

## Pulse Sequences to Clinical Applications in the Brain: Practical fMRI

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**Target audience.** Clinicians interested in learning the physical basis of functional MRI

### Highlights

- Functional MRI detects brain activity indirectly via the neurovasculature
- Rapid imaging with GRE-EPI is used, resulting in image artefacts
- Data are analyzed in each voxel to identify active brain regions
- Clinical applications require appropriate modification of standard approaches

### fMRI Methods

**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, 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 BOLD signal decreases. The textbooks by Buxton and Huettel et al provide 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 echo time (TE). BOLD signal changes occur over 3-6 seconds for most stimuli. 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). EPI rapidly cycles through the different slices to acquire a timeseries of volumes, which can then be analyzed as described below to find brain areas where the signal changes appear to reflect stimulus/task timings. GRE-EPI data suffers from intense image distortion and “black holes” of signal loss near air-tissue interfaces. The spatial resolution of EPI is typically a few millimeters. Methods to reduce artifacts and increase resolution are a topic of current research.

**Analyzing fMRI data.** fMRI data is typically analyzed by comparing signal changes over time in each voxel, to a model for the expected signal changes that accompany neuronal activity. This is typically done using linear regression, yielding images of statistical significance that are typically thresholded to display the areas involved in the task. There are widely-accepted methods for more sophisticated statistical analysis including comparison between different tasks at the individual subject level and for group-level statistical testing. A number of pre-processing steps are crucial, including image alignment, removal of slow signal drift and distortion correction. Post-processing steps include alignment to “standard space” atlases and correction of statistics for “multiple comparison”. See the textbooks edited by Jezzard et al and Friston.

### fMRI in the clinic

**Neurovascular coupling and other challenges.** One issue that is of particular relevance to clinical applications of fMRI is neurovascular coupling: the direct link (or lack thereof) between neuronal activity and the vascular response that drives BOLD signal changes. The overcompensation of blood flow and volume changes, compared to demand due to oxygen metabolism, makes the BOLD response an indirect measure of neuronal activity. Moreover, this relationship is not a fixed property of the neurovasculature, but varies with brain region, subjects, age, pharmaceuticals and neurovascular disease. This makes the interpretation of BOLD fMRI data highly problematic. Imaging patient populations introduces some additional challenges. The elicited signal changes tend to be smaller in aging and/or diseased patients; subject motion tends to be more severe; and brain atrophy can make the interpretation of fMRI data difficult. Patients with neurological impairment

may not be able to perform tasks designed for use on healthy subjects, requiring different stimulation paradigms.

**Clinical applications.** The use of fMRI in drug discovery is one recent example of the use of fMRI in clinical 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. fMRI may also lend insight into disease mechanisms. 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" fMRI may reveal useful information in disease. 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 or epilepsy, although a range of surgical interventions have been reported. In psychiatric disease, a major area of focus is in the use of multi-variate techniques to classify individuals (for example, to attempt to predict conversion from mild cognitive impairment to AD). The 2006 Special Issue of JMIR entitled "Clinical Potential of Brain Mapping Using MRI" provides articles on a broad range of clinical fMRI topics.