Functional MRI Methods for Clinicians
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The BOLD effect. Functional magnetic resonance imaging (FMRI) detects metabolic changes linked to brain activity, enabling us to infer where in the brain activity is occurring. Most FMRI is based on the blood oxygenation level dependent (BOLD) effect [Ogawa 1990], which detects deoxyhemoglobin, the form of the oxygen-carrying molecule in the blood that has been stripped of its oxygen. As the concentration of deoxyhemoglobin increases, the signal in a voxel decreases due to the BOLD effect. The dynamics of these changes during activation are somewhat unintuitive: although more oxygen is removed from the blood during activity, there is usually an accompanying increase in blood flow and volume that overcompensates for the increased oxygen consumption [Fox 1986]. The end result is a *reduced* deoxyhemoglobin concentration, and therefore an increase in signal, during activation [Ogawa 1992, Kwong 1992]. See the textbook by Buxton or Huettel *et a*l for a gentle but comprehensive introduction to FMRI.

Acquiring FMRI data. The sequence with greatest sensitivity to the BOLD effect is a gradient recalled echo (GRE). In this sequence, signal loss due to deoxyhemoglobin accumulates during the time between RF excitation and image acquisition, i.e. the echo time (TE). A useful rule of thumb is to set the TE equal to the signal decay time constant, T_2^* (ranging from about 60 ms at 1.5T to 20 ms at 7). BOLD signal changes occur over 3-6 seconds for most stimuli, which represents the fundamental temporal resolution of this technique. We therefore want to acquire images covering the brain over a similar timescale. The most common method is to acquire a series of 2D slices, each in a single “shot”, usually using echo-planar imaging (EPI), although spiral acquisitions are also possible. These methods rapidly cycle through different slices to acquire a time-series of 3D volumes, which can then be analyzed as described below to find brain areas where the signal changes appear to reflect stimulus/task timings. GRE data with these long TEs suffer from “black holes” of signal loss near air-tissue interfaces. The use of single-shot acquisitions also makes image distortion (EPI) or blurring (spiral) problematic. The spatial resolution of FMRI is typically a few millimeters, a limit that results in part from the constraints of single-shot image acquisition, but also from the higher signal levels that are obtained with larger voxels (i.e., high signal-to-noise ratio). Methods to reduce artifacts and increase resolution are a topic of current research.

Analyzing FMRI data. FMRI data is usually analyzed by comparing the signal fluctuations in each voxel to a model for the expected time signature for a region of activity. This is typically done using linear regression (often referred to as the “General Linear Model”, or GLM). By comparing the fitted effect size in each voxel to the residual signal fluctuations that are not explained by the fitted model, we can calculate the statistics indicating how confident we can be that a given voxel is active. These statistical maps are typically thresholded to identify the areas most likely to be involved in the task. More sophisticated statistical analysis can include comparison between different tasks at the individual subject level and group-level statistical testing. A number of pre-processing steps prior to statistical analysi are crucial to optimizing results, including image alignment, removal of slow signal drift and statistical pre-processing such as “pre-whitening”. Post-processing steps include alignment to “standard space” brain atlases, which are typically based on multi-subject spatial averaging. FMRI analysis is nicely covered in the textbooks edited by Jezzard et al and Friston.

Neurovascular coupling. One issue that is of particular relevance to clinical applications of FMRI is neurovascular coupling: the link (or lack thereof) between neuronal activity and the vascular response. The detection of oxygen metabolism associate with neuronal activity is itself an indirect measure; however, BOLD is further complicated by the fact that blood flow and volume changes are often larger than the change in oxygen metabolism. Moreover, this relationship is fixed, but varies across brain regions and subjects. Neurovascular disease and aging can affect neurovascular coupling [D’Esposito 2003]. This makes the interpretation of BOLD FMRI data highly problematic. The response can be drastically altered [Pineiro 2002, Rother 2002], even to the extent that no BOLD signal change occurs [Rossini 2004].

Challenges for clinical FMRI. Imaging patient populations introduces some additional challenges. The elicited signal changes tend to be smaller in aging and/or diseased patients [Huettel 2001]; subject motion tends to be more severe, and brain atrophy can make the interpretation of FMRI data difficult [Oakes 2007]. Finally, patients with neurological impairment may not be able to perform tasks designed for use on healthy subjects (for example, manual dexterity tasks in chronic stroke patients), requiring different stimulation paradigms. Despite having a major impact on basic neuroscience, FMRI has had limited application in the clinical arena, as discussed below.

Clinical applications. The potential for FMRI to contribute clinically can be roughly divided into two categories: (1) the study of patient populations and disease mechanisms as part of clinical research and (2) decision-making for individual patients as part of clinical practice. While the first category has many similarities to traditional FMRI in (non-clinical) neuroscience, the second category represents a significant departure. The use of FMRI in drug discovery is one recent example of the use of FMRI in populations, where the goal is to provide biomarker targets for pharmacological agents and/or tease apart a drug's affect on complicated neurological phenomena such as pain or dementia [Wise 2006]. The classic model for this kind of study involves a task or stimulus that targets a system of interest (e.g., memory in Alzheimer's disease), but recent work has also demonstrated that "resting-state" (non-task) FMRI may reveal useful information in disease [Greicius 2008]. The role of FMRI in treatment and care of individual patients has to date been limited. The most reported application is probably for pre-surgical planning of tumor resections [Sunaert 2006], although a range of surgical interventions have been reported [Bartsch 2006]. There is also hope that, in combination with other techniques, FMRI could provide sufficient quantitative information to provide useful markers in neurovascular disease [Jezzard 2006]. The 2006 Special Issue of JMRI entitled "Clinical Potential of Brain Mapping Using MRI" provides articles on a broad range of clinical FMRI topics, many of which are cited below.

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