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Review

About being BOLD

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Abstract

The last decade has seen an unprecedented increase in the use of functional magnetic resonance imaging (fMRI) to understand the neural basis of cognition and behavior. Being non-invasive and relatively easy to use, most studies relied on changes in the blood oxygenation level dependent (BOLD) contrast as an indirect marker of variations in brain activity. However, the fact that BOLD fMRI is dependent on the blood flow response that follows neural activity and does not measure neural activity per se is seen as an inherent cause for concern while interpreting data from these studies. In order to characterize the BOLD signal correctly, it is imperative that we have a better understanding of neural events that lead to the BOLD response. A review of recent studies that addressed several aspects of BOLD fMRI including events at the level of the synapse, the nature of the neurovascular coupling, and some parameters of the BOLD signal is provided. This is intended to serve as background information for the interpretation of fMRI data in normal subjects and in patients with compromised neurovascular coupling. One of the aims is also to encourage researchers to interpret the results of functional imaging studies in light of the dynamic interactions between different brain regions, something that often is neglected.
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Contents

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1. Introduction

Identifying active brain areas while executing different tasks—motor, sensory (somatic, visual, auditory), and cognitive (memory, attention, and other intellectual abilities), has been an important domain of neuroscience research since the introduction of functional brain imaging techniques such as Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI). The most common method of fMRI is blood oxygenation level dependent (BOLD) contrast imaging, in which hemoglobin is used as an endogenous contrast agent, relying on the difference in magnetic properties of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic) [103]. Functional MRI BOLD thus measures a correlate of neural activity, the hemodynamic response. The hemodynamic response, as the name implies is dynamic and depends on cerebral oxygenation, blood flow, and blood volume (for reviews see [2,5,19,58,60,81,82,95,128]). An important issue regarding interpretation of functional MRI signals (especially when using block designs) is that the functional brain maps that we see are static representations of this dynamic activity averaged over a long period of time. So, the accurate interpretation of the BOLD signal depends on how effectively one characterizes the nature of the underlying neural activity that gives rise to the hemodynamic response and how these two (neural activity and blood flow response) are coupled. This in turn warrants a better understanding of what happens in the brain at the level of neurons and their immediate microvasculature and also of other factors that modulate the BOLD signal. Heeger and Ress [58] grouped factors other than neurovascular coupling essentially into three

1. fMRI acquisition technique: Since BOLD fMRI provides a complex signal, which depends on blood flow, blood volume, and oxygenation, the signal is highly dependent on the details of local vasculature—i.e., the relation of draining veins, venules, and capillaries to the neural structure under consideration. Variations of the acquisition technique can be used to emphasize or suppress signals from these sources.
2. Behavioral and stimulation protocols and data analysis techniques: These determine the spatial and temporal resolution of the signal. For example, the traveling wave visual stimulation protocol [37], sparse temporal sampling [50,53].
3. How the neuronal activity is measured and quantified: The signal depends on whether one measures the activity of a whole population of neurons, or of a sub-population, the local field potential or the current source density.

Given the dynamic interconnectivity of neurons in the human brain and the complex nature of the fMRI BOLD response, it is easy to see why the interpretation of this signal is not straightforward. Previous work on BOLD fMRI focused mainly on one aspect of the signal—events at the synapse and neuroenergetics, neurovascular coupling, relation of the signal to neural spikes, or the basis of some part of the BOLD signal such as the initial dip or the temporal and spatial attributes. The aim of this article is to integrate results from most of these domains and give the reader a broader perspective on the origin and interpretation of the BOLD signal. First, a review of the neurometabolic events at the level of the synapses is given, followed by how they relate to neurovascular coupling. Later, some parameters of the BOLD signal are described along with their clinical significance. The paper concludes with a note of caution on the interpretation of BOLD signals and establishing structure–function relationships in the brain based on BOLD fMRI.

2. At the site of neural activity

Neuronal action potentials result in (1) the release of neurotransmitter into the synaptic cleft—glutamate being the most common excitatory neurotransmitter in the cerebral cortex and (2) changes in ionic gradients. Continuous neural activity and maintenance of homeostasis are dependent on active processes requiring energy such as restoration of ionic gradients and repacking of neurotransmitter molecules. Cerebral blood flow not only delivers glucose and O_2, but also carries away CO_2 and heat. Although Roy and Sherrington [114] postulated that vascular supply in the brain changes with local variations in functional activity, the demonstration of neurometabolic coupling was first possible by the development of the 2-deoxyglucose autoradiographic technique by Sokoloff and colleagues [125] and its later extension 2-fluorodeoxyglucose PET [123]. It is important to understand the mechanisms that bring about this neurometabolic coupling at the molecular level (for an excellent review see [85]).

2.1. Neurovascular coupling and metabolic events

Under normal resting conditions, the brain's energy demands are met (ATP production) almost exclusively by glucose oxidation. More than 90% of resting state glucose consumption is oxidative. Since the energy yield of glucose oxidation is much more than that of glycolysis (at least 15 times more ATP), more than 99% of the ATP production in the resting stage is by glucose oxidation [41], oxidizing glucose to water and CO_2. Fox et al. [41] reported that the mean whole brain cerebral metabolic rate for oxygen ($CMRO_2$) and that for glucose (CMRGlu) is in a 4.1:1 molar ratio during the resting state. This increased cerebral metabolic rate for O_2 verifies the finding of greater glucose oxidation and hence oxidative mechanisms for ATP production during rest. Functional activation increases cerebral metabolic rate for glucose and cerebral blood flow by about 50%. However, cerebral metabolic rate for O_2

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