

fMRI and its interpretations: an illustration on directional selectivity in area V5/MT

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fMRI is a tool to study brain function noninvasively that can reliably identify sites of neural involvement for a given task. However, to what extent can fMRI signals be related to measures obtained in electrophysiology? Can the blood-oxygen-level-dependent signal be interpreted as spatially pooled spiking activity? Here we combine knowledge from neurovascular coupling, functional imaging and neurophysiology to discuss whether fMRI has succeeded in demonstrating one of the most established functional properties in the visual brain, namely directional selectivity in the motion-processing region V5/MT+. We also discuss differences of fMRI and electrophysiology in their sensitivity to distinct physiological processes. We conclude that fMRI constitutes a complement, not a poor-resolution substitute, to invasive techniques, and that it deserves interpretations that acknowledge its stand as a separate signal.

Introduction

Functional magnetic resonance imaging (fMRI) produces reliable and reproducible results in various fields of research. Typically, fMRI signals are thought to represent changes in the activity of the neuronal populations responsible for the task at hand. This assumption has historical rather than scientific origins, as various degrees of stimulus or task selectivity have long been demonstrated with intracortical recordings from isolated single neurons in experimental animals. fMRI activation is thus presumed to reflect an increase in the spiking rate of those specialized neurons underlying the subject's behavior. Yet, research using diverse methodologies has also demonstrated that hemodynamic responses are more sensitive to integrative dendro-somatic processes than the spiking of a few stimulus- or task-selective cortical projection neurons. In other words, strong evidence exists that although fMRI undoubtedly provides valuable information regarding regional changes of neural activity, it does so by stressing neural processes that might be different from those reported in invasive animal experiments.

In this review, we examine to what extent common fMRI data reflect the functional properties of neurons by considering a special example: the neuroimaging data on neuronal directional selectivity, initially reported in

electrophysiological studies, in cortical area V5 (also known as MT). The aim is to show how imaging data can or should be interpreted. Can fMRI be seen to provide a pooled (yet whole-brain) version of signals otherwise provided by electrophysiology? Can clever experimental paradigms allow us to infer neuronal spiking properties from blood-oxygen-level-dependent (BOLD) signals? Can they circumvent the limits given by its spatial resolution? Given the exponential growth of noninvasive neuroimaging experiments in human, and given their ethical advantages over electrophysiology, these questions are central to basic science and to policymaking. With this aim, this review attempts to combine knowledge from neurophysiology, applied fMRI and neurovascular coupling (NVC) to address the above questions. We use concrete examples from functional studies and focus mainly on the cortical region of V5+/MT+, as it has been one of the most intensely studied regions both in physiology and imaging. We hope that any conclusions reached will have more general implications.

Functional properties of area V5

Many years of electrophysiological research have convincingly demonstrated that area V5 of the monkey brain contains an abundance of neurons selective for the direction of movement of the visual stimulus (e.g. see reviews in Refs [1–4]). In addition, single-cell recordings and microstimulation experiments also suggest that V5 neurons play a direct role in the perception of motion direction and speed, because spontaneous or electrically induced fluctuations of activity correlate with behavioral performance (e.g. see Refs [5,6]).

In accordance with such data, lesion studies demonstrated that damage in V5+ causes specifically a loss in the ability to perceive motion, while otherwise largely preserving normal visual performance in both human and monkey (for reviews, see Refs [3,4]). V5/MT is adjacent to MSTd and MSTl, areas that process more complex types of motion, such as visual flow in the case of MSTd. V5+ or MT+ refers to the group of regions. They project to higher-level regions such as VIP, which are thought to process flow and to integrate signals with cues of other modalities [7,8].

Functional imaging techniques such as positron emission tomography (PET) and fMRI identified the homologue of the V5+/MT+ complex in the human brain functionally

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by its strong response to moving compared to stationary stimuli [9]. Subsequent work showed that also monkey V5/MT and satellite regions can be identified using fMRI [10,11]. V5/MT responds exclusively to contralateral motion, and can on this basis be segregated from MSTd, which additionally responds to ipsilateral cues and to more complex flow patterns [12–14]. During free viewing of movies, responses of V5+/MT+ correlate with local object-related motion and depend on visual contrast, whereas hVIP responses correlate with global observer-induced motion in a contrast-invariant manner [15]. The use of controlled stimuli also indicates an increase in preference for flow from V5 to MSTd to VIP [16].

Similarities between the human and monkey visual brain strongly suggest that human V5+/MT+ neurons will also be found to possess directional selectivity. But to what extent can this property be inferred from fMRI alone? Our current knowledge of the origin of hemodynamic responses suggests that a great deal of caution is required when inferring cellular response properties from it, be it in V5 or in other areas whose neuronal selectivity is unknown.

Neurophysiology of BOLD signal

Even though fMRI measures neural activity indirectly and with a (standard) resolution in the range of millimeters across the whole brain, the mapping of certain features such as visual contrast, color, motion, faces and language have produced highly reliable results under various experimental conditions that coincide with those obtained in clinical as well as in electrophysiological studies [15,17–22]. The temporal resolution of BOLD signal with time constants in the range of seconds and its highly preserved lag with regard to neural events allow for the differentiation of neural response delays in the range of hundreds of milliseconds, and for the estimation of interareal connectivity [23–25]. The spatial resolution is affected by field strength, imaging parameters and vascular anatomy, and appears to offer more potential than previously thought, as illustrated by the mapping of ocular and even orientation-selective columns in primary visual cortex [26–28]. Nevertheless, the precise loci of activity in imaging must always be interpreted with care, because the most commonly used acquisition technique (gradient-recalled echo planar imaging) at the most often used low-magnetic fields might result in activations downstream from the actual neural events, through venous draining vessels [26,29]. Most importantly, it is important to keep in mind that all hemodynamic signals report neural mass activity rather than selective responses. As such, fMRI signals are likely to most often be indicators of mesoscopic neuronal signals, for example field potentials. We expand on this below.

Neurophysiological signals

The signal measured by microelectrodes reports both dendro-somatic integrative and spiking activity. The former is typically captured by the so-called local field potentials (LFP), which report population synaptic potentials and interneuronal interactions, that is, local cortical processing

[30]. LFP signals are spatially localized and stimulus selective [31–33].

Spikes, generally speaking, are the well-known electrical discharges of neurons. Without them, nothing would be happening in cortex. Yet, the usual spike responses reported in animal experiments do by no stretch of the imagination correspond to all ‘spiking’ in a cortical area. A typical microelectrode records spikes from a relatively large sphere 200–300 μm in diameter. But the recording technique suffers from a strong sampling bias. Captured only is the activity of large projection neurons. Cortical microcircuits are characterized by strong excitatory (E) and inhibitory (I) recurrence, and the contribution of the two can change proportionally or in opposite directions. In other words, increases or decreases of BOLD activity might reflect considerable changes in E–I balance – and hence in energy metabolism – that is not precisely reflected in firing of a few stimulus-selective projection neurons (for a recent detailed discussion, see Ref. [26]). This neuromodulation – possibly underlying changes in cognitive capacities, such as attention or short-term memory – might induce substantial changes in local processing with little effect on single-unit activity or multi-unit activity (MUA).

Neurovascular coupling

Because there are plenty of excellent reviews on NVC, we keep this section brief to merely aid as a reminder. BOLD signal reflects cerebral blood flow (CBF) and tissue oxygenation, which in turn change in proportion to the regional energy consumption. The latter is dominated by perisynaptic events, including neurotransmitter recycling and restoration of ionic gradients of postsynaptic membranes [26,30,34]. It is not spiking activity but this perisynaptic activity that dominates the control of vasodilation and contraction (and hence CBF changes), for example through release of messenger substances such as nitric oxide, adenosine, peptides or other substances as a direct consequence of synaptic activity [35–37]. Note, however, that both excitation and inhibition can lead to substantial metabolism increases [38] as well as to positive hemodynamic changes [36,39,40]. Inhibition, however, can also lead to BOLD signal decreases [41,42], most likely reflecting different types of inhibition (e.g. directly or via interneurons). It is therefore, in principle, possible that BOLD signal increases confuse inhibition and excitation or even reflect reduction of spiking output in the presence of increased field potentials, that is during enhanced local interneuronal activity [26,38].

Several *in vivo* experiments confirm the view that perisynaptic events might be the primary drive for BOLD signal. The correlation of BOLD to neural activity during sensory processing was demonstrated in simultaneous physiology and fMRI experiments in both anesthetized and alert, fixating monkeys [43,44]. BOLD signal was correlated with both spikes and field potentials, but only when these two neuronal measurements were correlated to each other. In cases of a mismatch between LFP and multi-unit activity, BOLD signal could only be predicted by concomitant LFP changes. Direct evidence for this also comes from cat visual cortex, where particular visual stimuli led to a segregation of tissue oxygenation and

LFPs from spiking activity [45]. It has also been shown that such results do not reflect differences in spatial summation between LFP and MUA signals, but rather the neural events that are captured by them directly [43,44].

Neuromodulators can also influence signal coupling, in that the application of serotonin during visual stimulation evoked strong LFP and BOLD signal responses in the absence of spike-rate increases [46,47]. Also, the balance of synaptic inhibition and excitation can play a major role in signal coupling. Experimental induction of simultaneous synaptic excitation and inhibition through microstimulation of cerebellar fibers led to strong blood flow responses in the absence of spikes, whereas in reverse, up to threefold spike increases in the absence of synaptic or blood flow signal changes were also observed [35,48]. Correspondingly, microstimulation in visual cortex led to BOLD signal in monosynaptically connected regions, reflecting their synaptic input in the likely absence of principal neuron spiking output [49,50].

All in all, given the neurovascular evidence and the functional evidence discussed here, a universal relationship between spiking activity and BOLD signal cannot be assumed. Especially not for more sophisticated experiments such as those discussed below, where, for example, excitation by one aspect of the stimulus can be shunted through inhibition induced by another – leading to a reduction in firing with concurrent increase in synaptic input, with hard-to-predict consequences for BOLD signal. Because it is often those complex experiments that aim at revealing single-neuron properties, their interpretations would be particularly vulnerable to dissociations between BOLD signal and neuronal spiking. What follows, thus, discusses the conclusive power of experimental approaches attempting to demonstrate the presence of distinct populations of neurons in V5 that are selective to different

motion directions in light of the above concerns as well as in light of new physiological evidence. We conclude that most studies relying purely on BOLD failed to reveal single-cell properties in human V5, but instead relied on the most likely interpretation of the data derived from physiological knowledge available at the time. This should be taken as a caveat, especially for fMRI studies of regions with properties that are by far less well understood than those of V5.

Evidence on the basis of fMRI adaptation experiments

The prime tool used in fMRI to circumvent the problem of resolution has relied on neural adaptation [51,52]. Note that in psychophysics, adaptation is highly valuable, as it provides unambiguous indication of a neural interaction between distinct stimulus conditions. Electrophysiology studies adaptation in its own right, for example to examine neural mechanisms of spatial integration as discussed below [53]. fMRI, by contrast, has attempted to *use* adaptation (fMRI-A) as a means to infer and map functional properties of neuronal subpopulations that are mixed within the resolution of a voxel.

One set of experiments tried to address the question of directional selectivity in V5+ exploiting the phenomenon of the motion aftereffect (MAE) that motion adaptation produces (for a review, see Ref. [54]): after prolonged exposure to a stimulus moving in one direction (unidirectional adaptation), subjects perceive a subsequent, static (or motion-balanced bidirectional) stimulus to move in the opposite direction. The ‘disinhibition’ theory of the MAE accounts for this by a distortion of the balance of mutual inhibition (opponency) between detectors for opposite directions of movement after adaptation (Figure 1c) [54,55]. A two-stage model supposes that detectors selective for opposite directions of motion in a first stage inhibit each other at a second stage, as in the standard Reichardt model [56]. Early

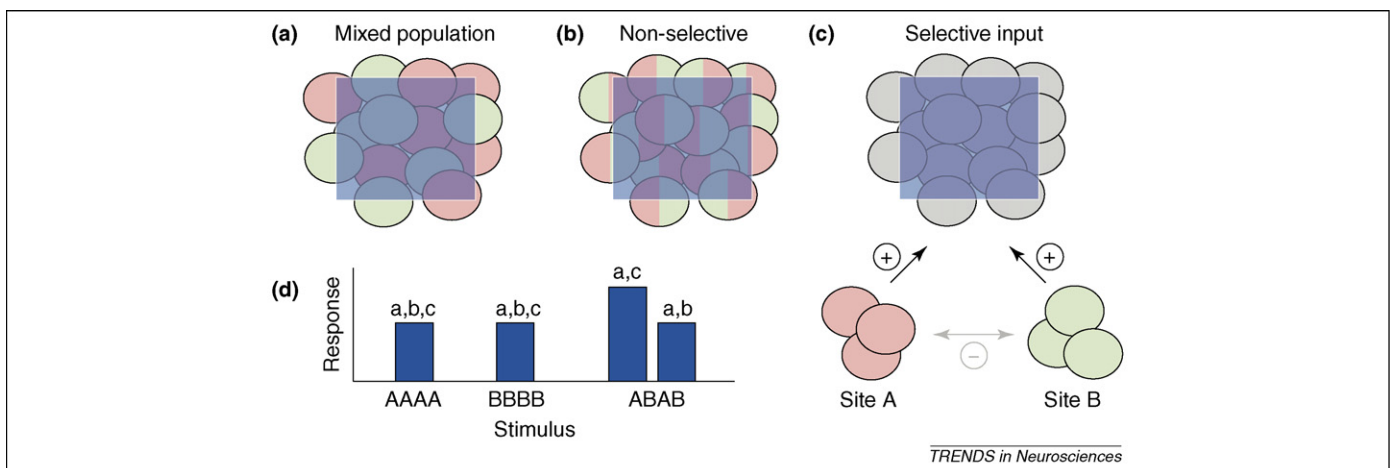


Figure 1. Ambiguities in interpreting fMRI adaptation results. (a)–(c) Neural functional organizations are illustrated within a voxel (in blue). Direct recordings of neurons (not relying on adaptation) would differentiate stimulus-selective (a) from nonselective neurons (b,c). The adaptation effects that fMRI-A relies on can, however, lead to ambiguous net effects (d). A mixed neural population (a) would adapt its spike rates more to same stimulus repeats (AAAA or BBBB) than to stimulus alternations (ABAB). NVC can render the BOLD effect of this differential spike-rate adaptation more apparent in the downstream site (e.g. V5/MT) whose input is affected rather than in the site where it originates (e.g. V1 [53]), especially when the mechanism of adaptation involves primarily intraneural spike-rate adaptation of the output neurons (with potentially little BOLD signal effect) rather than network adaptation (substantial BOLD effect). Hence the ambiguous outcome of (a) illustrated in (d). Nonselective sites should not reveal differential adaptation (b) – unless they get input from selective sites (c). In this case, adaptation can render neurons or sites that are not selective to motion direction to appear motion selective following adaptation [71]. (c) Illustration of how opponency effects (stronger response to unidirectional than to bidirectional motion) might derive from mechanisms at an earlier processing stage, for example if sites A and B inhibit each other (gray arrow).

electrophysiological studies in monkey have suggested that area V5 is the physiological substrate for this second stage [57].

In human, there are several reports that the fMRI signal from area V5 to the same stationary test stimulus is higher in cases when there is an MAE (after unidirectional adaptation) than in cases when there is not (after bidirectional adaptation), suggesting an organization of human V5 along the lines described above [58–61]. The idea is that if only one population of neurons is adapted (unidirectional adaptation), the other (unadapted) population should give a strong response in the test phase because (i) it is not adapted and (ii) it receives less inhibition from the adapted population. Thus, the stronger BOLD response after unidirectional adaptation was thought to match spike rates in electrophysiological recordings, and has been considered as proof for the presence of directionally selective neurons in human V5.

An important confound of the above studies is the fact that attention can modulate the strength of responses in V5 [62,63]: a stimulus with illusory motion might automatically draw more attention than one without. A carefully conducted study very nicely demonstrated that, when the attentional load was equated between conditions (using a threshold-detection task), no difference was found in the levels of V5 activation between MAE and non-MAE trials [64]. This is indicative of two issues: first, that attentional modulation appeared to account for the whole effect previously attributed to MAE, and that fMRI was very sensitive to attention. Second, however, it suggested that the differential neuronal spiking that induced the perceptual MAE escaped detection by fMRI once attention was controlled for.

Similar to other studies, the same study then proceeded to measure effects of adaptation to moving probes (as opposed to stationary ones as above); here direction-selective effects were found and are discussed below [64–66]. Note that the reasoning below applies to most studies using fMRI-A, and is not specific to motion or to the particular study discussed here. Because directionally selective neurons (DSN) adapt their spike rate upon prolonged or repeated unidirectional stimulation more than to multidirectional stimulation, one line of reasoning argues that fMRI would (i) identify the sites of direction-selective adaptation and (ii) therefore elegantly highlight regions containing direction-selective neurons. Indeed, BOLD signals in V5+ revealed the strongest directionally selective adaptation [64–66]. V1 was the least-adapting region (sixth rank) in one representative, carefully conducted study, whereas V4 ranked as third-most adapting region, although with far less effect than V5 and V3A, the two most prominent motion-processing regions [64].

The studies reviewed here were careful to avoid drawing explicit conclusions about the site of adaptation. But given the primary motivation of many fMRI-A studies to localize neural subpopulations using adaptation, we illustrate below the weakness of this approach.

Elegant electrophysiological experiments demonstrated that the site of direction-selective adaptation during prolonged unidirectional stimulation cannot reside in V5, because adaptation effects are spatially specific within

the receptive field (RF) of a given V5 neuron – in other words, if a motion adaptation stimulus was presented to only part of a V5 RF, only this part of the RF would reveal adaptation. This suggests that the actual adaptation does not occur in the V5 neuron, but in an input stage with smaller RFs, most likely to be V1 [53]. This study is thus a direct proof of downstream effects of adaptation that have been discussed before, questioning its specificity in localizing neural subpopulations (Figure 1) [51,52]. Importantly, note that this use of adaptation is tied to vascular imaging methods such as fMRI. We argue below that NVC might amplify the problem substantially.

Even though direction-selective neurons in both V1 (i.e. this site of adaptation) and V5 (downstream) reduce their firing rates following adaptation, the underlying reasons for this are entirely distinct and with important consequences for BOLD signals: synaptic input to V1 from subcortical sites is largely nonadapting, and V1 neurons reduce their firing rate primarily owing to mechanisms residing within neurons (such as opening of slow hyperpolarizing channels) [67]. The converse is true for V5. Following adaptation it receives a strongly reduced synaptic input owing to spike rate adaptation of its primary input area V1.

Now consider that BOLD signal might primarily reflect (peri)synaptic activity instead of principal neuron spiking activity. fMRI adaptation results might not only report downstream effects; instead, fMRI might de-emphasize (if not fail to detect) the site of the actual origin of adaptation, and emphasize sites receiving input from adapted sites one or more levels downstream.

This goes beyond ‘inheritance’ of adaptation effects when the receiving region has no or little neuronal specificity for the adapted property. In such situations, adaptation effects would still be observed in an area whose neurons were totally unselective to the direction of motion (see Figure 1). This has been long realized in the psychophysical literature of motion mechanisms. For example, the fact that, after motion adaptation, the contrast detection threshold for a moving grating is elevated in a direction-specific manner [68], cannot be taken as evidence that the perceptual detector is directionally selective, as only its input might have adapted (see Ref. [69]).

A recent study measured spike-rate adaptation to object images in inferotemporal cortex of monkeys, intentionally using paradigms similar to those used in fMRI-A [70]. Neurons that responded similarly well to images A and B nevertheless showed greater adaptation to same-image repeats (A-A or B-B) than to different-image repeats (A-B). This demonstrates that adaptation effects are not equivalent to direct measures of neuronal specificity. If the interpretation that is commonly used in fMRI adaptation was applied to this result, one might infer three populations of neurons – one responding to both A and B, and one image-A- and one image-B-selective population – even though these measurements stem from a single population. The observed effect might originate from adaptation in earlier areas or in neurons providing input to the ones measured.

These considerations might account for some of the adaptation observed in V4 discussed above. Indeed, in

monkey, adaptation has been shown to cause nondirectional V4 neurons to behave as directional, owing to an imbalance of the feedforward input, possibly from V1 [71] (see also Ref. [72]).

All in all, the presence or absence of adaptation in an area measured using fMRI therefore does not allow for the conclusive inference of either the presence or absence of the neural property in question.

fMRI-A studies thus often interpret their results using prior knowledge of the underlying single-cell physiology, rather than providing new, unambiguous knowledge of underlying physiological processes. Adaptation is interesting to study in its own right, and its downstream effects can provide crucial cues as to ‘who talks to whom.’ But its use to infer and map neural population properties using fMRI appears questionable (see also Refs [51,52] for reviews).

Complex motion: opponency and pattern integration

Another simple and compelling fMRI attempt to segregate sites containing DSN (e.g. V1) from those exhibiting DSN with motion opponency (e.g. V5; see above) was to expose human observers to unidirectionally drifting sinusoidal gratings, or to the sum of two superimposed gratings moving in opposite directions (counterphase gratings) [73,74]. The latter are perceived as stationary, contrast-inverting gratings, possibly as a result of the motion-opponency stage. In regions containing direction-selective cells without opponency, the single drifting grating would be expected to activate one population of direction-selective neurons, but the counterphase grating would activate two. In an area with opponency, however, the single drifting grating would be the stronger stimulus, because the counterphase grating would lead to a weaker response owing to mutual inhibition (illustrated using random dot motion in Figure 2).

If BOLD signal reported pyramidal spiking output only, and if opponency was regionally clearly segregated, this

approach would differentiate the processing stages. However, if BOLD also reflects input and local processing, then almost any outcome would be plausible. On the one hand, V5 pyramidal neurons fire most during drift grating, and BOLD signal can be highest then. On the other hand, the counterphase stimulus might lead to twice the input to V5 compared to the drift stimulus, and – if V5 contains the opponency stage – might additionally induce inhibitory local processing, thus leading to higher BOLD signal despite lower spike rates. Thus, BOLD signal can be lower, higher or equal in the two stimulus situations at the site of opponency (Figure 2). Experiments revealed that V1 responded similarly to both types of stimuli (with a preference for drift), and V5 responses were reduced for the counterphase stimulus compared to drift. It was entirely reasonable for the authors to argue that this speaks in favor of a regional segregation, with V5 reflecting the opponency stage [73,74]. However, had the outcome been the opposite or null (as it in fact turned out for low spatial frequencies), the current perspective shows that the same conclusions might have been drawn with equal correctness, only using a different interpretation of the origin of BOLD signal, as it was in the MAE experiments described above. Thus, in our view, the important result was the functionally segregated response in these regions, regardless of their sign.

Physiology complemented this study with evidence at the single-neuron level. Whereas neurons with opponency are primarily found in V5, their opponency is not complete, and it has been shown that neurons in early visual areas can also reveal opponency [10,57,75,76]. Thus, fMRI is highly compelling in its own right – comparisons with spiking data can be interesting, but they can hardly be deduced on the basis of fMRI signals. A congruence of BOLD signal and electrophysiology has been demonstrated in imaging results identifying V5 as the most pattern-motion-responsive cortical region in human,

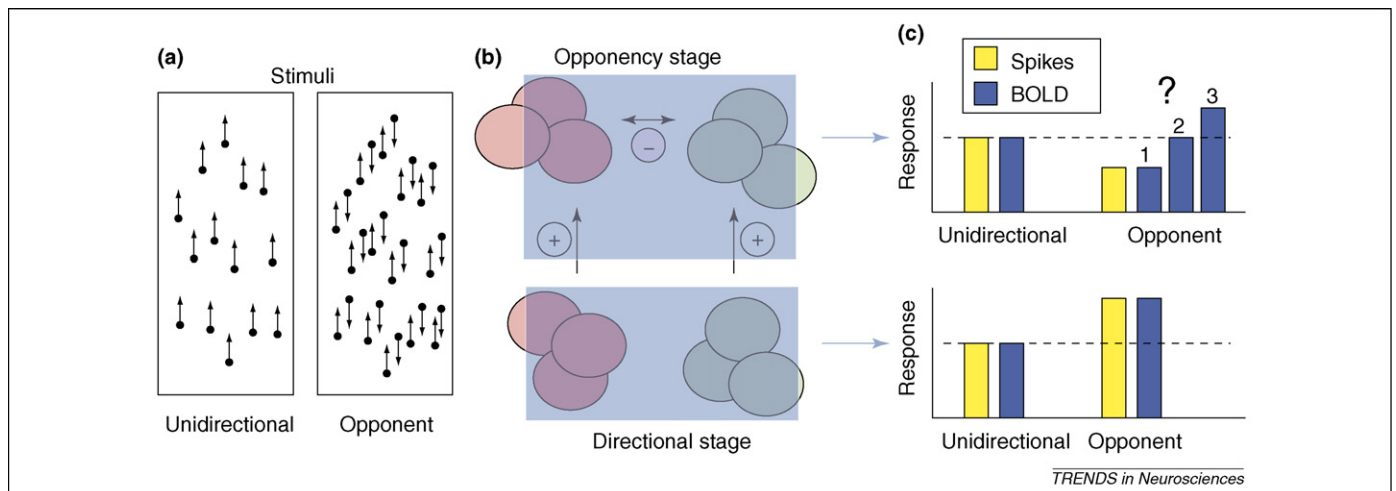


Figure 2. Opponency processing and potential associated BOLD signals. If a region is exposed to unidirectional or bidirectional visual motion stimuli (a), neural and BOLD signal will depend on its functional properties (b). A region containing directionally selective units that do not inhibit each other (lower box in [b], e.g. V1) will respond more to bidirectional than to unidirectional motion, both in terms of spikes and BOLD signal (c, lower panel). A potential downstream region with opponency (upper box in [b], e.g. V5/MT) will spike less to bidirectional than to unidirectional motion owing to opponency. Its BOLD response is, however, difficult to predict (c, upper panel): it might, like spiking, be less during bidirectional motion, or, alternatively, it might reflect the input and the synaptic inhibition and therefore be much higher during bidirectional than unidirectional motion, or it could be somewhere in between. Therefore, as long as NVC and the functional architecture of a region are not precisely understood, even the sign of a BOLD signal change for a given experimental condition can be difficult to predict – conversely, a given BOLD signal change cannot always be taken as a reliable indicator for changes in spiking activity.

coinciding with it containing a high abundance of pattern-responsive neurons [77]. Interestingly, however, recent electrophysiological evidence suggests that the neural mechanism for pattern-motion integration is located at a spatial resolution below that of V5 neurons, for example in V1, V2 or V5 dendrites, as it only occurs for stimuli overlapping even within a part of a V5 RF (like the motion adaptation above) [78,79].

The above examples have (i) not yet demonstrated independent evidence for directional selectivity in V5, and (ii) shown that especially in complex paradigms, the multitude of BOLD signal sources make interpretations in terms of spike rates in light of NVC increasingly difficult. Instead, results might be more compelling when interpreted in their own right. Examples might be the above discussed functional segregations of V5+ from other areas during sophisticated stimulus manipulations [64,73,74,77], the specific modulation of V5+ by attention to motion or to distracters, respectively [62–64], its response to local as opposed to global motion during movie viewing [15], the retinotopic organization of V5 [80] and the limitation of its receptive fields to the contralateral hemifield that differentiates it from MST, just as its comparably smaller response to flow [12–14].

Perception and attention

Physiological signals tend to be higher when stimuli are perceived as opposed to when they are not and, intriguingly, in some regions such as V5+, BOLD signal has appeared to reflect this more sensitively than electrophysiological measures [81–83]. This phenomenon has been addressed most extensively using bistable percepts, such as in binocular rivalry, where the percept alternates spontaneously, despite constant physical stimulation.

Higher areas including V4, V5 and inferotemporal regions show both substantial BOLD as well as spiking modulations as a function of the percept [82,84]. However, the two signals appear to diverge in early processing stages during bistable perception, with BOLD signal and some components of LFPs reflecting the percept better than spiking activity. LGN and V1/V2 have consistently revealed no or minimal modulation in spikes and multi-unit activity during bistable percepts, yet some limited modulations in LFPs [33,85–87]. BOLD signal modulations in human V1 and even in LGN by contrast were in some (yet not all) experiments nearly as large during perceptual transitions as those when the stimulus was changed physically (see e.g. Refs [88,89]). The most recent experiments demonstrated a percept-dependent dissociation of BOLD signal with spiking activity directly within the same animals [90]. Low-frequency LFPs and BOLD might thus reflect perceptually modulated local processing in V1 that is captured less well in spiking output rates.

Indeed, recent laminar LFP recordings revealed perceptually modulated changes in membrane currents within the upper layers of V1 that barely affect pyramidal neuron spiking output (A. Maier, pers. commun.). The above results therefore reveal a prominent dissociation between BOLD signal and spiking activity obtained in a normal behavioral setting, potentially owing to modulatory input

to V1. Another recent experiment demonstrated elegantly that synaptic input to V1 from LGN as assessed by LFPs can be largely dissociated from recorded MUA activity during visual processing, depending on the type of visual stimulus used [45]. Simultaneous measures revealed that one stimulus condition led to a complete dissociation of spiking activity from tissue oxygen changes that are thought to be tightly correlated to BOLD signal. Some frequencies of the LFP signal – primarily the lower gamma band – remained largely coupled to oxygen measures, not to spiking.

It might be no coincidence that a similar dissociation as in rivalry can be observed with attention, which is also associated with perceptual enhancement and with top-down modulation [91–93]. In V1, attention has usually revealed modest spike-rate modulations (a notable exception, however, being e.g. line-segmentation tasks [91,94]) [95], and in LGN no signal change has been detected [96,97]. These findings stand in contrast to human fMRI, reporting consistently strong attention effects in both V1 and LGN [92,98]. The discrepancy is unlikely to originate from species difference or task, as intracortical recordings of LFPs in human patients also revealed only modest attentional modulations, consistent with those obtained in monkey [93]. If one considers that attention also affects other properties such as spatial integration and even attribute preference in V1, and potentially neural states in LGN, and that this is mediated by thalamo-cortical loops and by the release of neuromodulators such as acetylcholine, it would be surprising if there was *no* discrepancy between a mass-action signal such as BOLD and the more limited electrophysiological measures [99–101]. The implication is that BOLD signals are not merely a low-resolution noninvasive version of multi-unit activity or LFPs, but that they constitute an independent, complementary measure. It might in many cases be correlated with other measures, but then in some important cases, it might not. Especially the latter deserve more attention and investigation.

Classifiers and high-resolution imaging

The key weakness in identifying direction-selective responses in V5+ is the mixed populations of neurons in V5+ within a single voxel. Adaptation methods failed to circumvent this problem as they rely on a spike-based interpretation of the signal, and additionally alter neural properties also in potentially nonselective downstream sites. However, the columnar organization of many cortical areas might allow for a direct identification of direction-selective responses (see Figure 3). To achieve this, the BOLD signal must be spatially sufficiently specific, and the imaging method must be able to resolve this [26]. High-field experiments suggest that imaging with resolutions in the hundreds of microns range should be possible, and have reliably mapped columns in primary visual cortex with ocular and even orientation selectivity [27,28,102]. Interestingly, such experiments also begin to unravel novel functional patterns, such as of domains with differential preferences for temporal frequencies [103]. There is no doubt that a similar success resolving direction-selective columns in V5 is imminent [104].

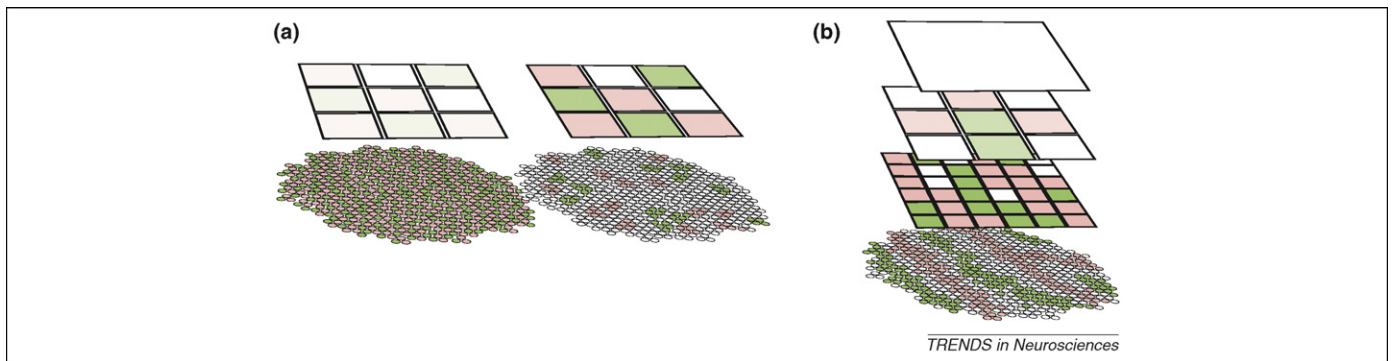


Figure 3. Effects of cortical functional organization on pattern classification and high-resolution imaging. (a) Schematic illustrating how a region (left) packet with feature-specific functional columns (circles, e.g. green responding to left and red to rightward motion) might lead to less feature biases in voxel responses (squares) – and therefore to worse multivariate statistical decoding success – compared to a region (right) containing far less but inhomogeneously distributed feature-responsive sites. Feature decoding thus depends on the conjunction of feature response *and* spatial organization. For example, decoding of motion in V5/MT has not been better, compared to other visual regions with lower density of directionally selective neurons [107]. This stands in contrast to univariate analyses, where areal response strength appears to be related to the density of directionally selective neurons. (b) Illustration of how increasing spatial voxel resolution can reveal qualitatively more information. Top level: the areal net response is not biased to red/green (e.g. left/right motion). Second level: medium- to high-resolution can lead to voxel-wise yet sub-threshold biases, allowing multivariate statistics to inform about the presence of feature-specific information in this region. Third level: high-resolution imaging can reveal the actual functional organization of the region – here stripes – using voxel-wise, standard univariate statistics.

An intermediate step, accessible to standard human scanners, relies not on true columnar resolution but on the biases a columnar organization can introduce even to much larger voxels (Figure 3). Because signal biases can be small and insignificant for single voxels, the approach relies on multivariate statistics (often implemented in the form of classifiers) that can detect and combine consistent trends of many data points (=voxels) [105,106]. Using this method, a recent study succeeded in demonstrating the presence of directional information of eight stimulus directions within V5 and also in areas V1–V4 [107].

In principle, such a result would be by far superior evidence for directional selectivity in V5 compared to the adaptation or pattern-integration studies presented above, and merely leave open whether neurons or some sort of neuronal population code might account for directional selectivity.

Because classifiers rely on feature selectivity *and* a spatial inhomogeneity of feature-selective responses, only their *conjunction* can lead to biased responses in segregated voxels. In the 2006 Kamitani and Tong study, for example, the classifier did not function better in area V5 than in any other visual area, and could equally well have missed it, not for functional reasons, but for reasons of functional anatomy – such as too closely spaced columns [104,107]. If, for example, V2 contained less directionally selective columns than V5 but spaced farther apart, classifiers might perform better on V2. Therefore, the degree of successful response classification in an area can by no means be interpreted as a degree of feature specificity in it (Figure 3). Despite this, a successful classification result clearly indicates the presence of information about the respective features in the studied region. However, the *interpretation* of such a result requires extreme caution. One reason for this is that classifier analyses are by far more sensitive to very small signal differences than the community is used to from single-voxel analyses. For example, it is conceivable that a classifier might distinguish between house or face

stimuli based on BOLD signal responses in V1, even though V1 is not known to contain object-selective neurons. *Post hoc*, one could attribute such a result, for example, to distinct spatial frequency properties of the two stimulus classes. Without *a priori* knowledge, however, one might be led to interpret V1 as a ‘face-selective’ region.

The motion classification study is perhaps one of the best controlled classification studies, as low-level features are matched and differential top-down influences are unlikely. Nevertheless, the extremely high sensitivity of multivariate statistics calls for caution, and unlikely but conceivable interpretations should be given even more consideration than usual. For example, astigmatism of the eye, which induces *orientated* visual distortions and orientation-dependent contrast changes, could contribute to the decoding of grating orientations, or to the improved classification of nonopposing motion directions [108,109]. Nevertheless, the successful classification of opposing motion directions clearly indicates directionally specific information in V5, even though of course fMRI cannot indicate whether this stems from DSN or other types of directionally selective signals in V5.

Therefore, although the presence of feature-selective neurons can potentially produce a successful classification result, the argument does not necessarily work the other way round.

Other noninvasive evidence for DSN in V5

The question remains whether there is any conclusive evidence for directionally selective neurons in *human* V5+. In one study, direct electrical stimulation of the visual cortex of an epileptic patient was shown to selectively impair motion perception in a particular direction, and some patients with damage in that region report similar deficits [110]. Unfortunately, the poor spatial specificity of both approaches left it unclear whether the effects really originated from V5+, therefore still leaving the question of directional selectivity in human V5 open (Box 1).

Box 1. Future questions

Just like any other technique, fMRI has limitations. These limitations are only to some extent related to methodology; they are also related to the circuitry and functional organization of the brain, and in practice also due to inappropriate experimental protocols. The most important limitation is the inability of fMRI to differentiate between function-specific processing and neuromodulation, between bottom-up and top-down signals and occasionally between excitation and inhibition [26]. This can, however, also be seen as a strength, as fMRI can and does report signals that can easily go undetected, for example, in spike-recordings alone.

MRI developments will improve neuroimaging. Parallel imaging with coil arrays, for instance, substantially improves the nominal resolution of MRI and fMRI, in particular when superconducting – and hence very low-noise – coils are used. The so potentially afforded high-resolution MRI might soon provide us with images of a fraction of a millimeter (e.g. 500^3 mm^3 isotropic) voxel size for multiple-slice imaging. Such resolution should be sufficient to discern different tangential (e.g. columns, hypercolumns) or radial (laminae) operational units and, in some cases, the information gained by such spatially resolved imaging might provide hints upon the origin of activations (i.e. feedforward, feedback, neuromodulatory). Spatially resolved imaging might therefore help to replace or better evaluate the results of adaptation paradigms or pattern classification analyses. Once fMRI provides more direct access to functional microarchitecture, some of the imaging effort might shift toward within-area rather than between-area mapping.

We believe BOLD signal can and should be used for what it really can: consistent and repeatable functional maps associated with sensory, cognitive or behavioral conditions can be informative in their own right. In combination with other techniques, fMRI could provide important hints of local processing, neuromodulation, feedback input or functional states that might otherwise go undetected, especially in situations of BOLD/spike dissociations. The success of such experiments in helping us understand neural mechanisms will entirely depend on the ingenuity of experimental questions, designs and analysis methods. Perhaps it is the ever-easier access to imaging facilities that is to blame for the key ‘weakness’ of this method, as it can delude researchers into neglecting the utterly needed ‘thinking’ required for it.

What concerns motion processing, directional selectivity is merely the much-studied tip of the iceberg. The brain uses motion cues in real life for a huge variety of functions, such as for the recreation of the third dimension of objects and of our environment, for the estimation of self-motion and for that of the biomechanical makeup of objects around us, for figure-ground segmentation, for the identification of emotional states and of social interactions, and much more. The identity and function of regions beyond V5/MT involved in these tasks, and their communication with shape, motor and limbic processing regions, are just a few of numerous questions that are likely to form an exciting field of research.

Conclusion

Our primary question here was to what extent noninvasive methods such as fMRI can inform about neural properties that are below the method’s resolving power. We specifically examined the evidence for directional selectivity in one of the best studied cortical regions in neuroscience, the motion-processing area V5 (MT). Whereas many functional properties have identified and established human V5 as a homologue of monkey V5/MT, most studies fail to convincingly demonstrate the directional selectivity of its neurons.

A key reason for this is that BOLD signal is not primarily driven by principal neuron spiking, but by the input and local processing of the area under investigation, and that in some cases the two can be entirely dissociated. fMRI is instead limited to ‘conditionally confirm’ prior knowledge from electrophysiology. This

conclusion might be interpreted as one that challenges the usefulness of this methodology. Miles away from the truth! fMRI cannot tell us, but also does not need to tell us about the spiking neurons reported in electrophysiological experiments. Instead it reports neural events going largely undetected in spike and sometimes even in LFP recordings. It is a most valuable methodology that provides complementary information to that obtained with local electrical measurements. The experiments that have brought this to light, using binocular rivalry, attention and specific stimulus configurations, might constitute only a fraction of these instances, given that the many cognitive questions investigated in fMRI likely involve complex, large-scale processing loops and considerable attentional modulation.

BOLD signal is an indicator for a multitude of functionally relevant processes, circumventing some of the biases observed for electrodes and therefore not only guiding but also complementing physiological recordings, in some cases perhaps even with a higher sensitivity. In many cases, fMRI results might be sufficient to formulate hypotheses about the neural involvement, function and interactions between specific areas. The detailed examination of such hypotheses and the elucidation of the actual neuronal events that underlie the examined cognitive capacities will require a continuous interplay between human neuroimaging and animal studies at all levels of neurophysiological investigation.

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