BOLD and its Relationship to Brain Activation

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Functional magnetic resonance imaging (fMRI) has become a powerful tool for investigating the working human brain based on the sensitivity of the MRI signal to local blood oxygenation. Functional MRI based on this blood oxygenation level dependent (BOLD) effect has been widely adopted by the neuroscience research community to investigate basic questions of brain functional anatomy. However, despite the widespread use of fMRI techniques, the basic physiological mechanisms underlying the observed signal changes are still poorly understood, and are the focus of active research. This talk will review current thinking on the mechanisms and origin of the BOLD effect and its relationship to cerebral energy metabolism and blood flow, including:

Biophysical origin of the BOLD effect: The BOLD effect is not a simple reflection of cerebral blood flow (CBF), nor even total deoxyhemoglobin. As a result, the interpretation of the BOLD effect, particularly in relation to other measures of activity (mean field potentials, tissue pO_2, near infrared reflectance, CBF measurements), is complex.

Physiological origin of the BOLD effect: The primary physiological phenomenon underlying the BOLD effect is that the oxygen extraction fraction decreases with activation. This may be a consequence of constraints on oxygen delivery to tissue, and appears to be consistent with maintenance of a constant ratio of $[O_2]/[CO_2]$ at the mitochondria.

A critical role for combined CBF and BOLD measurements: Arterial spin labeling (ASL) techniques, which allow measurement of cerebral blood flow (CBF) and the BOLD effect simultaneously, provide both a useful tool for investigating these physiological questions and a more specific probe of brain oxygen metabolism. Mathematical models of the BOLD effect play an important role in relating the measured CBF and BOLD signal changes to the underlying oxygen metabolism changes.

Dependence of the BOLD effect on the baseline physiologic state: Perturbations of the baseline state with drugs (e.g., acetazolamide, caffeine) or inhaled gases (CO_2 and O_2) alter the BOLD response to a stereotyped stimulus. Interestingly, however, in many cases the CBF change appears to be relatively constant independent of the baseline. The resulting variability of the BOLD response can be understood from mathematical models of the BOLD effect, and this variability due to the baseline state is a potentially significant confounding factor in BOLD studies of patient populations. The CBF change itself may be a more robust quantitative reflection of neural activity changes than the BOLD effect alone.

Relationship of BOLD and CBF changes to neural activity: In fMRI experiments the measured signals are due to the metabolic and blood flow responses to neural activation, not the neural activity itself. How do local rates of excitatory, inhibitory and spiking activity determine the resulting physiologic changes? This remains a fundamentally important question, and the answers are still not clear. Recent studies using a variety of experimental techniques have yielded interesting, but sometimes conflicting, results, and this remains an area of active research.

Clinical applications of BOLD-MRI: The BOLD effect has become a powerful tool for brain mapping, despite the fact that our understanding of this phenomenon is still incomplete. Clinical applications of BOLD-MRI have been limited, in part due to the difficulty of knowing how to interpret the signal in a quantitative way and in part due to the observed high variability of the BOLD effect. The combination of ASL techniques with BOLD imaging has the potential to be a more specific and robust probe of the energy state of the brain in clinical studies than BOLD imaging alone.