



Comments and Controversies

Is cortical vasculature functionally organized? ☆

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ABSTRACT

The cortical vasculature is a well-structured and organized system, but the extent to which it is organized with respect to the neuronal functional architecture is unknown. In particular, does vasculature follow the same functional organization as cortical columns? In principle, cortical columns that share tuning for stimulus features like orientation may often be active together and thus require oxygen and metabolic nutrients together. If the cortical vasculature is built to serve these needs, it may also tend to aggregate and amplify orientation specific signals and explain why they are available in fMRI data at very low resolution.

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The target article points out that classification of the orientation of a sinusoidal grating can be achieved even after spatial smoothing of data (Beeck, 2009–this issue; c.f. Gardner et al., 2006). Can we expect this result given what is known about the cortical vasculature? The biology of the cortical vasculature system is what makes functional magnetic resonance imaging (fMRI) possible. Indeed, it is a rather amazing biological fact that the cortical vasculature is so well constructed that it can deliver oxygenated blood to precisely the right area of cortical tissue that has just undergone neural activity. While this ability in a gross manner had been suggested for more than a century since the time of Sherrington (Roy and Sherrington, 1890), it is with the advent of blood oxygen level dependent (BOLD) fMRI (Ogawa et al., 1990; Ogawa et al., 1992), that we have seen an explosive development in our knowledge and inquiry into just how precise the spatiotemporal delivery of oxygenated blood to cortical tissue is. Because BOLD fMRI uses vasculature signals (or more precisely, changes in the concentration of deoxygenated hemoglobin) as a proxy measure for neural activity, the question of how and in what way the vasculature is organized with respect to cortical tissue has become an important and still open question for understanding precisely what is being measured with BOLD fMRI.

An important debate regarding our knowledge of the vasculature has centered on how spatially specific the architecture of the vasculature is; in particular, is it organized on the scale of cortical columns? A cortical column (Lorente de No, 1938; Mountcastle et al., 1957) consists of a vertically organized set of neurons that share similar tuning properties like a preference for the eye of origin of a visual signal (ocular dominance column) (Hubel and Wiesel, 1969) or the orientation of a visual stimulus (Hubel and Wiesel, 1963). While it

is not clear what purpose this columnar organization serves (Horton and Adams, 2005), it is often considered to be a fundamental unit of cortical computation. Being able to measure functional properties of cortical columns in normal human subjects as they perform behavioral tasks would open up a vast array of experimental possibilities. Perhaps narrowing the divide between what little we know of cortical processing in humans and what we know from invasive single-unit recording studies in awake behaving monkeys. Based on the fact that ocular dominance columns which are visualized with cytochrome oxidase staining of brains from patients who lost sight in one eye before death are about twice as large as those found in monkeys (Adams et al., 2007 Fig. 8; Horton et al., 1990; Horton and Hedley-Whyte, 1984), it is expected that functional columns like orientation and direction columns would be on the order of a half a mm in size. Accordingly, high-resolution fMRI work has been devoted to achieving fast and reliable sub-millimeter measurements, so as to image signals specific to cortical columns. Indeed, high-resolution fMRI measurements in humans have reported ocular dominance columns (Cheng et al., 2001; Menon et al., 1997; Yacoub et al., 2007), orientation columns (Yacoub et al., 2008) and temporal frequency domains (Sun et al., 2007).

The conventional view of using sub-millimeter resolution fMRI to infer neural activity from cortical columns was challenged by an unexpected finding from Kamitani and Tong (2005). Using conventional, $3 \times 3 \times 3$ mm, resolution imaging and a clever use of classification algorithms, they were able to show that they could classify the orientation of a visual stimulus by examining the pattern of activity found in fMRI voxels from early visual cortex. In effect, this result shows that even at a spatial resolution of $3 \times 3 \times 3$ mm there is a reliable orientation specific signal that classification algorithms can capitalize on to predict what orientation was presented. How is it possible to measure orientation selectivity in voxels so large? The thinking had been that a $3 \times 3 \times 3$ mm voxel would encompass multiple different orientation columns tuned for different orientations. Thus any residual

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orientation preference due to an imbalance in the number of columns tuned for one particular orientation would be expected to be too small to measure given the variability of fMRI response. But, Kamitani and Tong's result suggested otherwise.

It is instructive to examine a few of the reasons why a residual orientation bias appeared improbable before Kamitani and Tong published their result. From both optical imaging and fMRI studies, we know that even in the most favorable measuring conditions, columnar specific signals represent only a small fraction of the overall signal measured. Optical imaging using intrinsic signals is able to measure blood oxygenation signals (in particular a deoxyhemoglobin component, Hbr) similar to BOLD fMRI using changes in the reflection spectrum of light on the exposed cortex (essentially it uses the fact that oxygenated blood appears redder than non-oxygenated blood) to measure these signals (Grinvald et al., 1986). When mapping orientation columns with these signals, typically all of cortex responds to the visual stimulus regardless of orientation (this effect is known as the "global signal"). The difference between columns that are tuned for one orientation versus an orthogonal orientation ("mapping signal") is much smaller, ranging between 20 and 40% of the global signal (Fukuda et al., 2006; Malonek and Grinvald, 1996 Fig. 3), at least for the ideal case in which the effects of the large, surface vasculature have been removed or avoided to expose only effects in the capillary bed specific to the columnar signals.

fMRI measurements, particularly gradient recalled echo (GRE) measurements, are extremely sensitive to the signal from large draining veins (Frahm et al., 1994; Haacke et al., 1994; Hoogenraad et al., 1999; Kim et al., 1994; Lai et al., 1993; Lee et al., 1995; Segebarth et al., 1994) which might be expected to carry a more global signal. Indeed, fMRI measurements of ocular dominance columns in humans using GRE imaging have found that mapping signals are a small percentage of the global signal at 4 T (Cheng et al., 2001 Fig. 8) and 7 T (Yacoub et al., 2007 Fig. 10), similar to what was found in optical imaging studies. This potential influence of large surface vasculature will be even more pronounced at the lower magnetic fields (e.g. 3 T) in which the majority of classification experiments have been conducted. Because the apparent T2 of blood decreases approximately quadratically as field strength increases (Gati et al., 1997; Lee et al., 1999; Ogawa et al., 1993; Yacoub et al., 2001), the intravascular signal from large veins tends to drop out at high magnetic fields, but is more prominent at lower magnetic fields (Duong et al., 2003; Song et al., 1996; Yacoub et al., 2003; Yacoub et al., 2005). Thus the ratio between mapping and global signals may be expected to be quite small for fMRI experiments conducted at lower magnetic fields.

But the ability to detect orientation specific mapping signals in large voxels (e.g. $3 \times 3 \times 3$ mm) typically used in classification experiments, is expected to be much harder still. A cortical column that subtends an area of 0.5×0.5 mm across a part of cortex with 2.5 mm thickness would consist of a 0.625 mm^3 volume, roughly 40 times smaller than the volume of a typical voxel. If, for example, there were only columns tuned for 2 orthogonal orientations, than an overrepresentation of 4 columns for one of the orientations would be needed to get a 10% bias for that orientation. However, it is likely a much larger overrepresentation of one orientation would be needed to sustain a 10% bias. Head movements of a mm are extremely hard to suppress even in well trained subject using a bite-bar. Each movement would be expected to bring in a slightly different distribution of columns and create a different bias. Even more challenging, classification algorithms have been shown to work across sessions in which the subject's head position will necessarily be in a different place within the magnet on different days (Kamitani and Tong, 2005). The image registration and motion correction algorithms used to correct for these movements, even if they work perfectly (a big if) cannot completely undo this mixing of signals – indeed, these algorithms must interpolate the desired voxel location by mixing signals from neighboring voxels.

If the mapping signal is already roughly an order of magnitude smaller than the global signal, then these factors of voxel size and movement artifacts might be expected to decrease the orientation specific signal by yet another order of magnitude. Thus, if the response to turning on a stimulus causes a 1% signal change, then the difference in response between orientations will be expected to be nearly two orders of magnitude smaller, on the order of a hundredth of a percent of signal change. Typically, a 1% signal change response to the presentation of a visual stimulus measured using conventional sized voxels has a standard deviation of amplitude (contrast reversing sinusoidal gratings, unpublished data) on the order of 1% signal change. Therefore we might expect that the orientation specific signals would have a contrast to noise ratio (CNR) of approximately 0.01 or less.

These expectations of very low CNR for orientation bias with more conventional resolution imaging at lower magnetic fields is clearly contradicted by the recent results in classifying orientations in V1. In contrast to a 0.01 CNR, a 0.1 Z score difference between preferred and non-preferred orientations was actually found on average in V1 (Serences et al., 2009). Moreover, while classification algorithms can combine the signal from multiple noisy sources with a low CNR, analyses showing classification performance as a function of number of voxels typically shows classification performance above chance even with the inclusion of just a few voxels (Haynes and Rees, 2005), suggesting a signal within single voxels that is much more reliable than one with an CNR of 0.01.

What other explanation can there be for such robust measurements of orientation bias that leads to excellent classification performance? Clearly, we might just be wrong about how orientation columns are distributed in the human cortex – perhaps there are large scale biases for particular orientations or directions of motion that are grouped together in larger areas than what we expect for cortical columns (Sasaki et al., 2006). But, another intriguing possibility is that the vasculature system is organized around columnar architecture in a way that could amplify weak signals and make them more easily measurable by fMRI.

While people often derisively talk of fMRI measurements as simply inquiring about the plumbing – it turns out that the plumbing is a rather sophisticated and well-structured system. Though on first glance the system of arteries and veins appear infinitely complex, there is a simple and repeated pattern throughout the cortex. Large veins and arteries course across the surface of the gray matter and then dive down perpendicularly into the gray matter. From these penetrating arteries and emerging veins again another right angle forms as arterioles and venuoles branch off parallel to the layers of cortex. Around each principal emerging vein lies a circle of penetrating arteries and this pattern forms a repeating mosaic covering the cortex, termed a functional vascular unit (Duvernoy et al., 1981; Lauwers et al., 2008).

This pattern of cortical vasculature is put into place by a well organized developmental program that recent work has found to resemble that of the developing nervous system itself (Carmeliet and Tessier-Lavigne, 2005). Endothelial tip cells at the leading front of developing blood vessels put out and retract filipodia and are sensitive to vascular endothelial growth factors (VEGF, Gerhardt et al., 2003) similar to the axonal growth cone of developing neurons and their sensitivity to neural growth factors. Axon guidance molecules including semaphorins, slits and netrins also appear to play a role in guiding the patterning of vasculature during angiogenesis (Carmeliet and Tessier-Lavigne, 2005; Eichmann et al., 2005). For example, netrin-1 acting through an uncoordinated 5 (UNC5) family receptor is a negative regulator of capillary branching (Larrivee et al., 2007; Lu et al., 2004) and also an inhibitor of axon growth (Low et al., 2008). There is evidence that nerves, at least in the sensory periphery, are able to guide developing arteries using VEGF (Mukouyama et al., 2005; Mukouyama et al., 2002), and conversely smooth muscle cells

of developing vessels can produce factors that guide nerves (Honma et al., 2002). These common and bi-directional signals suggest a developmental organization that insures a well orchestrated mapping between wiring and plumbing of the nervous system.

We don't know how closely matched the architecture of the vasculature is to the *functional* architecture of the nervous system. Are functional vascular units arranged in concert with columnar maps? Do they vary their size and separation to match local functional circuitry? In principle, if the vasculature follows functional organization (much like the way horizontal projections of cortical neurons do (Gilbert and Wiesel, 1983, 1989)), it could serve to vastly amplify weak functional signals by aggregating across numerous cortical columns that share the same functional tuning. In fact, we know that at least at a coarse level the vasculature system does follow functional organization. For instance, using scanning electron microscopy to examine corrosion casts of the vascular anatomy has found that there are completely distinct capillaries beds that serve auditory cortex (as defined by optical imaging) and neighboring non-auditory cortex in the chinchilla brain (Harrison et al., 2002). Cytochrome-oxidase rich blobs found in the primary visual cortex are more highly vascularized than interblob areas (Weber et al., 2008; Zheng et al., 1991).

Taken to the level of cortical columns, it could be that single arteries provide oxygenated blood to functionally defined units like a cortical column, and perhaps even to a number of columns that are all active together because they share the same tuning properties. Single draining veins might be arranged in conjunction to drain these areas together. This is an appealing idea, at least conceptually, in that areas that are active together (for example because they all are responding to the same visual feature like a movement in a particular direction or an oriented edge), would typically need metabolic energy at the same time. Thus, one might think that neurons that fire together not only wire together, but that shared tuning drums up correlated activity that plumbs them up together as well. While this idea is still speculative, by combining high-resolution functional imaging with other non-invasive imaging techniques that can separately visualize arteries and veins (Bolan et al., 2006; Haacke et al., 2009; Haacke et al., 2004; Park et al., 2008), the degree to which the vasculature follows functional architecture can now be tested.

If the vasculature system follows functional architecture by plumbing together cortical columns that are active together, what consequences would this have for functional imaging? On the one hand, high spatial resolution imaging that attempts to uncover the functional architecture of the cortex by mapping cortical columns would display distorted maps of the underlying neural activity. However, this is already a well known problem and all serious studies of columnar organization already go to great lengths (just as optical imaging studies do (Vanzetta et al., 2004)) to minimize these effects of large vasculature, aiming to maximize localized signals from the capillary bed which is more closely localized to the true underlying neural activity. On the other hand, if one is interested not in the spatial layout of the cortical columns, but instead wants a proxy measure of how orientation selectivity or direction selectivity changes with behavioral demands, then these vasculature signals would still provide a valid, if indirect measure. Thus, the ability of classifiers to work even, as the target article suggests, at very low spatial resolutions, may be a consequence of a well-structured vasculature aligned to the functional architecture of the cortex. This potential structure of the cortical vasculature may not only serve to efficiently provide nutrients to concurrently active cortex, but may also have the fortunate side-effect of making possible fMRI experiments that bridge the gap between what we know of human and monkey cortical physiology.

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