From BOLD to Neurons

Richard B. Buxton
Center for Functional MRI
Department of Radiology
University of California San Diego
rbuxton@ucsd.edu

Background

Functional magnetic resonance imaging (fMRI) based on the detection of blood oxygenation level dependent (BOLD) signal changes has had an enormous influence on human neuroscience studies, providing a sensitive and noninvasive tool for detecting a change in neural activity in response to a stimulus or during spontaneous neural fluctuations. With neural activation cerebral blood flow (CBF) increases much more than the cerebral metabolic rate of oxygen ($CMRO_2$). This increases the local venous blood oxygenation, reducing the level of deoxyhemoglobin (dHb). Because the presence of dHb reduces the MR signal, this reduction of dHb increases the MR signal—the BOLD effect. While it is widely understood that the BOLD response is not a direct reflection of neural activity, there is nevertheless a tendency to think of it as a relatively simple two-step process: increased neural activity leads to a CBF change (neurovascular coupling), which then produces a BOLD signal change. However, this view is too simplistic, because it leaves out the important role played by $CMRO_2$: when neural activity increases, the CBF increase tends to wash out dHb, while the $CMRO_2$ increase tends to create more dHb. For this reason, the BOLD signal depends strongly on the coupling ratio n, the ratio of the fractional changes in CBF and $CMRO_2$. Interpreting the BOLD response in terms of the underlying neural activity is not just a question of understanding neurovascular coupling; we must also understand neuro-metabolic coupling.

The challenge for BOLD-fMRI

These physiological considerations emphasize the difficulty of interpreting the BOLD response in a quantitative way. Most fMRI investigators would support the view that if a local BOLD signal change is detected in response to a stimulus, it suggests that there is some underlying change in neural activity, the basis of using the BOLD response as a mapping signal. However, if we focus on questions comparing BOLD responses under different conditions, or in different populations, the interpretation becomes more problematic: Does a difference of the underlying neural activity in response to a stimulus in two populations necessarily lead to a difference of the BOLD signal change? Or, if the BOLD response is different comparing two conditions, such as pre- and post-medication, does the magnitude of the difference reflect the magnitude of the underlying physiological differences? These are more difficult questions to answer, and reflect a key

shift from simply asking *where* activation occurs to asking *how much* activation occurs. This as the fundamental challenge for fMRI: how can we interpret the magnitude of the BOLD signal in a quantitative way in terms of the underlying physiological activity? This talk will touch on three current questions related to the quantitative interpretation of the BOLD response.

1. Can the magnitude of the BOLD response be interpreted as a quantitative reflection of the underlying physiological changes?

The complexity of the BOLD signal is that it is driven by the change in CBF, but also strongly modulated by the CBF/$CMRO_2$ coupling ratio *n* and the local physiological baseline state of the brain. The essential aspect of the baseline state is the amount of deoxyhemoglobin present, because this defines the ceiling effect on the BOLD signal: there is a maximum possible signal increase corresponding to complete removal of dHb. Due to this complexity, the magnitude of the BOLD response is an unreliable measure of the magnitude of the underlying physiological changes, particularly in comparing healthy and disease populations where there may be significant differences in the baseline state due to the disease process itself or to medications. However, quantitative fMRI methods, based on measuring CBF with arterial spin labeling (ASL) methods in conjunction with BOLD imaging, can provide a much clearer picture of the underlying physiology. The results of recent modeling studies (*1, 2*) and experimental studies will be used to illustrate these basic ideas, including experiments in human visual cortex investigating changes in the physiological responses with increasing stimulus contrast (*3*), attention (*4*), adaptation (*5*), and after ingesting caffeine (*6, 7*).

2. Do variations in the coupling of blood flow and oxygen metabolism reflect differences in the underlying neural activity?

Current thinking is that the acute CBF response to a stimulus is not driven directly by the change in energy metabolism, but rather by signals related to the neural activity itself (*8*). This essentially feed-forward mechanism provides a way to avoid a potentially dangerous drop in tissue O_2 concentration by increasing CBF in anticipation of a greater need for oxygen (*9*). The need for a relatively fast CBF response is that there is very little O_2 available in tissue to serve as a buffer (tissue O_2 in gray matter would be depleted in about 1 second for normal $CMRO_2$ (*9*)), and a quick increase in $CMRO_2$ could lead to a sharp drop in available O_2 in the tissue unless CBF also quickly rises. This feed-forward nature of neurovascular coupling means that we must think of CBF and $CMRO_2$ as being driven in parallel by neural activity, and potentially by different aspects of that activity. This raises the possibility that the CBF/$CMRO_2$ coupling ratio could vary depending on the detailed nature of the evoked neural activity.

Across a number of our studies an empirical pattern is emerging in the way CBF and $CMRO_2$ changes are coupled to neural activation (*10*): if the stimulus is modulated to create a stronger response (e.g., increasing stimulus contrast), CBF is modulated more than $CMRO_2$; on the other hand, if the brain state is altered such that the response to the

same stimulus is increased (e.g., modulating attention, adaptation or excitability), $CMRO_2$ is modulated more than CBF. Because CBF and $CMRO_2$ changes conflict in producing BOLD signal changes, this finding has an important implication for conventional BOLD-fMRI studies: the BOLD response exaggerates the effects of stimulus variation but is only weakly sensitive to modulations of the brain state that alter the response to a standard stimulus. A speculative hypothesis will be discussed that the variability of the coupling ratio of the CBF and $CMRO_2$ responses may reflect different proportions of inhibitory and excitatory evoked activity, potentially providing a new window on neural activity in the human brain (*10*).

3. Does the large change in blood flow with neural activation have a thermodynamic origin in terms of preserving tissue pO_2 and the energy state of the tissue?

Although the precise ratio of CBF and $CMRO_2$ changes varies, the blood flow change is always larger than the oxygen metabolism change. That is, the oxygen extraction fraction (OEF) *decreases* when $CMRO_2$ increases, and the capillary pO_2 is raised. The degree of mismatch is about the right amount to increase the O_2 gradient from capillary to mitochondria to support the increased $CMRO_2$ without letting tissue pO_2 fall. That is, we can think of the large change in CBF as a mechanism for maintaining tissue pO_2 despite variations in $CMRO_2$ (*9, 11*).

This raises the question of why the brain needs to preserve tissue pO_2 at a very high level (~25 mm Hg). This is puzzling because it has long been thought that the pO_2 level does not limit $CMRO_2$ until it is much lower (<1 mm Hg). Recent and earlier work by Wilson and colleagues may provide an explanation (*12, 13*). While the kinetics of $CMRO_2$ can be maintained down to very low pO_2 values, there is a cost: the energy state of the tissue (the free energy available from ATP: the phosphorylation potential [ATP]/[ADP][Pi]) begins to degrade at much higher values of pO_2 (~12 mm Hg). A thermodynamic explanation of this could be that the free energy available from oxidative metabolism must be larger than the free energy required for the uphill reaction driving ADP back to ATP. As pO_2 lowers, the free energy available from oxidative metabolism is reduced, but the linked reactions can still proceed if there is a corresponding reduction of the free energy required for converting ADP back to ATP—a reduction of the energy state of the tissue (reduced phosphorylation potential) (*9*). By this idea, preserving tissue pO_2 is the fundamental role played by CBF, in order to preserve the tissue energy state. This requires the counterintuitive phenomenon of a large CBF change to support a smaller $CMRO_2$ change, leading to the BOLD effect.

If this thermodynamic hypothesis is true, the implications for pathological conditions (such as stroke) would be that the fundamentally important physiological parameter is tissue pO_2, rather than CBF alone, because mechanisms to reduce $CMRO_2$ (e.g., inhibition of neural activity) could potentially preserve tissue pO_2 as CBF is reduced.

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