixels from two halves of data ($P < 0.0001$, 0.001, 0.0001 for subject 1, 2 and 3, respectively). More importantly, when plotting *ODCI* from one half of data against *ODCI* from the other half of data for all reproducible pixels (Fig. 6b, c and d), the slopes were very close to unity for all subjects (0.94, 0.84 and 0.90 for the three subjects, respectively). Plotting all reproducible pixels from one half of data against the other half of data from all subjects gives

a slope of 0.92 (Fig. 6e). These results indicate that not only *ODCI* pattern and ODC maps generated from separated data sets are statistically reproducible, but also *ODCI* values (or suppression ratio values) are reproducible for pixels in the maps. Collectively, based on the quantitative results in the distribution of *ODCI*, reproducibility rate and consistency of *ODCI* value, ODC maps generated from two separate data sets within the same fMRI sessions are reproducible in both inhibitory and excitatory patterns and in inhibitory and excitatory levels of ODCs.

Discussion

In this study, we demonstrated the feasibility of simultaneously mapping both excitatory and inhibitory neuronal processing at the columnar level by utilizing binocular interaction between the two ODC groups and high-resolution fMRI. The morphological features of mapped ODCs in the maps created using this method are conform to those of human ODCs revealed in postmortem experiments with respect to column appearance, size and orientation. In addition, the ODC maps generated are statistically reproducible. Taken together, these results suggest that it is feasible to map excitatory and inhibitory columnar structures by combining high-resolution fMRI and the mechanism of neuronal interaction, and this method may potentially provide a novel tool to study the neural circuitry and brain function at the level of elementary cortical processing unit.

Binocular inhibitory interactions were investigated in several fMRI studies (Menon and Goodyear 1999; Zhu et al. 2001; Buchert et al. 2002). Lateral fiber connections between the left-eye columnar neurons and right-eye columnar neurons have been found in primates (Blasdel et al. 1985). These fiber connections provide physical pathways for the communications between the neighboring columns. The local circuits at the ODCs in primates revealed by Katz et al. suggest that direct inhibitory interaction exists between adjacent columns (Katz et al. 1989). Buchert et al. observed that alternating monocular stimulation led to a significant larger BOLD response compared to binocular stimulation in the striate area near the calcarine fissure (Buchert et al. 2002). Menon and Goodyear found that in the ODCs driven by one eye, the BOLD response to binocular stimulation was lower than that to monocular stimulation to the appropriate eye (Menon and Goodyear 1999). These results provide strong evidence suggesting that the activity of one-eye ODCs can inhibit the activity of the fellow-eye ODCs.

In our previous study, we investigated the temporal dynamics of the binocular interaction between the two ODC groups using relative BOLD amplitude variations at different ISIs using relatively low spatial resolution, in which each image pixel included both inhibited and non-inhibited ODCs. We found that one-eye stimulation can selectively suppress the BOLD response to the subsequent stimulation of the other eye if the delay between the paired monocular stimuli is ~30–90 ms. This suppression is progressively reduced and eventually disappearing as ISI gets longer to ~300–400 ms (Zhu et al. 2001). The temporal dynamics of inter-ocular interaction revealed in that study are very likely to provide important information for understanding a number of visual phenomena such as binocular rivalry. However, the lack of sufficient spatial resolution to differentiate activities from different columns highlights a critical gap to eventually achieving these challenging tasks.

Therefore, in this study, we have further explored the feasibility of non-invasively differentiating neuronal excitation and inhibition in individual columns using the mechanism of binocular interaction in combination with high-resolution fMRI at a high magnetic field. Validity of this study was examined from two perspectives: Qualitatively, we inspected whether the ODCs mapped using this method contain morphological features of human ODCs;

quantitatively, we investigated whether the ODC maps created using this method are statistically reproducible.

The architecture of ODCs provides a clear example of columnar organization within the cortex, that is, neurons with similar receptive fields tend to cluster together to form orderly arranged columns. In the visual cortex, neurons within one ODC are dominantly driven by either left-eye or right-eye input. The strongest ocular dominance occurs in layer IVc of V1 (Hubel and Wiesel 1962, 1968) where the geniculocortical projections from the left and right eyes are strictly segregated. The ocular dominance strength varies in the layers above and below layer IVc; however, the dominance consistently spans across the whole cortical layers from the pial surface to the white matter (Hubel and Wiesel 1962, 1968; Kennedy et al. 1976; Tootell et al. 1988). Across the horizontal extent, the left-eye ODCs alternate with the right-eye ODCs in a periodic pattern. The individual column width is ~1 mm in humans (Hitchcock and Hickey 1980). An ODC map should approximately be conform to all these morphological features with respect to the column appearance, size and orientation (Horton and Hedley-Whyte 1984; Horton et al. 1990). The fMRI slice prescription used in this study makes it possible to coarsely anticipate the appearance of ODCs in terms of orientation, pattern and dimension in the fMRI map. Consistent with this expectation, the mapped ODCs in the present study are largely orthogonal to the interhemispheric fissure and display an alternating ODC-like pattern with an inter-column distance of approximately 1 mm. Quantitatively, the ODC maps created from two halves of data acquired within the same session are statistically reproducible not only in consistency of inhibitory and excitatory patterns of ODCs (reflected from significant reproducibility rates), but also in consistency of inhibitory and excitatory levels of all activated ROI pixels (reflected from reproducible *ODCI* values and distributions). Overall, these results collectively suggest that it is feasible to use the proposed fMRI method to simultaneously map neuronal inhibition and excitation at the columnar level in the human brain.

The feasibility of spatially differentiating the inhibitory and excitatory ODC populations in this study provides direct evidence indicating that the activation of one-eye ODC can indeed significantly inhibit the activity of the fellow-eye ODC under appropriate stimulation conditions. This lateral inhibitory mechanism between the two ODC populations has an important impact on understanding the neural basis underlying binocular vision processing including binocular rivalry, which is still a debated topic in the neuroscience field (Logothetis and Schall 1989; Leopold and Logothetis 1996; Sheinberg and Logothetis 1997; Tong and Engel 2001; Haynes et al. 2005; Wunderlich et al. 2005). The capability of non-invasively mapping the two ODC populations should enable directly and simultaneously recording the activities from the inhibited and excited ODCs during binocular rivalry. Along with the behavioral measurement, this recording may reveal the exact brain sites where rivalry occurs.

In contrast to the prevalent subtraction method that differentiates ODCs based on the difference of BOLD activities at neighboring columns induced by either left- or right-eye stimulation, the proposed method herein utilizes the BOLD magnitude variation induced by binocular inhibition between neighboring columns. Although more localized, the reduction in BOLD magnitude at inhibited ODCs may be smaller than BOLD amplitude difference between right- and left-eye only stimulations. That is to say, the sensitivity of mapping columns of the proposed method may not be better than that of the subtraction technique. However, the proposed fMRI method made it possible for the first time to simultaneously and non-invasively localize excited and inhibited columns; it should find its impact on neuroscience research.

The success in localizing ODCs with this non-invasive fMRI method paves the way for future studies that aim at understanding inhibitory behaviors in neural circuitry at the columnar level. This method also tremendously overcomes the limitations imposed by other techniques such as neuron recording. For example, it is known that neurons in primary visual cortex have

considerable difference in ocular dominance distribution between cat and monkey (Hubel 1988). Therefore, it is conceivable that the binocular inhibitory interaction and many relevant visual behaviors might be different between these species. However, to study these issues at the columnar level, the currently available techniques require invasive procedures and/or are incapable of mapping neuronal behaviors across multiple columns. With the proposed method, it can be anticipated that more useful information can be obtained from both animal models and human brains non-invasively and efficiently. Finally, similar fMRI approach and concept as demonstrated in this study, in principal, can be applied to map other neuronal interaction down to the functional columns such as the iso-orientation columns considering the fact that short-range inhibition among proximal orientation columns has been found (Sillito et al. 1995; Das and Gilbert 1999).

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Fig. 1. Illustration of a high-resolution GE-EPI image ($0.5 \times 0.5 \text{ mm}^2$ in-plane resolution), a selection of ROI and an ODC map created using the proposed fMRI method

Fig. 2. Histogram of *ODCI* of all activated ROI voxels from **a** one subject; and **b** averaged results of all three subjects. The activated ROI pixels clearly cluster into two populations: an inhibited population ($ODCI < 1$) and an excited population ($ODCI > 2$)

Fig. 3.

ODC maps in the first subject. **a** ODC map generated the whole data set acquired in one fMRI session. **b** ODC map generated from the first half of data. **c** ODC map generated from the second half of data acquired within the same fMRI session as **(b)**. **d** Overlap of reproducible pixels from **(b)** and **(c)**. The lower row is blurred version of the corresponding upper row

Fig. 4.

ODC maps in the second subject. **a** ODC map generated the whole data set acquired in one fMRI session. **b** ODC map generated from the first half of data. **c** ODC map generated from the second half of data acquired within the same fMRI session as (**b**). **d** Overlap of reproducible pixels from (**b**) and (**c**). The lower row is blurred version of the corresponding upper row

Fig. 5.

ODC maps in the third subject. **a** ODC map generated the whole data set acquired in one fMRI session. **b** ODC map generated from the first half of data. **c** ODC map generated from the second half of data acquired within the same fMRI session as **(b)**. **d** Overlap of reproducible pixels from **(b)** and **(c)**. The lower row is blurred version of the corresponding upper row

Fig. 6.

a Correlation of *ODCI* of all activated ROI pixels between the first and second half of data in one subject. **b** Correlation of *ODCI* of all reproducible pixels between the first and second half of data in the first subject. **c** Correlation of *ODCI* of all reproducible pixels between the first and second half of data in the second subject. **d** Correlation of *ODCI* of all reproducible pixels between the first and second half of data in the third subject. **e** Correlation of *ODCI* of all reproducible pixels between the first and second half of data in all three subjects

Means and variances of the *ODCI* Gaussian distributions of inhibitor pixel group (*ODCI*<1.5) and excitatory pixel group (*ODCI*>1.5), respectively, from both halves of fMRI data set acquired within the same study session from three subjects

Table 1

		Subject 1		Subject 2		Subject 3	
		First half	Second half	First half	Second half	First half	Second half
Inhibited pixels	Mean	0.70	0.66	0.48	0.52	0.68	0.64
	Variance	0.41	0.35	0.36	0.37	0.37	0.34
Excited pixels	Mean	2.27	2.22	2.35	2.30	2.10	2.13
	Variance	0.39	0.35	0.36	0.36	0.40	0.41