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Visual Mapping Using BOLD fMRI

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Synopsis

Functional magnetic resonance imaging (fMRI) is used clinically to map visual cortex prior to brain surgery or other invasive treatments in order to achieve an optimal balance between therapeutic effect and the avoidance of post-operative vision deficits. Clinically optimized stimuli, behavioral task, analysis and displays permit identification of cortical subregions supporting high acuity central vision that is critical for reading and other essential visual functions. A novel data display permits instant appreciation of the functional relationship between the pattern of fMRI brain activation and the pattern of vision loss and preservation within the patient's field of view. Neurovascular uncoupling and its detection in visual cortex are key issues for the interpretation of fMRI results in patients with existing brain pathology. Emerging techniques such as resting state fMRI may facilitate the use of fMRI-based vision mapping with a broader range of patients.

Keywords

human; fMRI; brain mapping; visual cortex; cancer; arteriovenous malformation; epilepsy

Introduction

Being the most essential of our senses, the intricacy and brilliance of vision are perhaps most appreciated when compromised due to damage or disease. Though we lack a comprehensive account of the processes by which quanta of light falling on the retinae are translated into subjective visual experience, recent advances, particularly from functional neuroimaging, have allowed us to sketch out the functional organization of the human visual system and thus provide a framework for understanding the sensory and perceptual effects of central vision pathology. For instance, we now know that vision-related cortex, once thought to reside primarily in the calcarine fissure of the occipital lobe, extends throughout the entire lobe and into adjoining portions of the temporal and parietal lobes (Figure 1) and even to remote locations in the frontal lobes^{1–4}. Though highly interconnected, this extensive network can be subdivided into well over a dozen functionally distinct visual areas which, if selectively damaged, can result in deficits ranging from simple scotomata (localized regions of blindness) to complex agnosias and higher-order perceptual

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deficiencies^{5–12}. For the clinician, staying abreast of all these developments can be daunting and of questionable therapeutic value given our limited ability to “cure” central nervous system damage. However, there are clinical applications, such as the guidance of neurosurgery and the documentation of disease progression for which detailed assessment of visual system involvement may be warranted to avoid potentially debilitating vision deficits. Accordingly, this article outlines some of the more clinically relevant tools developed in the last decade for mapping the human visual system and highlights key interpretational issues as well as future trends.

From a clinical applications perspective, it is noteworthy that some of the earliest accounts of vision loss due to brain damage noted the relationship between the anatomical site of damage and the location and severity of a visual scotoma within the patient’s field of view^{13–19}. This perspective is re-iterated today in the use of fMRI to provide retinotopic maps of visual cortex potentially at risk from invasive surgical and radiation treatment of nearby brain tumors, arteriovenous malformations or epileptic foci. fMRI is used to map eloquent neural responses evoked by sensory, motor, or cognitive tasks by measuring localized changes in the oxygenation of blood hemoglobin that are triggered by focal changes in neural activity. Though fMRI is, therefore, an indirect measure of neuronal function, it is non-invasive, well-tolerated by patients, rapidly acquired in as little as 20 minutes, and can provide extensive maps of eloquent brain tissue that if damaged could result in a post-treatment visual deficit.

Visual Mapping Paradigm and Analysis

Early approaches to mapping human visual cortex were as simple as turning the lights on and off, or flashing a large checkerboard. While such stimuli can evoke activation of visual cortex, the resulting fMRI maps do not reveal even the most rudimentary features of functional organization such as the distinction between the cortical representations of peripheral versus central vision, the latter being particularly critical for many day-to-day visual tasks such as reading. Today, more comprehensive and informative approaches are available. (For detailed reviews of methodology and the functional organization of visual cortex, see Gill, Ulmer, & DeYoe, 2008²⁰, and DeYoe et al., 2011²¹). Mapping of visual field eccentricity and angular position using fMRI scans of approximately 4 min each, can yield more informative cortical maps that delineate multiple, functionally distinct, visual areas and differentiate subregions supporting central versus peripheral vision. This can be done efficiently through sequential display of a slowly expanding checkered annulus and a slowly rotating checkered wedge respectively (Figure 2). The checkerboard patterns are composed of high contrast, black and white checks that counterphase flicker at 8 Hz, resulting in strong neural activation and, subsequently, relatively large increases in the BOLD fMRI signal in visually responsive brain areas. The stimuli are presented in a temporal phase mapping sequence, meaning that locations in the visual field differing in eccentricity (distance from center of gaze) or angular (clock) position are stimulated at different times (temporal phases). Consequently, this approach uses the timing of the fMRI response to identify the location in the patient’s visual field that, when stimulated, most strongly activates each responsive brain voxel. Although this stimulus sequence can be viewed passively with good results, the patient can be asked to watch a small marker at the

center of the video display and press a button whenever the marker briefly disappears at random intervals. The button task is advantageous in that it provides independent verification that the patient is viewing the display throughout the fMRI scan and documents that the patient is paying attention to the stimulus. Also, actively attending to the visual stimulus can significantly enhance the brain response in both primary and later stage (extrastriate) visual areas. Complementary information garnered by using both the annulus and wedge stimuli yields detailed retinotopic maps of visual cortex as well as any focal defects due to pathology.

Together, the eccentricity and angular mapping data can be used to generate a novel Functional Field Map (FFMap), which displays the brain activation in the form of a map of the patient's visual field (Figure 2). Each circle symbol in the FFMap corresponds to a visually responsive voxel in the cortex, its position determined by the eccentricity and angle of the ring and wedge stimuli to which the voxel responded most strongly. The color of each circle indicates the strength of the fMRI response, while the size represents an estimate of the error in measuring the preferred stimulus position. For a healthy individual, the FFMap will contain circle symbols distributed throughout the visual field. But, if the visual cortex is focally damaged, symbols will be missing or less numerous within the retinotopic zone of the visual field affected by the pathology as illustrated in Figure 3, which shows the FFMap from a patient with an upper left quadrant scotoma (indicated by the black area in the underlying Humphrey visual perimetry map). In sum, the FFMap provides a unique display that can instantly reveal the relationship between a cortical pattern of focal pathology and its effects on the patient's vision.

Clinical Application

In general, the primary clinical application of fMRI vision mapping has been for presurgical planning in patients with pathology or potential surgical involvement of the visual pathways. When resection is necessary, neurosurgeons are able to use knowledge gained from the fMRI maps to help plan an optimal approach and extent of resection that maximizes therapeutic value yet avoids damage to neighboring eloquent cortex that may be critical for daily visual functions. Though aggressive resection of a tumor can significantly improve long-term outcome, potentially debilitating postoperative deficits can arise if neighboring eloquent cortex is damaged^{22–24}. Traditionally, identification of eloquent brain tissue using intraoperative cortical stimulation (ICS) has been the method of choice for neurosurgeons. Consequently, a number of studies have compared task-fMRI activation with ICS maps to help establish the validity of fMRI for presurgical planning. (For reviews see Sunaert (2006)²⁴, Dimou et al. (2013)²⁵, Giussani et al. (2013)²⁶). FMRI maps of sensorimotor areas are generally in good agreement with ICS, though results have been more variable in language areas, possibly due to higher variation in the behavioral task activation and the more diffuse anatomy of language networks. Nevertheless, fMRI has been widely implemented for presurgical mapping of both sensorimotor and language areas. Studies comparing fMRI and ICS maps in visual cortex have also reported good correspondence^{27,28}. Yet for a variety of reasons, fMRI vision mapping has not been used as widely in the clinic despite its potential utility (see DeYoe et al., 2011²¹).

As the clinical use of fMRI grows, reliance on visual mapping paradigms optimized for clinical, rather than research applications, will also become increasingly important. Such optimization includes use of visual stimuli extending out to visual field eccentricities of 10°–20° or more in order to obtain reasonably complete retinotopic maps. Use of time efficient paradigms such as temporal phase mapping can reduce MRI scan time, which promotes patient compliance and permits acquisition of additional scan paradigms such as diffusion tensor imaging (DTI) to map white matter tracts and breath-hold cerebrovascular reactivity to detect hemodynamic pathology (see Neurovascular Uncoupling below.) As mentioned above, use of a button-press task is highly recommended since it helps the physician to distinguish fMRI signals that are compromised due to brain pathology from signals compromised by poor patient compliance, sedation, or other non-specific effects. Even so, fMRI vision mapping under passive viewing conditions can successfully reveal fMRI activation when other task paradigms fail. Finally, fMRI visual field mapping and the FMap display technology have been shown to yield diagnostic information that can help to differentiate an apparent sensory deficit from higher order perceptual problems such as hemi-spatial neglect ²¹.

Resting State fMRI of Visual Cortex

Despite the widespread availability of fMRI, behavioral task requirements can limit the number of patients for whom it can be used successfully. This can exclude patients who are behaviorally or cognitively impaired and young children who may struggle with performing a specific task or adhering to instructions²⁹. To circumvent this limitation, resting-state fMRI (rsfMRI) provides a potential alternative to task-based fMRI for clinical brain mapping. RsfMRI can reveal functional organization through the analysis of intrinsic BOLD signals that are temporally correlated within, but not between, functional subsystems^{30–32}. The technique has been used in a wide variety of studies since Biswal et al. (1995)³⁰ reported its usefulness for mapping “functional connectivity” in subjects who simply rest quietly with eyes open or closed during an otherwise conventional fMRI scan. Moreover, several studies have shown that visual cortex can be selectively mapped using rsfMRI^{33–35}.

At the time of this writing, the validity of rsfMRI for clinical presurgical mapping and for mapping of visual cortex in particular has yet to be fully established. A handful of preliminary studies have compared rsfMRI maps in tumor patients with tbfMRI and sometimes with ICS ^{36–41}. The results of these studies have suggested that rsfMRI maps can indeed provide useful information for presurgical planning. So far, however, validity assessments of rsfMRI for clinical brain mapping have focused almost exclusively on sensorimotor cortex. As mentioned earlier, tbfMRI vision mapping and ICS mapping of visual cortex show good concordance, suggesting that this is likely to be true for rsfMRI mapping as well. In this context, it is noteworthy that visual cortex may provide an ideal “test bed” for such validity assessments. Like sensorimotor cortex, visual cortex is functionally and anatomically well defined. But visual cortex can be mapped with tbfMRI using a passive viewing task which may minimize behavioral sources of variation and thus maximize the likelihood of obtaining concordance with rsfMRI maps.

In a preliminary comparison of rsfMRI and tbfMRI in visual cortex of both tumor patients and healthy individuals, we found that the two paradigms generate quite similar activation maps (Figures 4B,C). Indeed a subsequent analysis showed that the pattern of rsfMRI activation can be used as a predictor of the presence of tbfMRI activation on a voxel-by-voxel basis. Figure 4D shows the color-coded comparison for each voxel within an occipital region of interest (Fig 4A). Exact matches are indicated by green colors (true positive and true negative predictions) while mismatches are shown in contrasting orange and red colors (false positive and false negative predictions). Interestingly, the results suggest that rsfMRI may provide more complete maps that include voxels representing portions of the visual field at eccentricities beyond the outer limits of the video stimulus display or hidden by the fixation marker at the center of the display – orange colors in Fig 4D). Overall, this type of analysis indicates that, as an indicator of BOLD activation, rsfMRI is at least as valid or better than tbfMRI for 80% of voxels.

While the foregoing results are encouraging, it is likely premature to treat rsfMRI as a replacement for tbfMRI in presurgical planning. More likely, rsfMRI can be used as an adjunct to tbfMRI under select conditions in which a task-based paradigm is impractical. One example of this potential is illustrated in Figure 5. RsfMRI was used to map visual cortex in a patient who had recently been rendered blind by a midbrain tumor causing increased intracranial CSF pressure and subsequent dysfunction of visual afferent pathways (e.g. optic radiations - note distended ventricles in Figure 5 left 2 columns). Though tbfMRI vision mapping was obviously impossible for this patient, we were able to use rsfMRI to demonstrate that cortical components of the visual system were still functionally connected in an apparently normal manner consistent with the pattern observed in a healthy volunteer (center 2 columns) using identical methods and with atlas components from the 100 Connectomes database⁴² (right 2 columns).

Currently, widespread acceptance of rsfMRI as a clinical tool is hampered by a lack of consensus regarding the preferred method of data analysis. In particular, both seed-based and independent component analysis (ICA)⁴³ have been widely used for rsfMRI data though both have limitations for clinical use. ICA yields multiple networks that are not necessarily mutually exclusive or wholly consistent across patients and that can split conventional networks, such as the visual system, into multiple subcomponents (cf. Figure 5). The resulting ICA components must be either manually identified based on expert knowledge, a prohibitively time consuming process, or auto-classified by computational comparison with an atlas such as the 1000 Connectomes^{42,44}, Human Connectome⁴⁵ or other published data⁴⁶. Seed-based analyses can suffer from many of the same weaknesses but offer the advantage that the functional connectivity of individual voxels or zones bordering a planned resection can be selectively visualized. However, the resulting connectivity pattern may or may not correspond to a network whose brain function, and hence its clinical importance, is easily identified. Additional analytic tools based on graph theory hold promise for identifying critical brain sites that, if damaged, may produce debilitating functional deficits due to their widespread connectivity^{47,48}. At present, though, the reliability and validity of such analyses across patients having variable brain pathology has yet to be established. Even seemingly rudimentary issues such as the most appropriate setting of the statistical threshold for differentiating valid rsfMRI signals from noise have yet to be fully explored in a clinical

context (though this is also true for tbfMRI). This is particularly problematic for the analysis of data from single subjects/patients^{40,49–52} Despite these issues, rsfMRI offers potentially overriding advantages for clinical use including the simplicity and brevity of data acquisition combined with comprehensive coverage of key functional networks for virtually any patient capable of resting quietly in an MRI scanner.

Neurovascular Uncoupling in Visual Cortex

An important consideration for the clinical interpretation of both task-based and resting state fMRI data is that they both are indirect measures of neural activity/connectivity. As outlined in Figure 6 excerpted from Attwell et al.⁵³, the BOLD fMRI signal arises from a cascade of cellular and chemical events that link neural activity to local changes in cerebral blood flow, volume, and oxygenation^{53–55}, which together alter the relative volume of oxygenated to de-oxygenated hemoglobin contained in each imaging voxel. Typically, as neural activity within a voxel increases, the proportion of oxygenated hemoglobin also rises thereby reducing local magnetic field distortion which, in turn, allows water protons to emit a stronger, more coherent magnetic resonance signal. However, focal brain pathology can directly disrupt this hemodynamic cascade without grossly affecting the underlying neural activity. This can then reduce or eliminate the BOLD fMRI response in voxels that are nevertheless neurally responsive – a phenomenon known as neurovascular uncoupling (NVU). NVU can arise from dysfunction at any point along the aforementioned cascade, as well as from defects in the underlying vasculature⁵⁶. NVU poses a significant challenge for the use of functional neuroimaging in clinical applications since it compromises the validity of the BOLD signal as a biomarker of neural activity.

If fMRI is used to identify eloquent brain tissue near a planned resection site, failure to consider NVU could result in inadvertent resection of healthy tissue. The danger of NVU in this context lies primarily in the generation of false negative indicators of brain activity. If a brain region is, in fact, neurally active but is not indicated as such in the fMRI brain map, the surgeon may falsely assume that the region can be resected without causing postoperative impairment. Consequently, testing for NVU in prospective neurosurgical patients is highly recommended. This can be especially important for patients suspected of having existing cerebrovascular pathology such as local ischemia, arteriovenous malformations, highly vascularized tumors, or cerebral infarcts.

Fortunately, testing for NVU is now becoming a standard component of the patient workup for presurgical planning⁵⁶, though the most appropriate method to assess NVU is still under consideration. Cerebrovascular reactivity (CVR) mapping using a simple breath-hold task or administration of inhaled CO₂ can provide brain-wide maps of vascular responsiveness, a necessary, though not sufficient, condition for BOLD activation. These techniques induce a transient state of hypercapnia, which normally produces observable changes in BOLD signal throughout the brain^{56–59}. A reduced or absent CO₂ response can mark zones of potential NVU (see the article in this volume on Special considerations/technical limitations of BOLD fMRI in this issue). Though helpful, such tests only probe the ability of the vascular smooth muscles to respond to changes in blood CO₂, leaving open the potential for disruption of the neurovascular cascade at any stage preceding the smooth muscle response (cf. Figure 6).

Whether NVU can actually be caused by factors acting at different stages of the neurovascular cascade remains unclear at the time of this writing. So, while it is true that the absence of a CVR response indicates the likely presence of NVU, the inverse is not necessarily true; the presence of a CVR response does not definitively indicate that NVU is absent. For example, it is conceivable that, in some cases, NVU might be caused by a selective effect of pathology on glial cells that link neuronal activation to the vascular smooth muscles (cf. Figure 6). In such case, a CVR test may appear normal, yet the fMRI BOLD response could be absent. To distinguish between these potentially distinct causes of NVU, we will refer to a CO₂ challenge as a test for “late stage” NVU. Making such a distinction is potentially important since other methods are capable of detecting both early- and late-stage NVU. For example, Figure 7A illustrates the case of a patient with a right occipital AVM showing minimal fMRI activation. In apparent agreement, the patient’s FFMMap shows little fMRI activation in the contra-lesional, left visual field suggestive of a nearly complete hemianopia. (Note paucity of orange circles in left visual field of Figure 7B). Yet, the patient’s Humphrey perimetry chart shown in the background of Figure 7B indicates normal vision in the lower left quadrant (light stipple with blue shading). Normal visual sensitivity in that quadrant verifies that the corresponding neural function is viable yet fails to trigger a BOLD hemodynamic response... *de facto* NVU. Though definitive for detecting both early and late stage NVU, such a behavioral test is mainly of use for patients with visual system pathology. Identification of a practical test that is definitive for both early and late stage NVU and that is anatomically comprehensive awaits future development.

Conclusion

Task-based fMRI has proven to be a valuable technology for elucidating the functional anatomy of visual cortex in patients having operable brain diseases. Clinically, it can provide key information for planning and guiding brain surgery or other invasive treatments in patients with pathologies impacting visual cortex of the occipital, temporal and parietal lobes. Vision mapping paradigms can provide detailed maps of the retinotopic organization of visual cortex thereby permitting identification of brain sites supporting critical central vision in individual patients. FFMMaps provide a novel display of brain activation that can be used to quickly assess the behavioral relevance of fMRI patterns that are potentially compromised by pathology or a specific surgical approach. FFMMaps can also be used to detect regions of NVU, making them additionally valuable for presurgical planning. Taskless, resting state fMRI has received increasing attention from clinicians due to its ease of application and potential use with a wider range of patients. However, with these exciting technological developments has come increased awareness of potential limitations and interpretational issues. Researchers should remain cognizant that fMRI is an indirect indicator of neuronal activity, and NVU should always be taken into consideration, especially in clinical populations. Ongoing research is likely to identify improved methods for detecting NVU and to develop more clinically practical methods for the analysis of rsfMRI data. Despite its limitations, fMRI in conjunction with diffusion tensor imaging and other methodologies now provide physicians with an unprecedented array of information that can be used to inform and refine the diagnosis and treatment of operable brain pathologies involving the human visual system.

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Key Points

1. fMRI mapping of visual cortex can be used to identify healthy brain tissue near a site of operable brain pathology.
2. fMRI mapping using an advanced stimulus/task paradigm permits identification of brain subregions supporting central vision that is critical for reading and other visual functions.
3. Novel functional field map (FFMap) displays permit instant appreciation of the behavioral relevance of visual cortex activation, especially with respect to existing and treatment-induced visual field deficits.
4. Neurovascular uncoupling (NVU) can complicate interpretation of fMRI data, but this can be ameliorated by use of new methods to detect and map NVU.
5. Resting state fMRI can be used to map visual cortex in patients who are behaviorally compromised.

Figure 1.

Subdivisions of human visual cortex displayed on a surface model of the standard brain of Talairach and Tournoux⁶⁰. Whole brain at right shows plane used to create separate occipital lobe model. Yellow asterisks mark tip of occipital pole. Colored patches on occipital models mark approximate locations of functionally distinct visual areas. **Medial View:** Pink with yellow asterisk – primary visual cortex, V1, which is flanked above and below by purple V2. Magenta (cuneus) – dorsal division of V3. **Ventral View:** Blue-gray – ventral division of V3. Dark blue – V4. Light blue - VO complex³. Dark green - fusiform face area⁶¹. **Lateral View:** Red in LOS – TOS complex³. Yellow - Lateral occipital complex^{62,63}. Abbreviations: CoS – collateral sulcus, Fus g – fusiform gyrus, IPS – intraparietal sulcus, LOS – lateral occipital sulcus, MTg – middle temporal gyrus, OTS – Occipitotemporal sulcus, POS – parietal occipital sulcus, STS – superior temporal sulcus, TOS – transverse occipital sulcus.

Figure 2.

Stimuli for visual field mapping and construction of Functional Field Maps (FFMaps).

Retinotopic mapping stimuli consist of an expanding, black and white, checkered annulus (A) or a rotating wedge (B) counterphase flickered at 8 Hz presented in a temporal phase mapping paradigm. A single expansion/rotation sequence takes 32 sec. and is repeated 5 times within a 168 sec scan run. (The initial 8 sec. of the scan containing the equilibration transient are discarded.) Outer radius of visual display extends to 20° eccentricity.

Expanding annuli are not scaled linearly in size and eccentricity but, rather, are scaled non-linearly so as to activate roughly equal areas of V1 as estimated using the retino-cortical mapping function of Balasubramanian et al. (2002)⁶⁴. The subject's task during each mapping sequence is to fixate a small dot at the center of the display and press a button when the dot blinks off for 0.125 sec. varied randomly every 4–8 sec. This task helps ensure that the patient attends to the mapping stimulus and maintains gaze at the center of the display.

Post-processing of the resulting fMRI data yield an estimate of the visual field coordinates (eccentricity [ρ], angle [θ]) at which the mapping stimuli activate each voxel most strongly. Using these coordinates, a circle symbol can be placed at the corresponding location on a diagram of the patient's view of the stimulus display (right). The symbol is colored to show the amplitude of the fMRI response according to the pseudocolor scale above. The size of the symbol represents the error in estimating the preferred stimulus location for that voxel (approx. 70% confidence interval). Symbols for all visually responsive voxels are placed on the diagram to yield a Functional Field Map (FFMap) that allows the physician to determine instantly if the patient's visual cortex is responding to all locations within his/her field of view.

Figure 3.

FMRI mapping of visual field eccentricity in an epileptic patient whose right anterior temporal lobe (left side of upper figure) was previously resected to remove epileptogenic tissue in that region. **Upper:** Axial view. fMRI activation (small squares) are colored according to the eccentricity of the stimulus (cf Figure 2) that maximally activated each voxel. Color code shown by inset at upper right. **Lower:** Functional field map (FFMap) showing robust fMRI activation (red-orange circles) associated with portions of the visual field having normal visual sensitivity as indicated by light stippling in the Humphrey perimetry chart shown in the background. Note lack of fMRI response in the blind upper left quadrant extending into peripheral lower left quadrant. FFMap color scale shows relative amplitude of fMRI activation.

Figure 4.

Quantitative comparison of resting state (B) and task based (C) fMRI activation patterns in medial occipital cortex. (A) - region of interest in which the presence/absence of statistically significant fMRI activation was compared on a voxel-by-voxel basis. For each voxel, the status of rsfMRI was taken as a predictor of the status of tbfMRI activation. Matched activation status is colored light green (true positive) or dark green (true negative) in D. Mismatched activation status is colored orange (false positive) or red (false negative). Note presence of a significant zone of orange indicating that resting state activation may engage portions of visual cortex that are not stimulated by the limited extent of the task-based visual stimuli (see text).

Figure 5.

Comparison of rsfMRI brain maps for a recently blind patient (left 2 columns), a single healthy control (middle 2 columns) and the average of more than 1400 subjects taken from the 1000 Connectomes database⁴². This example demonstrates the viability of using resting state fMRI as an alternative to task fMRI with patients for whom a task (e.g. viewing a visual stimulus) may be impractical or impossible.

Figure 6.

Schematic diagram of the neurovascular coupling cascade excerpted from Attwell et al.⁵³. Pathways from astrocytes and neurons (left) that regulate blood flow by sending messengers (arrows) to influence the smooth muscles around the arterioles that supply oxygen and glucose to the cells (right, shown as the vessel lumen surrounded by endothelial cells and smooth muscle). In neurons, synaptically released glutamate acts on N-methyl-D-aspartate receptors (NMDAR) to raise $[Ca^{2+}]_i$, causing neuronal nitric oxide synthase (nNOS) to release NO, which activates smooth muscle guanylate cyclase. This generates cGMP to dilate vessels. Raised $[Ca^{2+}]_i$ may also (dashed line) generate arachidonic acid (AA) from phospholipase A₂ (PLA₂), which is converted by COX2 to prostaglandins (PG) that dilate vessels. Glutamate raises $[Ca^{2+}]_i$ in astrocytes by activating metabotropic glutamate receptors (mGluR), generating arachidonic acid and thus three types of metabolite: prostaglandins (by COX1/3, and COX2 in pathological situations) and EETs (by P450 epoxygenase) in astrocytes, which dilate vessels, and 20-HETE (by ω -hydroxylase) in smooth muscle, which constricts vessels. A rise of $[Ca^{2+}]_i$ in astrocyte endfeet may activate Ca^{2+} -gated K^+ channels ($g_{K(Ca)}$), releasing K^+ , which also dilates vessels. Note that pathologic disruption of this cascade could occur at many stages, both early and late, to cause neurovascular uncoupling.

Figure 7.

fMRI-based mapping of visual cortex in a patient with an arteriovenous malformation in right occipito-parietal cortex (A). fMRI activation is color coded to indicate the visual field eccentricity of the ring stimulus that most strongly activated each voxel (inset shows color code). (B) Functional field map showing robust fMRI activation (orange circles) limited mainly to the right visual field. However, the patient's Humphrey perimetry chart shown in the background indicates that vision was normal (sparse stipple) in the lower left quadrant thus marking a zone of neurovascular uncoupling (blue shading).