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Revealing Columnar Architectures Using fMRI: Challenges and Possibilities

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Among the many neuroimaging tools available for studying human brain functions, functional magnetic resonance imaging (fMRI) is the most widely used today. One advantage of fMRI over other imaging techniques is its relatively high spatial resolution. High-resolution fMRI, with its superb signal-to-noise ratio and improved tissue-vessel specificity, has strengthened the capability of fMRI and allowed mapping of fine cortical architectures in the human brain. In this presentation, I will first explain the factors limiting the spatial specificity of the blood oxygenation level-dependent (BOLD) effect, based on which most of fMRI experiments are conducted, and the measures dealing with these factors. I will then introduce several high-resolution (sub-millimeter) studies on the functional organization of human primary visual cortex (V1), including mapping of ocular dominance columns, mapping of temporal frequency dependent domains and direct demonstration of tuning to stimulus orientation. Finally, I will present some recent results from high-resolution studies revealing orientation specific responses in large draining veins, a finding closely related to the interpretation as why conventional low-resolution (~3 mm) fMRI signals can be reliably used to decode stimulus orientations.

1. The principle of BOLD fMRI

Following sensory stimulation or mental operation, the increased neuronal activity leads to the relaxation of arterioles. The exact mechanism for the relaxation is not very well understood, but recent evidence suggests that fine structures around arteriole-capillary intersections, such as vascular pericytes and capillary constrictions, may control this relaxation[1]. Consequently, the local cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic rate of oxygen ($CMRO_2$) all increase. However, due probably to the imperfect vessel-tissue diffusion, there is an over-supply of oxygen[2]. As a result, the blood is more oxygenated during activation, or in other words, the concentration of deoxygenated hemoglobin in the blood decreases during activation. Since deoxygenated hemoglobin is paramagnetic, its existence causes the inhomogeneity of local magnetic field, which leads to the decrease of MR signal. During activation, the decreased deoxygenated hemoglobin actually acts to mitigate the field inhomogeneity, which is the reason why MR signal increases. This effect during activation, that is, the BOLD effect, depends critically on the change in the local concentration of deoxygenated hemoglobin, and is largest when TE (time of echo) is approximately equal to the T2* (in gradient-echo recalled measurements) or T2 (in spin-echo measurements) of the brain tissue and can be described either as a prolonged T2* or T2 or as increased MR signal at a given TE[3,4].

2. Dependence of the BOLD effect on other hemodynamic and metabolic responses

The BOLD effect is known to be proportional to the change in local CBF and inversely proportional to the changes in local CBV and $CMRO_2$. The spatial specificity of the BOLD effect is thus related to (but not completely governed by) the spatial specificities of these hemodynamic and metabolic components.

Recent studies in animals have shown that both CBF[5] and CBV[6] are regulated at fine spatial scales (within a millimeter). Functional mappings using these hemodynamic components have successfully revealed columnar and laminar structures in cat visual cortex. However, due to the prolonged scan time and the usage of toxic contrast agent, these mapping techniques are still not available for studies in humans. Furthermore, although it is thought that $CMRO_2$ is also spatially finely regulated, as it reflects the increased demand in the oxidative metabolism by activated neurons, there is currently no method to measure the change in $CMRO_2$ directly.

3. Factors limiting the spatial specificity of the BOLD effect

As BOLD fMRI is most widely used neuroimaging tool, a practical and important question is, therefore, how finely the BOLD response following a neuronal event is regulated. To better address this question, it is necessary to review the cerebral vasculature in the context of the BOLD mechanism.

The brain is covered with a delicate network of surface vessels. The arteries penetrate vertically into the cortex and draining veins emerge from the cortex. Inside the cortex, neurons are distributed around capillaries, from which they extract oxygen. Since arteries are completely oxygenated, they contain almost no deoxygenated hemoglobin. The BOLD effect, thus, is primarily observed downstream in the capillary bed with less deoxygenated blood and in the veins whose blood is more deoxygenated.

An obvious and critical issue is which venous compartment contributes most to the BOLD effect. If it is an effect primarily from the

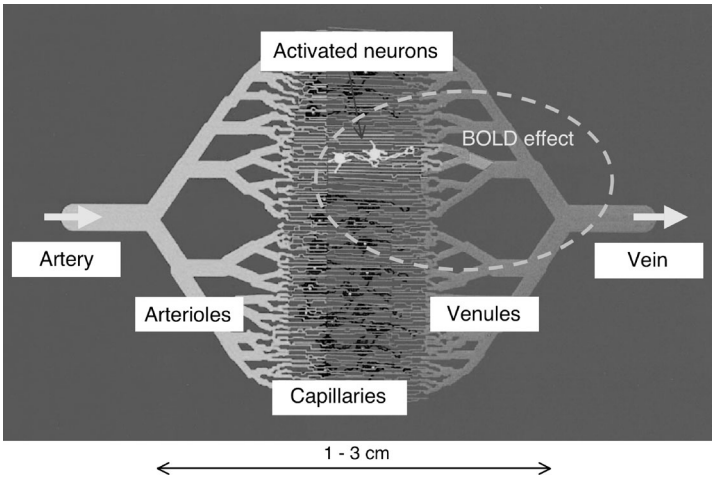

Fig. 1. A schematic drawing showing the BOLD effect in different compartments of the vasculature. Other than the capillary bed around activated neurons, large draining veins away from activated neurons also contribute significantly to the BOLD effect. Adapted with modifications from[7].

capillary bed, it should be near activated neurons. On the other hand, if it is mainly from large veins, then the BOLD effect may be away from the activation site. In fact, we know that both large veins, including those on the cortical surface and small veins, including venules and capillaries, contribute to the BOLD effect. In addition, there is also an intravascular contribution, coming from the blood itself.

4. Improved spatial specificity of the BOLD effect at high fields

It has been documented in many studies that gradient-echo recalled BOLD (most commonly used method) signal at low fields comes mostly from large veins. In the extravascular space, considering the signal attenuation from the signal with fully oxygenated blood as a function of blood oxygenation, the change around the veins from the resting state to activation state is typically around 1.5–2%, whereas the change around capillaries from the resting state to activation state is merely a small fraction of 1%. Similarly, in the intravascular space (that is, the blood), the change is also much bigger in the veins. However, because the intravascular signal change is an order larger than those in the extravascular space, the blood contribution is still very substantial even though the blood only occupies a few percents of the brain tissue[8].

The contribution from the blood can be suppressed by introducing diffusion-weighted gradients, or bipolar gradients as commonly known. Bipolar gradients induce diffusion-dependent signal loss so they suppress signal from moving blood because of inhomogeneous velocities within a vessel. This method has been used to quantify the blood contribution to the BOLD effect. At 1.5 T, BOLD signal disappeared almost completely when stronger bipolar gradients are used, indicating that the BOLD signal at 1.5 T comes mostly from the blood[9]. At 4 T or 7 T, such a drastic reduction of BOLD signal is not observed, suggesting that blood makes little contribution to BOLD signal at high fields[10].

In the extravascular space, Seiji Ogawa in his original BOLD model predicted that the BOLD effect increases linearly with the field strength around large veins and quadratically around venules and capillaries[11]. While the difference is negligible at low fields, the model predicts increased contribution to the BOLD effect from small vessels at high fields. Experimentally, Gati and Menon have compared the BOLD effects at 0.5 T, 1.5 T and 4 T under otherwise identical conditions. At a spatial resolution of $0.625 \times 0.625\ mm^2$, they could differentiate signal from large veins and those from the tissue region containing capillaries, venules and small veins, and found that the BOLD contrast-to-noise ratio (quantitative measure of the BOLD effect) was less linear in large veins and greater than linear in the tissue at 4 T, thereby confirming Seiji Ogawa's prediction that contribution from small vessels (including capillaries) to the BOLD effect increases at high fields[12]. This increased spatial specificity of the BOLD effect at high fields is the primary reason why imaging centers moved to introducing high-field systems.

5. Feasibility of high-resolution studies with improved SNR and signal specificity at high fields

The nice features of high-resolution fMRI are obvious. A high-resolution map contains more details and because of the reduced partial-voluming effect, activated voxels are usually localized within the brain tissue. On the other hand, the reason why not everyone is doing high-resolution fMRI is also very obvious—it takes very long time to acquire a single high-

resolution image. Using a typical single-shot echo-planar imaging (EPI), it takes only 50–70 ms to acquire a single image, whereas it takes 2–4 seconds to acquire a multi-shot EPI image. The spatial resolution in principle can be as high as one likes, which is only limited by SNR. SNR in an image is determined by the strength of magnetic field, voxel size and total scan time. When the scan time is limited (the time for scanning living human subjects is ultimately limited), the voxel size cannot be made too small. Therefore, the obvious benefit by going to high-fields is that SNR is proportional to the field strength. For a given voxel size (spatial resolution), SNR increases almost linearly with the field strength, from 1.5 T to 7 T[13].

In effect, high-field fMRI can be best used for high-resolution experiments[13]. This is because at high fields, physiological noise from heartbeat and respiration becomes more prominent. As a result, the high image SNR, which is dominated by the thermal noise cannot be transferred to a proportionally high temporal SNR, meaning that the time-course is more fluctuated at high fields. The real gain at high fields is when high-resolution (in-plane voxel size smaller than $1.5\times1.5\,mm^2$) experiments are conducted. When low-resolution experiments are conducted at high-fields, one must seriously consider the problem caused by the physiological noise.

Recently, we found that the point spread function measured using our 4 T system is ~1.8 mm (full-width at half maximum of a Gaussian convolved response profile in space). Interestingly, this measurement is not very different from those measured using 7 T systems, indicating that the point spread function probably is not dictated by the field strength, rather it may be an intrinsic property governed by the underlying vasculature or cortical horizontal connections. It should be emphasized that a point spread function of ~1.8 mm is really not that bad. A stimulation study based on this point spread function suggests that columnar structures in humans, which measure ~1 mm in width, can be spatially resolved if a differential mapping method (comparing two orthogonal stimulation conditions) is adopted. Below I will introduce our recent efforts in revealing functional architectures in human V1, including the mapping of ocular dominance columns, the mapping of temporal frequency dependent domains and the direct demonstration of tuning to stimulus orientation.

6. Mapping ocular dominance columns

The system of ocular dominance columns (ODCs) is one of the clearest examples of the distinct functional architecture within the cortex. We have mapped ODCs in normal human subjects using 4 T fMRI with a segmented gradient-echo echo-planar imaging (GE-EPI) technique and an in-plane resolution of $0.47\times0.47\,mm^2$. The differential responses to extended left or right eye stimulation can be reliably resolved in anatomically well-defined sections of V1 that is flat, less sulcated and generally void of surface veins. The orientation (roughly parallel to the representation of iso-eccentricities) and width (~1 mm) of mapped ODC stripes conform to those previously revealed in postmortem brains stained with cytochrome oxidase (CO). More importantly, we showed that mapped ODC patterns can be largely reproduced[14].

7. Mapping temporal frequency dependent domains

Using experimental procedures and imaging parameters similar to those used in the ODC experiment, we discovered that the strength of

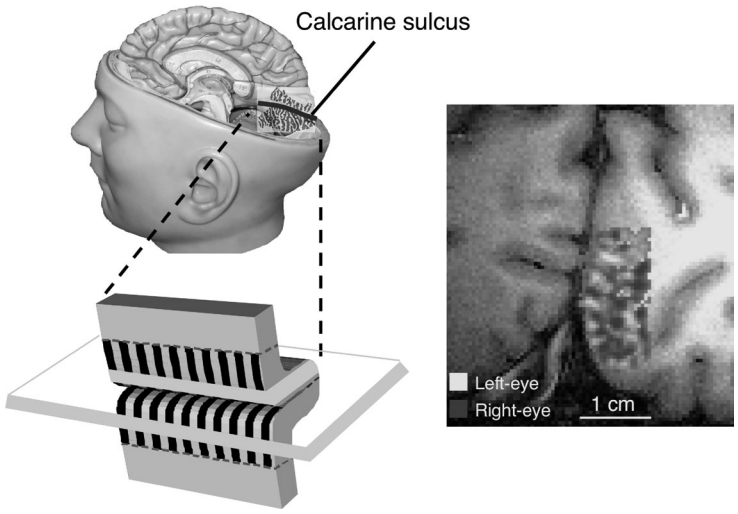

Fig. 2. Geometry of ODCs and the patterns of mapped ODCS using high-resolution (0.47×0.47×3 mm) fMRI. A cartoon diagram is depicted in the left to show the relationship between the orientation of human ODC stripes and the geometry of the calcarine V1. A slice parallel to and containing the upper or lower bank of the calcarine sulcus is prescribed to reveal alternating ODCs as shown in the right. To add in visualizing the patterns, the differential original ODC map was smoothed. To be able to reveal such patterns, it is critical to study human subjects who have a flat and wide portion of V1.

the BOLD signal depends little on the temporal frequency of the contrast reversal checkerboard, but low and high reversal frequencies preferentially activate spatially distinct patch-like domains in human V1. Such a temporal frequency-dependent spatial heterogeneity, which may be related to the CO blobs and interblobs in layers 2 and 3 of V1, has not been revealed in previous studies. The results suggest strongly that there may exist a distinct functional architecture in human V1, where visual information of different temporal frequencies is represented.

8. Direct demonstration of tuning to stimulus orientation

More recently, we have devised a novel stimulation paradigm that allows for efficient and continuous presentation of stimuli along a given stimulus dimension. This paradigm, together with a newly developed data-driven method for analyzing event-related fMRI data, has been successfully used for revealing the tuning of fMRI responses to stimulus orientation (0°–180°) at single-voxel level (0.5×0.5×3 mm^3) in human V1. These results provide the first demonstration that orientation selectivity in humans can be directly studied using fMRI. This new stimulation paradigm is currently being adopted in exploring functional architectures in other high-order areas beyond human V1.

9. High spatial resolution fMRI reveals orientation specific responses in large draining veins

Recently, a couple of studies have used classifier analysis with conventional resolution fMRI (3 mm isotropic voxels) to decode the orientation of a grating stimulus from the fMRI responses of early visual cortex; thus demonstrating that some of the voxels in the analysis display reliable and repeatable

orientation biased responses[15,16]. These results are intriguing because they probe a neural representation thought to be organized in cortical columns; presumably on the submillimeter scale. However, given that the large voxels used in the analysis would be expected to cover many orientation columns of different specificity, why such large voxels retain specificity for orientation is unknown. One possibility is that local inhomogenieties in the cortical orientation maps give rise to biased responses even in large voxels. We tested this hypothesis by examining the spatial scale of the bias that gives rise to classifier performance. We have conducted high spatial resolution imaging (0.75×0.75 mm inplane resolution) and have explored the consequences for classifier (linear support vector machines and Fisher's linear discriminant) performance of resampling at progressively lower resolution. Classifiers could still correctly identify the orientation of a stimulus at above chance levels even with voxels resampled to an inplane resolution of approximately 1 cm×1 cm. Examination of the weights of the classifier analysis at high spatial resolution shows that the orientation specificity is due to draining veins. We found that long elongated areas along the cortical surface were weighted heavily in the analysis because they had consistent and repeatable orientation biases. These areas aligned precisely with large draining veins that were visualized in T2* weighted venograms. This was surprising to us given that these veins would be expected to drain a large enough cortical area as to sample many different orientation columns. We hypothesize that the orientation specificity of these draining veins is either due to sampling a large-scale bias in the part of the visual field represented by the vein, or that draining veins are not neutral to the underlying columnar organization; i.e. veins may drain specifically from cortical columns that are functionally related. The specificity of veins may distort maps of functional organization, but may nevertheless provide a solid basis for using classifier analysis to sample columnarly organized responses using conventional resolution fMRI.

References

1) R. V. Harrison, N. Harel, J. Panesar and R. J. Mount: Blood capillary distribution correlates with hemodynamic-based functional imaging in cerebral cortex. *Cerebral Cortex*, **12**, 225–233, 2002.
2) R. B. Buxton and L. R. Frank: A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *Journal of Cerebral Blood Flow and Metabolism*, **17**, 64–72, 1997.
3) S. Ogawa, T. M. Lee, A. R. Kay and D. W. Tank: Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Science of the United States of America*, **87**, 9868–9872, 1990.
4) S. Ogawa, D. W. Tank, R. Menon, J. M. Ellermann, S. Kim, H. Merkle and K. Ugurbil: Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Science of the United States of America*, **89**, 5951–5955, 1992.
5) T. Q. Duong, D. S. Kim, K. Ugurbil and S. G. Kim: Localized cerebral blood flow response at submillimeter columnar resolution. *Proceedings of the National Academy of Science of the United States of America*, **98**, 10904–10909, 2001.
6) F. Zhao, P. Wang, K. Hendrich and S. G. Kim: Spatial specificity of cerebral blood volume-weighted fMRI responses at columnar resolution. *Neuroimage*, **27**, 416–424, 2005.

7) R. S. Menon and S. G. Kim: Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends in Cognitive Sciences*, **3**, 207–216, 1999.
8) R. B. Buxton: *Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques*. Cambridge University Press, 2002.
9) A. W. Song, E. C. Wong, S. G. Tan and J. S. Hyde: Diffusion weighted fMRI at 1.5 T. *Magnetic Resonance in Medicine*, **35**, 155–158, 1996.
10) T. Q. Duong, E. Yacoub, G. Adriany, X. Hu, K. Ugurbil and S. G. Kim: Microvascular BOLD contribution at 4 and 7 T in the human brain: gradient-echo and spin-echo fMRI with suppression of blood effects. *Magnetic Resonance in Medicine*, **49**, 1019–1027, 2003.
11) S. Ogawa, R. S. Menon, D. W. Tank, S. G. Kim, H. Merkle, J. M. Ellermann and K Ugurbil: Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophysical Journal*, **64**, 803–812, 1993.
12) J. S. Gati, R. S. Menon, K. Ugurbil and B. K. Rutt: Experimental determination of the BOLD field strength dependence in vessels and tissue. *Magnetic Resonance in Medicine*, **38**, 296–302, 1997.
13) C. Triantafyllou, R. D. Hoge, G. Krueger, C. J. Wiggins, A. Potthast, G. C. Wiggins and L. L. Wald: Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. *Neuroimage*, **26**, 243–250, 2005.
14) K. Cheng, R. A. Waggoner and K. Tanaka: Human ocular dominance columns as revealed by high-field functional magnetic resonance imaging. *Neuron*, **32**, 359–374, 2001.
15) Y. Kamitani and F. Tong: Decoding the visual and subjective contents of the human brain. *Nature Neuroscience*, **8**, 679–685, 2005.
16) J. D. Hayes and G. Gees: Predicting the orientation of invisible stimuli from activity in human primary visual cortex. *Nature Neuroscience*, **8**, 686–691, 2005.