

How well do we understand the neural origins of the fMRI BOLD signal?

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The successful use of functional magnetic resonance imaging (fMRI) as a way of visualizing cortical function depends largely on the important relationships between the signal observed and the underlying neuronal activity that it is believed to represent. Currently, a relatively direct correlation seems to be favoured between fMRI signals and population synaptic activity (including inhibitory and excitatory activity), with a secondary and potentially more variable correlation with cellular action potentials.

Functional magnetic resonance imaging (fMRI) is becoming a popular non-invasive tool for imaging functionally active brain regions in health and in disease. The commonest method of fMRI is blood oxygenation level-dependent (BOLD) imaging, which has dominated this field since its discovery [1]. BOLD fMRI employs haemoglobin as a convenient endogenous contrast agent, relying on the magnetization difference between oxy- and deoxyhaemoglobin to create the fMRI signal [2,3].

fMRI BOLD therefore measures neuronal activity indirectly via its assumed haemodynamic correlate. The accurate interpretation of the BOLD signal is crucially dependent on fully characterizing the nature of the underlying neural activity that gives rise to the haemodynamic response, and the way in which these two aspects of neurobiology are linked – known as neurovascular coupling. Despite the recent increase in fMRI-related publications, the exact nature of this coupling remains largely unknown, with regard to both the nature and origin of the communicating signal between neurone and vessel [4,5]. Other determinants of the BOLD response include the nature of the haemodynamic response itself, and the way in which this response is detected by the MRI scanner (Box 1). This article examines our current understanding of the neural basis of the fMRI BOLD signal, and ways in which it might be improved.

Empirically, without a corresponding index of neuronal electrical activity, any changes in BOLD signal observed upon stimulation might have occurred through changes in neuronal activity, the coupling mechanism, or both. In order to examine this, there is clearly a need to measure changes in

neuronal activity and haemodynamic responses in parallel or, ideally, simultaneously. Significant advances have been made in this regard by Logothetis and colleagues, who have pioneered the simultaneous acquisition of electrical and fMRI data in primates. Their recent work has shown that the BOLD response directly reflects an increase in neural activity, correlating in particular with local field potential (LFP) measures, which represent the synchronized synaptic inputs of a given neural population [6]. This is in agreement with recent data that show a significant correlation between fMRI BOLD responses and evoked potentials in humans [7], and the literature regarding evoked field potentials and cerebral blood flow in animals [8–13].

Evoked potentials (and similarly, LFPs) are mainly attributed to extracellular currents from summated postsynaptic potentials [14–17], and thus represent a measure of population synaptic activity, rather than neuronal firing rates. Nevertheless, by comparing human fMRI and primate single-cell data, important findings in the visual cortex have been interpreted as suggesting that human fMRI BOLD is also proportional to the aggregate neuronal firing rate [18,19]. This was estimated as 0.4 spikes/s per neurone for each 1% fMRI signal change in area V1, and 9 spikes/s per neurone in V5.

'...up to 95% of regional cerebellar blood flow increases might be dependent on postsynaptic activity!'

Because the BOLD signal is dependent on many physiological and biophysical parameters (Box 1), which could vary between different species, these relationships can be considered as semi-quantitative. The effect of different anaesthetics used in animal studies on neurovascular coupling is also a potential variable (for example, in rats, α -chloralose decreases resting metabolic and presumably cellular activity [20]). However, it is interesting to note that recent papers [6,7,18,19] have found a predominantly linear correlation between neuronal activity and haemodynamic responses (although this is not the case in all animal experiments [21]). In those cases where non-linearities were modelled [19], they improved the relationship in only some cortical areas, suggesting that these relationships are not influenced by the nonlinear relationship between metabolic demand and BOLD signal [22].

Interestingly, there are early reports that both action potentials [18,19] and synaptic activity [6–8,12,13] correlate with the fMRI BOLD signal, so the relationship between these two types of neuronal activity merits further consideration. Empirical evidence suggests that the action potential firing

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Box 1. The haemodynamic response and fMRI BOLD signals

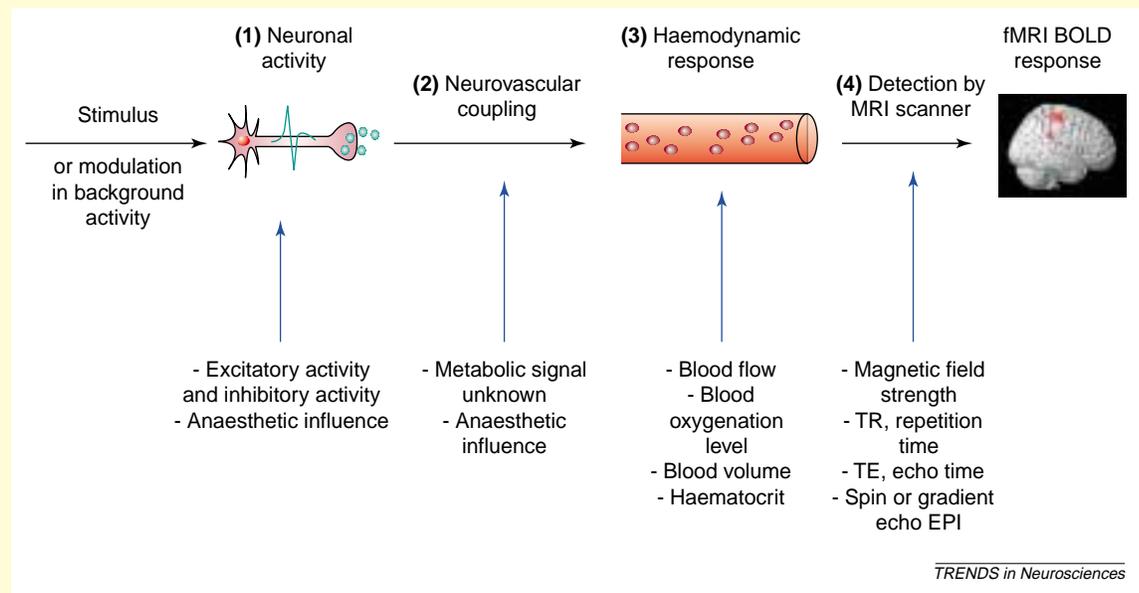


Fig. 1. The BOLD signal has several constituents: (1) the neuronal response to a stimulus or background modulation; (2) the complex relationship between neuronal activity and triggering a haemodynamic response (termed neurovascular coupling); (3) the haemodynamic response itself; and (4) the way in which this response is detected by an MRI scanner.

The blood oxygenation level-dependent (BOLD) signal can be thought of as having several key determinants (shown from left to right in Fig. 1): the neuronal response to a stimulus; the complex relationship between neuronal activity and triggering a haemodynamic response; the haemodynamic response itself; and the way in which this response is detected by a magnetic resonance imaging (MRI) scanner.

The many experimental parameters in functional MRI (fMRI) scanning that affect the amount of BOLD signal observed by any particular scanner include magnetic field strength, echo time and the type of imaging technique involved. For example, a 1% BOLD signal at an echo time of 30 ms is equivalent to 2% at an echo time of 60 ms, even if the haemodynamic

response is constant. BOLD imaging is also susceptible to various artefacts, including head motion, ghosting and field in-homogeneities [a]. Together, many factors will affect the amount by which the BOLD response reflects a given haemodynamic response, which makes the response difficult to quantify.

Much work has been carried out to identify the nature of the haemodynamic response itself, in particular by Friston *et al.* [b], furthering the Balloon model of Buxton *et al.* [c]. The vascular basis of the BOLD signal is predominantly believed to be a relative imbalance between increases in local cerebral blood flow (CBF) and concurrent (albeit smaller) increases in oxygen metabolism, which causes a transient drop in the deoxyhaemoglobin:oxyhaemoglobin ratio, and is discussed in detail elsewhere [c–e]. Other physiological factors that also contribute to changes in deoxyhaemoglobin concentration include blood volume, vascular geometry, haematocrit and basal oxygenation levels [f,g]. These important initial

activity of cortical cells contributes little to the metabolic demand of the brain, estimated maximally as 3% of the resting cortical energy consumption [23]. Thus, even if neuronal firing rate doubled, the effect on local metabolism would be small compared with the apparent changes recorded in imaging experiments. By comparison, the major determinant of cortical oxygen and glucose consumption is the re-establishment of ionic concentrations via the $\text{Na}^+ - \text{K}^+$ ATPase after synaptic activity, defined here in its broadest terms [24–26]. In the rat, for example, up to 95% of regional cerebellar blood flow increases might be dependent on postsynaptic activity [11]. Thus, the major energy-demanding cortical process

is synaptic activity, to which one would expect fMRI BOLD signals to be ultimately related. It is even feasible that, in principle, fMRI activations might be observed in areas with minimal recordable single-cell activity. These data emphasize the apparent dominance of synaptic activity, but how does this relate to simultaneous cellular spiking activity itself?

Relevance of the relationship between action potentials and synaptic activity

A neuronal action potential can be defined as occurring when the membrane potential reaches threshold by depolarization, which is, in turn,

factors aside, the haemodynamic response can vary widely across cortical areas and between species. Different aspects of the haemodynamic response might change on different timescales, and might have different neural determinants and different consequences for the BOLD signal.

It is also widely recognized that the BOLD signal occurs not only at the capillary level but also at large draining veins, potentially a few centimetres downstream from the neuronally active regions [f,h]. By implication, such signal changes would be spatially displaced from the activated neural tissue. Thus, the spatial resolution of BOLD-based fMRI is clearly more likely to be limited by the microvascular density, which will always be lower than that of neurones [e] and is hampered by large vessel contributions, known as the 'brain versus vein' debate [i]. Spin-echo fMRI techniques minimize these venous contributions and thus might be useful in resolving fMRI BOLD more precisely to its neural origins, but at the expense of signal to noise [j,k]. At higher field strengths, the capillaries exert a larger effect on image intensity [l,m]. In combination, these two might therefore become increasingly helpful.

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determined by the integration of incoming postsynaptic potentials, whether excitatory or inhibitory (EPSPs or IPSPs, respectively). Even if EPSPs summed linearly, then at least 75 afferent neurones would be needed to fire simultaneously for the 10 mV change in depolarization that is needed for a single postsynaptic neurone to reach firing threshold [27]. Simultaneous IPSPs would also decrease the probability of cell firing (Box 2). Spiking activity thereafter adapts quickly, whereas synaptic LFP activity might be maintained during stimulus presentation [6], suggesting that the relationship between cortical synaptic activity and cell spiking activity is difficult to standardize and quantify, and

that it could vary over time and between cortical areas. As fMRI BOLD inherently measures relative changes (from an active versus resting state), rather than absolute measurements, the relative contributions of these various activities are currently unclear.

Logically, however, one would expect an approximately linear relationship between action potential firing rate and the related synaptic metabolic activity [28] to prevent information loss between axon and dendrite of the same neurone. Synaptic activity should therefore correlate with the firing rates of the presynaptic neurone, but not necessarily the postsynaptic neurone. If this is true – and the relationship between synaptic activity and BOLD signal is linear – then we would expect the BOLD signal to be approximately linearly correlated to spiking activity. Ultimately, this variable and circular relationship between synaptic activity and action potentials might also be important in the spatial resolution of fMRI (Box 1) because sub-threshold activity often extends further in space than active firing. This might serve to explain, or confound, the intrinsic spatial smoothing within the fMRI signal, which has been described as how 'the brain waters the whole garden for the sake of a single flower-bed' [29]. So what potential effect does all this have upon the activated territories?

fMRI BOLD detects population activity

The best current resolution of fMRI BOLD is at the level of one cortical column, which contains ~10⁵ neurones [30]. Most fMRI scanning paradigms will compromise shorter acquisition times with a lower spatial resolution of ~8–50 mm³ (1–3mm³ dimensions), containing at least 10⁶ neurones. Even within an individual voxel, fMRI BOLD will therefore measure the haemodynamic result of a population of cells. As a result of this scale, conventional BOLD imaging (and similarly, scalp electrophysiology) might focus on the many neurones firing at initially low rates, whose individual firing rates vary little with activation, but cause the largest changes in evoked population activation by summation [31]. It is currently unclear whether fMRI can differentiate between these small activity changes in large cellular populations, and large changes in small populations, or how this balance varies with task or cortical site. Neuronal action potentials are best recorded by conventional single or multicellular recordings, but these recordings will favour those relatively few neurones that show the greatest changes in firing rate. Taking things to the next stage, a further problem is how to relate the spiking or synaptic activity of these selectively activated neurones to the ensemble synaptic activity of a neuronal population, in particular in the context of combined excitatory and inhibitory synaptic connections [32] (Box 2). The relationship of the haemodynamic response to these

Box 2. Does inhibitory activity contribute to the BOLD signal?

There is currently no evidence that the recycling and repackaging of neurotransmitters and the restoration of ionic concentrations after synaptic transmission differs between excitatory and inhibitory synapses. Because cortical glucose use reflects presynaptic rather than postsynaptic activity [a], the release of inhibitory or excitatory transmitters must both be energy-consuming processes; for example, inhibitory activity results in an increase in glucose metabolism in the hippocampus [b].

Inhibitory synaptic activity might modulate the functional magnetic resonance imaging (fMRI) blood oxygenation level-dependent (BOLD) response by changing metabolic demand, or might reduce the BOLD response by reducing net spiking activity. Increases in inhibitory activity demand greater excitatory input in order to achieve supra-threshold activity, in other words, more synaptic activity is required for each action potential fired. The energy required to recycle inhibitory neurotransmitters might also feasibly cancel out the reduction in activity of the inhibited postsynaptic cell. However, it is unlikely that a substantial volume of cortex could sustain a high level of inhibitory activity, producing a simultaneously low firing rate and high metabolic rate [c]. The majority of the cortex (70–80%) consists of pyramidal cells, which are excitatory regular-spiking neurones, with the remaining non-pyramidal cells being mostly inhibitory [d,e] (approximately one inhibitory synapse for every five excitatory synapses [f]). It has been argued that because of their reduced number, strategically superior location and increased efficiency [g], there could be lower metabolic demand during inhibition compared with excitation. Accordingly, one group has proposed that inhibition, unlike excitation, does not elicit a measurable change in the BOLD signal [h]. However, other groups have observed fMRI BOLD signals even under conditions that appear to involve inhibitory interactions [i]. Both empirical and theoretical studies suggest that excitatory and inhibitory neurones are likely to be balanced so that it is unlikely that one would observe an increase in one without an increase in the other [j], albeit not in temporal unison [k], because otherwise no cell would reach threshold. A recent model suggests that inhibition might increase the BOLD response if there is a low prevailing level of excitation, but that it can reduce it when excitation is generally high [l].

The cerebellum provides an interesting opportunity to study the neural origin of fMRI BOLD, because its principal cortical cells, the Purkinje cells, are inhibitory. However, in rats, no simple correlation has been found between blood flow and Purkinje cell firing [m,n]. Cerebellar blood flow (CeBF) responses are unrelated to postsynaptic GABA (inhibitory) activity; but are attenuated when synaptic potentials are abolished by blocking glutamate-mediated (excitatory) responses. This suggests that excitatory activity alone provides the basis for the vascular responses observed, although this is confounded by the simultaneous activation of inhibitory interneuronal firing. The cerebellum is a

multi-layered structure containing many types of cell, and there are also several other possibilities that could cause an increase in blood flow (S-J. Blakemore, PhD thesis, University College London, 2000). However, these results seem to generalize to somatosensory cortex [o]. Further investigation into the cellular basis of haemodynamic change in the cerebellum might address the contribution of inhibitory firing to the BOLD response. Firing rates in different areas of cortex with different levels of excitatory and inhibitory activity might therefore create distinct relationships between neural activity and the BOLD response. Pharmacological intervention during fMRI [p] using known neural (but not directly vascular) drugs, for example, GABA-mediated inhibitory blockers, might reveal some of the true contributions of inhibitory and excitatory activity to the BOLD response in cortex-specific areas.

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differences in firing patterns remains to be determined.

Another factor in this area of the debate is whether fMRI BOLD can take into account changes in overall population or background activity. It is

important that fMRI BOLD has the potential to include many other functionally significant neuronal events such as bursts, oscillations and changes in neuronal synchrony. Global scaling techniques can minimize the contributions of steady population

firing in order to select out the seemingly more important local changes, but this might discard potentially relevant information, because background modulations might be induced by important cognitive states such as attention. Furthermore, arousal and sensory processing could lead to a qualitative reorganization of neuronal activity (e.g. desynchronization) caused by synaptic changes – feasibly without significant changes in net regional firing activity [23,33–35]. Assuming that fMRI signals are representative of global synaptic activity levels, they might indeed be sensitive to changes in synchronization, provided that the normal relationship between firing rates and synchronization is intact [35]. This has a secondary bearing upon the non-absolute nature of all fMRI BOLD signals, and the varying relationship between action potentials and synaptic energy demand. It is arguable that background modulations induced by

attention could result in reduced or undetectable relative changes between active and 'resting' state, masking true underlying neuronal changes, although attentional modulation of fMRI BOLD signals have been observed [35,36]. It is therefore not necessarily predictable how fMRI might express stimulus-correlated activation changes on top of simultaneous background modulations.

To conclude, fMRI BOLD signals are clearly dependent on the variability and inter-relationships of several factors. The debate currently favours a relatively direct correlation between fMRI signals and population synaptic activity (including inhibitory and excitatory activity) with a secondary and potentially more variable correlation with cellular action potentials. Further investigation of this relationship between electrical activity and fMRI BOLD imaging will be very exciting, with paradigms targeted specifically at these factors *de novo*.

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