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Key relationships between non-invasive functional neuroimaging and the underlying neuronal activity

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Abstract

Functional neuroimaging using MRI relies on measurements of blood oxygenation level dependent (BOLD) signals from which inferences are made about the underlying neuronal activity. This is possible because neuronal activity elicits increases in blood flow via neurovascular coupling, which gives rise to the BOLD signal. Hence, an accurate interpretation of what BOLD signals mean in terms of neural activity depends on a full understanding of the mechanisms that underlie the measured signal, including neurovascular and neurometabolic coupling, contribution of different cells types to local signaling, and regional differences in these mechanisms. Furthermore, the contributions of systemic functions to blood flow may vary with ageing, disease and arousal states, in both neuronal and vascular function. In addition, recent developments in non-invasive imaging technology, such as high field fMRI, and comparative inter-species analysis allow connections between non-invasive data and mechanistic knowledge gained from invasive cellular-level studies. Considered together, these factors have immense potential to improve BOLD signal interpretation and bring us closer to the ultimate purpose of decoding human cognition. This themed issue covers a range of recent advances in these topics, providing a multidisciplinary scientific and technical framework for future work in the neurovascular and cognitive sciences.

Introduction

The human brain has been estimated to have around 100 billion neurons and a roughly equal number of glial cells. The neurons are linked by an estimated 100 trillion connections. These numbers are based on observations that are difficult to make, but to give a sense of scale, it is sometimes pointed out as a comparison of magnitude that the Milky Way has between 200 to 400 billion stars. The complexity of the brain has been studied using multiple approaches. Over the last four decades, substantial progress has been made by use of noninvasive imaging techniques to study brain function. Although initial studies were limited mainly to topographical analysis, neuroimaging is increasingly being used to investigate cognitive processing in both normal and abnormal neural systems. Several noninvasive techniques have been applied for this purpose, but the most developed and widely used current approach is that of functional magnetic resonance imaging (fMRI).

The fMRI technique takes advantage of activity-coupled blood flow changes from which blood oxygen level dependent (BOLD) signals can be obtained to infer neural activity. This inference is justified because neuronal activity drives increases in local blood flow via processes collectively termed neurovascular coupling. However, the BOLD signal is not straightforward; rather it is an integration of the oxidative metabolism in the tissue, which utilizes oxygen, and the increase in local blood flow, which supplies the oxygen. If there were matched fractional changes in the cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow (CBF), such that the fraction of oxygen extracted from the blood did not change, then the BOLD signal would not be obviously linked to neural activity. However, activated brain areas usually display CBF increases that are substantially greater than $CMRO_2$ changes. Therefore, the oxygen extraction fraction is minimized and local deoxyhemoglobin is decreased. Since deoxyhemoglobin is paramagnetic and disrupts magnetic resonance, a decrease in deoxyhemoglobin produces a local increase in magnetic resonance signals during neural activation, thus yielding BOLD signals. In most physiologically normal conditions, this signal faithfully reflects neural activity. Therefore, BOLD fMRI is a very useful non-invasive method to study brain function *in vivo*, especially in the context of human cognition. However, because BOLD responses do not directly reflect neural activity, it is critically important to have a clear understanding of how the measurable signals, comprising the metabolic demand and oxygen supply, are related to the underlying computations to provide an accurate interpretation of neural activity.

Recent advances aimed at improving BOLD signal interpretation

The manuscripts presented in this themed issue highlight recent advances and relate current research in the following areas:

- A thermodynamic framework proposing that the mismatch between oxygen usage and supply exists in order to maintain a sufficient O_2:CO_2 ratio to sustain mitochondrial respiration (Buxton)
- Variation in BOLD signals in different brain regions, based on current models of neural networks and regional vascular differences (Ekstrom)
- How different cell types in the brain, including inhibitory neurons, glial, and vascular cells (Howarth et al.), and non-neural systemic physiology (Das et al.) affect BOLD signals.
- Hardware and software developments that have resulted in high spatial resolution MRI (Fukuda et al. and Weldon and Olman)
- Effects of aging on neurovascular coupling (Tsvetanov et al.)
- Cross-species investigations to relate discoveries from invasive (animal models) and non-invasive (human) techniques (Barron et al.)
- The necessity of studying brain function at all levels, from microscale molecular to macroscale neuroimaging, in order to derive optimal models of brain activity (Love)

The thermodynamics of the brain

The increase in CBF that follows neural activity typically results in a larger oxygen supply than appears necessary to support metabolism, a phenomenon that allows the BOLD signal to occur. The reason for this large CBF increase, and thus the need for neurovascular coupling, continues to be a matter of debate. In the first paper in this issue, Buxton suggests this apparent mismatch between oxidative metabolism and CBF changes could be explained using a thermodynamic framework in which the preservation of entropy change of oxidative metabolism is critical [1]. Buxton proposes that rather than simply increasing the delivery of energy substrates, the key outcome of neurovascular coupling is to maintain the O_2:CO_2 ratio, which allows mitochondrial oxidative metabolism to occur unperturbed. The quantitative predictions of this thermodynamic framework are consistent with experimental data from several different paradigms, including changes in CBF driven by neural activity and those driven by non-neural factors such as hypercapnia and hypoxia. By providing a physiologically relevant explanation for the mismatches between metabolism and oxygen supply, this framework may help resolve some

of the existing debates regarding the necessity of neurovascular coupling for healthy brain function.

Regional variability

Analysis of BOLD signals generally assumes a constant relationship between BOLD signals and underlying neural activity across the brain. However, there may be region-specific differences in how neural activity is translated into BOLD responses. For example, research in neocortical regions supports the idea that BOLD signals reflect changes in the envelope of the gamma-band frequency of the local field potential, presumably reflecting alterations in spiking of excitatory and inhibitory neurons. However, investigations in deeper brain regions, such as the hippocampus, do not find such a relationship. The paper by Ekstrom in this issue evaluates such regional differences in the processes underlying BOLD, focusing on four significant factors: correlations between neural activity and BOLD signals, differences in regional vasculature, models of neural coding, and signal quality [2]. In addition, the potential of multivariate pattern analysis to reveal the neural information reflected in the BOLD signal is discussed.

Contribution of neuronal and non-neuronal cells to neurovascular coupling

BOLD signals have traditionally been interpreted as a reflection of excitatory neuronal activity, but much work in recent years has highlighted the dominant role of inhibitory neurons and astrocytes in regulating neurovascular coupling. It also appears that seemingly independent, parallel signaling processes control neurovascular coupling at different levels of the vascular tree, with the contribution of astrocytes being most prominent at the capillary level. The integration of signals received by these interconnected components of the vascular tree (capillaries vs arterioles), as well as the propagation of signals between vascular cells, orchestrate activity-dependent increases in CBF. The contribution of each of these cell types (neurons, glia, vascular cells) to neurovascular coupling pathways and their matching metabolic characteristics are discussed in depth by Howarth et al. [3].

Advantages and pitfalls of high field fMRI

Previous studies utilizing fMRI signals were limited to blood flow changes occurring in large veins, because of the resolution and specificity of the technology available. However, since neurovascular coupling can occur at the microvascular capillary level, improvements made in non-invasive imaging techniques should provide better spatial resolution and yield more informative data regarding the underlying neural activity. Recent advances in high field fMRI have

provided these increases in spatial resolution and permitted laminar and columnar analyses of brain function. Despite these advances, there are many open questions and problems. One outstanding question pertains to the accuracy of these techniques in determining actual locations of neuronal activity. Fukuda et al. use hemoglobin based optical imaging, cerebral blood flow, and cerebral blood volume alongside high field fMRI to examine functional columns and layers in animals [4] to address this issue. They further assess the degree of spatial specificity of fMRI to sites of neuronal activity and use this information to synthesize insights into neurovascular coupling. In a complementary paper, Weldon and Olman highlight technical problems related to high field fMRI data acquisition and analysis approaches [5]. For example, the improved resolution allowed by high field fMRI comes at the cost of reduced spatial coverage. Weldon and Olman discuss techniques that can increase effective voxel size by substantial amounts and enable avoidance of incorrect interpretations. They stress the importance of documenting and sharing challenges in order to accelerate progress in the field of ultra-high field fMRI [5].

Hemodynamic changes due to brain-extrinsic signals

Systemic and vascular physiology that are not directly related to neural activity can also significantly alter CBF. These components include regulatory processes that maintain overall bodily function, such as heart rate and breathing, as well as fluctuations that are intrinsic to vascular systems. The effect of such components on the hemodynamic signals may be as large, or even larger than, the portion due to neural activity. An evaluation of these processes and how they alter CBF unrelated to neural activity, which must be considered for the analysis of BOLD signals, is presented by Das et al. [6]. This is especially relevant in the context of resting state fMRI, which is used to infer brain activity during passive ‘resting’ states under the assumption that the observed variations in blood oxygenation and flow are directly related to spontaneous neural activity in the brain. Das et al. also propose tools and methods to correct for such non-neural effects on CBF and BOLD signals.

Effect of ageing on neural and vascular compartments

The hemodynamic contribution of signals extrinsic to the brain presents another important confounding factor in BOLD signal interpretation when investigating disease and ageing-related processes. Systemic physiology, intrinsic vascular function, and neural parameters can be differentially affected by ageing and, hence, the correlation between neural activity and the BOLD signal can change. In the field of neurocognitive ageing, in which fMRI is often interpreted as reflecting neuronal metabolism, care must be taken to address the potential confounds of vascular

ageing and age-related differences in vascular function. Tsvetanov et al. highlight neurovascular ageing as an important consideration that must be assessed and present current approaches to dissociate neural and vascular components of BOLD-based fMRI [7]. They further discuss evidence suggesting that neurovascular interactions influence neuronal function, supporting the idea that a two-way signaling between the nervous and vascular systems exists.

Translating invasive, microscopic discoveries to non-invasive macroscopic data

Despite the enormous amounts of data generated by fMRI studies, the application of these data toward understanding biological mechanisms of cognition and behavior are still limited. Recent advances in invasive imaging techniques have allowed scientists to glean important new ideas regarding the mechanisms of cognition, at the microscopic level, in animal models. However, these methods are not available for studies on humans, where methodology must almost always be non-invasive and typically results in macroscopic levels of detail. Therefore, multidisciplinary, cross-species investigations are increasingly being employed to bridge this gap. Barron et al. discuss some of these approaches for cross-species investigations with the goal of focusing different measurements of neural activity into a common space. Such investigations will be a necessary step to translate cellular and molecular mechanisms to higher-level processes [8].

The need for cross-level examination

Lastly, a philosophical discussion of neuroscience by Love emphasizes the value of pursuing research at different levels, and bridging the gap between them, to reach the ultimate truth of biological reality [9]. Cognitive scientists have relied heavily on model-based fMRI to develop theories of how the brain works, and often the cellular and molecular processes underlying these phenomena are ignored as not being important enough for the purposes of the deductions. Yet, a model is only as good as its assumptions, which are defined, to some extent, by what we already know to put into the model. Turning a blind eye to the cellular bases of neural function prevents us from constraining potential models by the processing that is possible with real biological hardware. In the other direction, cellular neuroscientists tend to consider higher-level cognitive theories as just ‘models’: if they are not rooted in biochemical and biophysical bases, they must not be biologically plausible, yet these higher level models are necessary to help us understand complex cognitive processes. However, given that we are all studying the same system–the brain–we must start considering the value of our chosen level of analysis (e.g., genetic, cellular, systems, cognitive etc.) in relation to those above and below it. Indeed, each

level can inform predictions and update models in adjacent levels such that we may, together, arrive at a model of how the brain functions that is closer to the truth.

In conclusion, this issue discusses the cellular processes underlying the BOLD response, how these processes vary across brain regions and with age, and proposes a biochemical explanation driving the BOLD signal based on thermodynamics. The relationships being elucidated at the cellular level and the recent technical advances that boost the resolution of fMRI signals can together be used to guide interpretation of BOLD signals and derive more accurate, biologically relevant models of cognition.

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