Specialty area: Absolute Beginners Guide to Neuroimaging Methods: fMRI
Speaker : Natalia Petridou D.Sc., email: N.Petridou@umcutrecht.nl

Highlights

- fMRI measures local changes in cerebral hemodynamics associated with neuronal activation
- Blood-Oxygenation-Level-Dependent (BOLD) is the most widely used fMRI contrast
- BOLD fMRI data are typically acquired while subjects perform a (cognitive) task
- BOLD specificity and sensitivity varies with acquisition strategy

Title: fMRI Basics

Target audience: Technical or clinical audience with little or no background in fMRI
Outcome: After this lecture participants will be able to understand the physiological and MR mechanisms that contribute to fMRI signals and design and implement a simple fMRI experiment.

Functional magnetic resonance imaging (fMRI) is the primary means used to measure brain function non-invasively in humans, because of the advantages it offers in terms of high spatiotemporal resolution and localization as compared to other non-invasive modalities (e.g. EEG, MEG). Since its emergence about 20 years ago, it has rapidly evolved into the mainstay of functional neuroimaging for neuroscience and in the clinic, currently yielding more than 7 peer reviewed manuscripts per day.

fMRI measures brain function indirectly via hemodynamic changes that arise from neuronal activation. The physiologic mechanism is based on the fact that neuronal (and glial) activity consumes energy which is mainly met via oxidative metabolism, translating to a local increase in oxygen consumption and cerebral metabolic rate of oxygen ($CMRO_2$). As oxygen is provided by the blood, this triggers a local increase in cerebral blood flow (CBF) and cerebral blood volume (CBV) in the target region (1-4). This hemodynamic response occurs via an intricate and highly organized vascular tree of several groups of vessels arranged according to their diameter (~5-100 μm) and cortical depth they penetrate (5). In simple terms, oxygenated blood flows from arteries at the cortical pial surface toward the capillary bed[1] within gray matter, where oxygen exchange takes place, and deoxygenated blood is then passively drained by intra-cortical veins toward the pial surface (6-7). Notably, the temporal evolution of the hemodynamic response is much slower than that of the underlying neuronal response (sec vs. msec). Changes in CBF occur at the arterial side of the vasculature, CBV changes involve both the arterial and venous side, and changes in blood oxygenation are evident at the venous side that drains from active neuronal sites.

Several fMRI techniques exist that target these different aspects of the hemodynamic response; for example perfusion-based arterial-spin-labeling (ASL; e.g. (8)) can be used to assess CBF, the vascular space occupancy technique (VASO; (9)) can be used to assess CBV, and blood-oxygenation-level-dependent (BOLD; (10)) based techniques can be used to assess changes in blood oxygenation. By far, the most widely used fMRI technique is based on the BOLD contrast because of the higher sensitivity afforded as compared to other fMRI techniques. BOLD is an endogenous contrast that capitalizes on the magnetic properties of deoxygenated hemoglobin (deoxy-Hb) in the blood, specifically in the venous side of the vasculature (capillaries, venules, intracortical veins, pial vessels). Deoxy-Hb is paramagnetic and causes a distortion of the magnetic field inside (intra-vascular) and around (extra-vascular) the vessels which alters the T2 and T2* decay of the MR signal in that region. The mechanism is somewhat counter-intuitive: with increases in neuronal activity there is an oversupply of oxygenated blood.

[1] The capillary bed is the smallest element of the vascular tree (diameters ~5μm per vessel) found within deeper cortical layers; it is the bridge between the arterial and venous side of the cortical vasculature.

Because not all oxygen is absorbed in the tissue this results in a decrease of deoxy-Hb in the venous side (Figure 1). In other words, there is a mismatch between increases in $CMRO_2$ and increases in CBF. This in turn lengthens the T2(*) yielding a local increase in the MR signal intensity that can be detected with either gradient-echo (T2*-weighted) or spin-echo (T2-weighted) techniques. An optimal BOLD functional contrast is obtained for a TE comparable to the T2(*) of gray matter. Ideally, this functional contrast would be specific to extra-vascular signals (i.e. within tissue) at the capillary bed that serves active neuronal sites. However, extra- and intra-vascular signals from the larger veins can have a prominent contribution to the measured BOLD contrast which can degrade the spatial specificity of BOLD fMRI (11); this contribution varies with field strength, and is different for extra- and intra-vascular signals as well as GE and SE based sequences. With increasing field strength, intra-vascular signals are reduced (e.g. 3T vs 7T) as the T2(*) of blood is shorter than that of gray matter, while extra-vascular signals are increased (12,13). Spin-echo based fMRI allows for improved specificity to the capillary bed because the 180^0 refocusing pulse acts to suppress signals from the larger veins; the downside is a severe loss in sensitivity as compared to gradient-echo based techniques thus it's use is generally limited though it can be advantageous at high fields (13,14). In sum, gradient-echo T2*-weighted BOLD is to date the method of choice for most fMRI applications. The degradation in spatial specificity can be on the order of several mm at 1.5T, improving with increasing field strength to about 1mm at 7T.

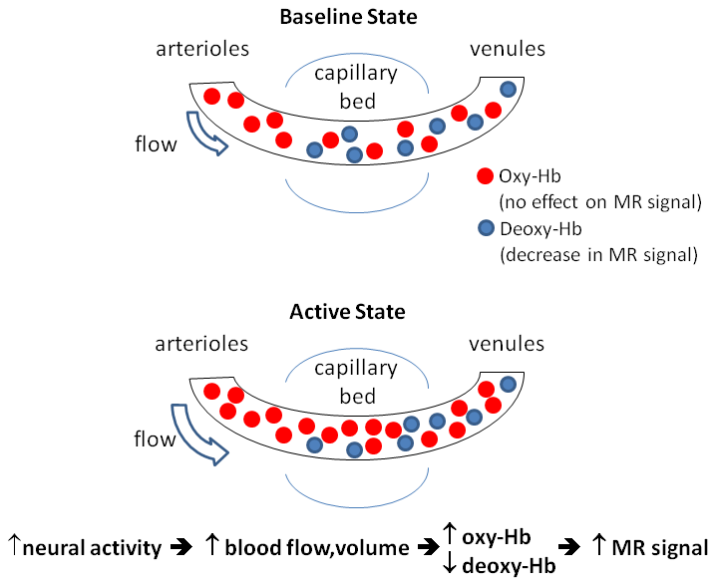

Figure 1. Schematic of the BOLD contrast mechanism. At baseline, oxygenated blood flows from the arterial network to the capillary bed where oxygen is absorbed into the tissue and oxygenated hemoglobin (oxy-Hb; red dots) becomes deoxy-Hb (blue dots). Oxy-Hb is diamagnetic and has no effect on the MR signal while deoxy-Hb is paramagnetic and decreases the signal. Upon increases in neuronal activity, blood flow and volume increase resulting in increased levels of oxy-Hb as compared to deoxy-Hb. With proportionately less paramagnetic material in the venous blood, T2*/T2 increases thus the MR signal increases.

fMRI applications are quite varied. For instance, fMRI is used to associate brain regions or networks with functions (mapping), characterize groups of individuals (e.g. patients from healthy controls), characterize brain function changes over time (e.g. adaptation within an experiment or changes across days/years, or assessment of recovery), or for pre-surgical localization of critical viable tissue to avoid resection. A typical fMRI experiment involves acquiring a time series of multiple gradient-echo volumes[2] with a fast imaging technique, commonly echo-planar-imaging (EPI), while the subject performs a given task imposed by the experimenter. Notably though, neuronal activity induced hemodynamic changes can also occur in the absence of a task imposed by the experimenter; task-independent fMRI (or resting-state) is increasingly applied in recent years to study brain function in health and disease (e.g. 15, 16).

[2] Therefore fMRI data are 4D

Tasks can range from passive viewing of visual stimuli to assess for example the organization of visual cortex (17), to more complex cognitive manipulations such as pattern memorization, for instance to assess working memory function between patients and controls (18). fMRI signals can be observed by alternating task periods with periods of rest in a regular manner (block design) or, more commonly, with a random alternation between task and rest, or between different task conditions (event-related design) (Figure 2). The latter offers advantages in time efficiency and higher sampling of hemodynamic signal changes. Hemodynamic responses however endure for several seconds beyond cessation of neuronal activation, even for very brief stimuli (few msec). Thus the speed of alternation, i.e. the efficacy in differentiating signals between task periods or conditions, depends on the duration of the hemodynamic response. Typical values of inter-stimulus intervals (duration of rest between tasks) for event-related designs range between 4sec to 16sec, randomly distributed during an experiment (Figure 2).

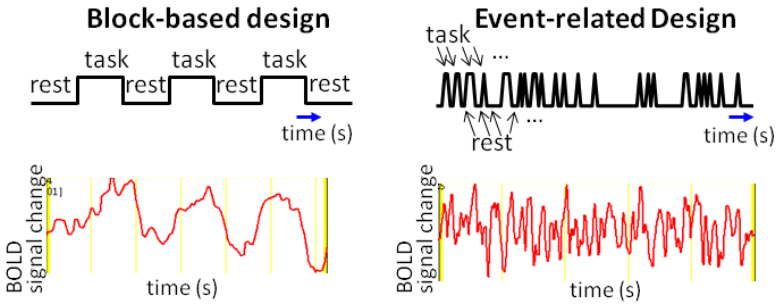

Figure 2. Illustration of Block-based (left) and Event-related (right) task design. Example BOLD time courses per design are shown below, for one task engaging the same cortical region for both designs.

On the acquisition side, several parameters can be manipulated (e.g. spatial resolution, averaging, TE, TR, parallel imaging, pulse sequence, field strength) and can yield different fMRI sensitivity, specificity and efficiency. Though this apparent freedom can be confusing, parameters can be chosen depending on the requirements at hand (e.g. whole brain coverage for a 10 min scan at 3T) and the acceptable signal to noise ratio. For whole brain, or lower brain coverage, it is beneficial to use a TE that is shorter than that of the nominal T2* of gray matter, because lower brain regions are relatively prone to susceptibility artifacts for instance due to air tissue interfaces (e.g. ear canal) hence the T2* is overall shorter in these regions. Importantly, fMRI sensitivity depends on the temporal signal to noise ratio, described by the voxel-wise mean signal intensity over time divided by the standard deviation of the signal over the time. This ratio can be degraded by systematic (hardware, acceleration factor) noise but also by signal fluctuations of physiological origin due to subject motion, respiration, or heart-rate (19). However, physiological noise can be filtered out (20) or its contribution can be minimized by the choice of imaging parameters, for example by using a spatial resolution where thermal noise dominates (e.g. 19,21). Finally, BOLD signal changes are small (ranging from about 1% at 1.5T to about 10% at 7T) so averaging over several task repetitions presented during the experiment is typically required to enhance the detectability of BOLD signals, also contingent on the temporal signal to noise (22).

1. Buxton RB. Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques. 2nd Edition, Cambridge University Press, 2009
2. Attwell D et al. Glial and neuronal control of brain blood flow. Nature 2010; 468:232-243
3. Logothetis NK et al. Neurophysiological investigation of the basis of the fMRI signal. Nature 2001; 412:150–157.
4. Kim S-G, Ogawa S. Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. JCBFM 2012; 32: 1188–1206
5. Duvernoy HM, Delon S, Vannson JL. Cortical blood vessels of the human brain. Brain Res Bull 1981; 7:519-79

6. Tian P et al. Cortical depth-specific microvascular dilation underlies laminar differences in blood oxygenation level-dependent functional MRI signal. Proc Natl Acad Sci USA 2010; 107:15246–51
7. Siero JCW et al. Cortical depth-dependent temporal dynamics of the BOLD response in the human brain. J Cereb Blood Flow Metab 2011; 31(10):1999-2008
8. Kim SG. Quantification of relative cerebral blood flow change by flow-sensitive alternating inversion recovery (FAIR) technique: application to functional mapping. Magn Reson Med 1995*;* 34*:*293*–301*
9. Lu H et al. Functional magnetic resonance imaging based on changes in vascular space occupancy. Magn Reson Med 2003; 50:263–74
10. Ogawa S et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci USA 1992; 89:591–5955
11. Turner R. How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. Neuroimage 2002; 16:1062–7
12. Yacoub E et al. Imaging brain function in humans at 7 Tesla. Magn Reson Med 2001; 45:588-94
13. Uludag K et al, An integrative model for neuronal activity-induced signal changes for gradient and spin echo functional imaging. Neuroimage 2009; 48: 150–165
14. Norris DG. Spin-echo fMRI: The poor relation? Neuroimage 2012; 62: 1109-1115
15. Raichle ME. Two views of brain function. Trends Cogn Sci 2010; 14(4):180-190
16. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 2011; 15:483–506.
17. Wandell BA, Dumoulin SO, Brewer AA. Visual Field Maps in Human Cortex. Neuron 2007; 56:366-383
18. Jansma JM, et al. Working memory capacity in schizophrenia: a parametric fMRI study. Schizophr Res 2004; 68(2-3):159-71
19. Triantafyllou C, et al. Comparison of physiological noise at 1.5 T, 3 T and 7 T and optimization of fMRI acquisition parameters. Neuroimage 2005; 26: 243-50
20. Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn Reson Med 2000; 44:162–7
21. Bodurka J et al. Mapping the MRI voxel volume in which thermal noise matches physiological noise – implications for fMRI. Neuroimage 2007; 34(2): 542-549
22. Murphy K, Bodurka J, Bandettini PA. How long to scan? The relationship between fMRI temporal signal to noise ratio and necessary scan duration. Neuroimage 2007; 34(2):565-74