Introduction to fMRI: The Physiological Basis of the fMRI Signal

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Highlights

BOLD signal arises from changes in deoxyhemoglobin (dHb) concentrations

dHb changes due to changes in oxidative metabolism, blood flow and blood volume

BOLD signal related to local field potentials

BOLD is an ambiguous signal and comparisons between groups should be interpreted with caution

Target audience

Students and researchers who use or wish to start using the BOLD fMRI signal.

Purpose

Functional MRI (fMRI) is based on the Blood Oxygen Level Dependent (BOLD) signal. This signal is not a direct measure of neuronal activity, but rather a surrogate marker that captures a mixture of oxidative metabolism, blood flow and blood volume. This course will give the users of BOLD a better understanding of the origin of this signal, to refine interpretations and better design experiments.

BOLD fMRI

BOLD signal arises from the fact that oxygenated and deoxygenated hemoglobin have different magnetic properties. While oxyhemoglobin is diamagnetic, deoxyhemoglobin is paramagnetic. The paramagnetic nature of dHb means that blood that is not fully oxygenated causes an attenuation of the T2* signal from increased dephasing of nearby water spins. Since arterial blood is almost fully oxygenated in healthy humans, this means that venous blood is darker than arterial blood and that tissue containing parenchymal deoxyhemoglobin also shows a signal attenuation (1).

During performance of a task, active brain regions consume oxygen to function, so that local brain activity is associated with an increase in local dHb. It is debatable whether the local increase in dHb is actually detectable using MRI scanners, especially at 1.5 or 3 Tesla (2). However, concomitant with this increased dHb production comes a local vasodilation of blood vessels, which in turn causes an increase in local blood flow. This increase in blood flow is larger than the increase in dHb that it accompanies. This is thought to reflect the need for the O_2 gradient from arterial blood to metabolizing tissue to be steep for effective diffusion of blood O_2 into active tissue more distal to vessels (3-5). One of the corollary of this larger fractional blood flow change is that for a given

increase in dHb concentration through local metabolism, there is a corresponding larger increase in blood flow to the same area. Because the inflowing blood is fully oxygenated, this causes an increase in BOLD signal from a local reduction in the dHb concentration. This vascular response is called the hemodynamic response and functional MRI techniques measure it to make inferences about the underlying neuronal activity that triggers it.

Underlying neuronal activity

Functional imaging using hemodynamic methods such as BOLD are based on the assumption that the signal changes observed are strongly correlated with underlying neuronal activity, despite being vascular in nature. Convincing evidence that this is the case comes from simultaneous electrophysiological and fMRI recordings in monkeys (6, 7). In these studies, electrodes are implanted in monkey visual cortex and simultaneous recordings during spontaneous or visual task-elicited activity of neuronal currents and fMRI signal.

Early studies of this type have established that while BOLD signal amplitude is correlated with all aspects of neuronal firing, it is most closely linked with local field potentials (LFPs) than to other electrical activity such as spikes from action potential firing (6). LFPs are thought to reflect a variety of neural processes including synaptic potentials, somato-dendritic spikes and voltage-gated membrane oscillations (8).

Sources of dHb concentration changes

The main energy expenditure of neurons is to maintain the potential across it's membrane to be ready to fire and relay information when the need arises. To do so, the brain uses energy in the form of adenosine tri-phosphate (ATP). This ATP is derived from the metabolism of glucose. Two form of glucose metabolism exist: anaerobic, which does not use oxygen, and aerobic, which uses oxygen in the mitochondrial electron transport chain. Aerobic glycolysis is highly efficient, as it can lead to the formation of as many as 38 ATP molecules from a single glucose molecule. Anaerobic glycolysis on the other hand is faster, but only produces 2 ATP molecules. The first steps of both pathways are the same, but in aerobic metabolism, pyruvate (which is created by the common pathway) goes to the mitochondria to generate more ATP molecules by going through the Krebs cycle and oxidative phosphorylation. Because aerobic glycolysis is much more efficient at energy production and because the brain is known to be an avid user of oxygen, it is thought that oxidative metabolism is the main form of metabolism used in the brain. For example, interruption of the brain's oxygen supply leads to unconsciousness within seconds and irreversible tissue damage within minutes.

Implications for the BOLD signal

During neuronal activity, oxygen consumption increases. This creates an increase in local dHb concentration and therefore a decrease in BOLD signal. However, at the same time, vasodilation occurs to bring fresh blood into the area. Since this influx of blood is larger than the increase in oxygen consumption, this creates a net decrease in dHb concentration and therefore an increase in BOLD signal. This is why the BOLD signal we measure following neuronal activity is an increased signal.

Another confounding factor in the interpretation of the BOLD signal in terms of neuronal activity comes from the fact that this vasodilation to increase blood flow also results in an increased local blood volume (9). This increase in blood volume spans both the arterial and venous component. Increased venous blood volume is associated with an increase in local dHb concentration, which decreases the BOLD signal. Therefore, the BOLD signal we measure is a combination of decreased BOLD signal due to increased oxygen consumption and increased venous blood volume, and a larger fractional change in blood flow which brings fully oxygenated blood to the area and causes an increased BOLD signal.

Because of these opposing contributions, the BOLD signal is not only and indirect measure of neuronal activity, but also a an ambiguous one. When we compare a BOLD signal between different people or different conditions, we assume that the BOLD signal means the same thing in terms of neuronal activity. However, if this balance between the different sub-components is changed, the BOLD signal is no longer linked in the same way to neuronal activity and BOLD signal changes can no longer be compared directly. This is thought to be particularly problematic in studies of aging and diseases, such as cardio- or neurovascular diseases, dementia, etc (10-13). Other techniques such as Arterial Spin Labeling (ASL) to measure flow (14), VAscular Space Occupancy (VASO) to measure blood volume (15) and calibrated fMRI to measure oxidative metabolism (16, 17) can however be used to get around some of these issues.

Bibliography

1. Ogawa S, Lee TM, Kay AR, & Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 87(24): 9868-9872.
2. Kim SG & Ogawa S (2012) Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. *J Cereb Blood Flow Metab*.
3. Buxton RB (2010) Interpreting oxygenation-based neuroimaging signals: the importance and the challenge of understanding brain oxygen metabolism. *Front Neuroenergetics* 2:8.
4. Buxton RB & Frank LR (1997) A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *J Cereb Blood Flow Metab* 17(1):64-72.
5. Devor A*, et al.* (2011) "Overshoot" of O is required to maintain baseline tissue oxygenation at locations distal to blood vessels. *J Neurosci* 31(38):13676-13681.
6. Logothetis NK, Pauls J, Augath M, Trinath T, & Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412(6843): 150-157.
7. Shmuel A*, et al.* (2002) Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. *Neuron* 36(6):1195-1210.
8. Magri C, Schridde U, Murayama Y, Panzeri S, & Logothetis NK (2012) The amplitude and timing of the BOLD signal reflects the relationship between local field potential power at different frequencies. *J Neurosci* 32(4):1395-1407.

9. Chen JJ & Pike GB (2009) BOLD-specific cerebral blood volume and blood flow changes during neuronal activation in humans. *NMR Biomed* 22(10):1054-1062.
10. Gauthier CJ*, et al.* (2012) Age dependence of hemodynamic response characteristics in human functional magnetic resonance imaging. *Neurobiol Aging*.
11. Bokkers RP, van Osch MJ, Klijn CJ, Kappelle LJ, & Hendrikse J (2011) Cerebrovascular reactivity within perfusion territories in patients with an internal carotid artery occlusion. *J Neurol Neurosurg Psychiatry* 82(9):1011-1016.
12. Cantin S*, et al.* (2011) Impaired cerebral vasoreactivity to CO2 in Alzheimer's disease using BOLD fMRI. *Neuroimage* 58(2):579-587.
13. Suri S*, et al.* (2014) Reduced cerebrovascular reactivity in young adults carrying the APOE epsilon4 allele. *Alzheimers Dement*.
14. Detre JA*, et al.* (1994) Tissue specific perfusion imaging using arterial spin labeling. *NMR Biomed* 7(1-2):75-82.
15. Lu H, Golay X, Pekar JJ, & Van Zijl PC (2003) Functional magnetic resonance imaging based on changes in vascular space occupancy. *Magn Reson Med* 50(2): 263-274.
16. Davis TL, et al. (1998) Calibrated functional MRI: mapping the dynamics of oxidative metabolism. *Proc Natl Acad Sci U S A* 95(4):1834-1839.
17. Hoge RD*, et al.* (1999) Investigation of BOLD signal dependence on cerebral blood flow and oxygen consumption: the deoxyhemoglobin dilution model. *Magn Reson Med* 42(5):849-863.