Review Article

Functional Magnetic Resonance Imaging: An Overview

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Abstract

Magnetic Resonance Imaging (MRI) is the most widely used non-invasive diagnostic imaging modality. Functional MRI (fMRI), a sub-domain of MRI evaluates task/ condition induced time-varying changes in brain metabolism. The method is sensitive to T2* contrast and is best acquired using 'Gradient Echo Sequence'. 'Statistical Parametric Mapping' is the freely available software, used widely for analysis of fMRI data and the findings are presented in the form of regional brain activations. The technique has deciphered roles of several brain regions corresponding to specific tasks.

Keywords: Magnetic Resonance Imaging, Functional Magnetic Resonance Imaging, Statistical Parametric Mapping, functional brain activations, functional connectivity.

Key Messages: Functional Magnetic Resonance is important to unveil functions of different brain regions.

Introduction

Magnetic Resonance Imaging (MRI) has evolved as a sophisticated, indispensable modality in diagnostic imaging. NMR history dates back to 1938, when Dr. Isidor Rabi demonstrated that molecules could emit radio waves at a specific frequency by exposure to an external magnetic field. He significantly contributed in discovering magnetic moments of nuclei. In 1942, Dr. CT Gorter coined the term 'Nuclear Magnetic Resonance' attributing the term to Prof. Isidor Rabi. In 1944, Prof. Isidor Rabi received the Nobel prize in Physics for his contributions in the field of NMR. Dr. Felix Bloch and Dr. Edward Purcell, independently demonstrated that certain nuclei (depending upon their 'periodic table position'), when placed in magnetic field, absorb energy in electromagnetic spectrum and further emission of this energy takes place when the nuclei come back to the ground state. Magnetic field strength and radiofrequency (RF) corresponded each other as per Larmor equation. They successfully measured RF signal of spins in water and paraffin, and were jointly awarded 1952 Nobel Prize in Physics. Dr. Raymond Damadian measured T1 and T2 relaxation times of excised cancerous and normal rat tissues in 1971 and demonstrated tumorous tissues to have longer relaxation times in comparison to normal samples. This experiment founded future research on clinical applications of NMR. Prof. Paul C. Lauterbur and Prof. Sir Peter Mansfield in 1974, independently demonstrated the utility of magnetic field gradients in spatial localization of NMR signals. Both of them attempted creation of images from NMR signals and are pioneers in the field of MRI. They jointly received 2003 Nobel prize in Physiology. In the year 1975, Prof. Richard Ernst postulated the utility of Fourier Transformation (FT) of phase and frequency encoding for rapid reconstruction of an image from NMR signals. He was awarded 1991 Nobel Prize in Chemistry for his valuable contribution in the form of FT that formed the basis of today's MRI.[1,2]

MRI came into routine diagnostic practice in the year 1984.[3] First functional MRI (fMRI) image was created by the 'active minus rest' approach of the two brain blood volume maps produced using two sequential Gadolinium injection during time series echo planar imaging (EPI) data collection, for creating cerebral blood volume before and after visual stimulation.[4] Since then, several groups started working on this area and fMRI research using exogenous contrast. During spring to summer 1991, Minnesota and MGH groups, especially Kwong, working on developing methods to extract brain activity and metabolism information using MRI; Ogawa and Ugurbil, pioneer in Blood Oxygen Level Dependent (BOLD)-based maps of human brain activity, obtained successful results with endog-

enous BOLD contrast in fMRI.[5-7] Since then (1991), the field of fMRI has seen tremendous development both in acquisition and processing.

Functional magnetic resonance imaging (fMRI)

Blood oxygenation level dependent (BOLD) fMRI is sensitive to alteration in blood oxygenation accompanying neuronal activity. The method allows spatial resolution of the order of a few millimeters and temporal resolution of a few seconds. BOLD contrast is mostly captured by T2* relaxation.

Processes involved in the neural signaling of brain demand energy in the form of adenosine triphosphate (ATP). Whenever a region of brain gets upregulated by a given task, energy requirement of the region gets elevated. Enhanced cerebral metabolic rate of oxygen (CMRO2) results in consumption of oxygen stores (within tissues adjacent to capillaries) during the process of glycolysis and thus causes production of waste/ by- products (CO2, NO, H+) leading to vasodilation. Vasodilation causes increased blood flow to meet Oxygen demands and physiologically, more oxygen is delivered than is required. This excess of Oxygen causes increase in the ratio of oxy to deoxyhemoglobin (Hb) in the region of neural activity. Oxygenated and deoxygenated Hb are diamagnetic and paramagnetic respectively. Enhanced microscopic field inhomogeneity due to the presence of deoxy-Hb shortens T2* relaxation times. Thus, regions of enhanced neural activity with more of Oxygenated Hb (due to enhanced blood flow to those regions compared to other areas) lead to enhancement in T2* relaxation times and thus enhanced MRI signal intensity relative to the baseline state (figure 1). The difference in signal intensity generates the BOLD MR contrast (figure 2).[8]

In general, Echo-Planar Imaging (EPI) (GRE-EPI) sequence is used for BOLD imaging. EPI sequences can significantly shorten the magnetic resonance (MR) imaging times allowing acquisitions in 20-100ms duration. The enhanced time resolution reduces motion artifacts. Thus, the sequence is suitable for imaging of rapidly changing physiological processes. In EPI imaging, multiple lines of k-space get acquired post single RF excitation. In conventional EPI, after the excitation RF pulse (SE or GRE), frequency encoding gradient oscillations (from positive to negative amplitude) lead to the formation of a chain of gradient echoes. Each of these echoes are differently phase encoded by phase encoding blips on the phase encoding axis. Each oscillations of the frequency encoding gradient corresponds to one line in imaging data in k-space and each blip corresponds to transition from one line to the next in k-space (figure 3).[9]

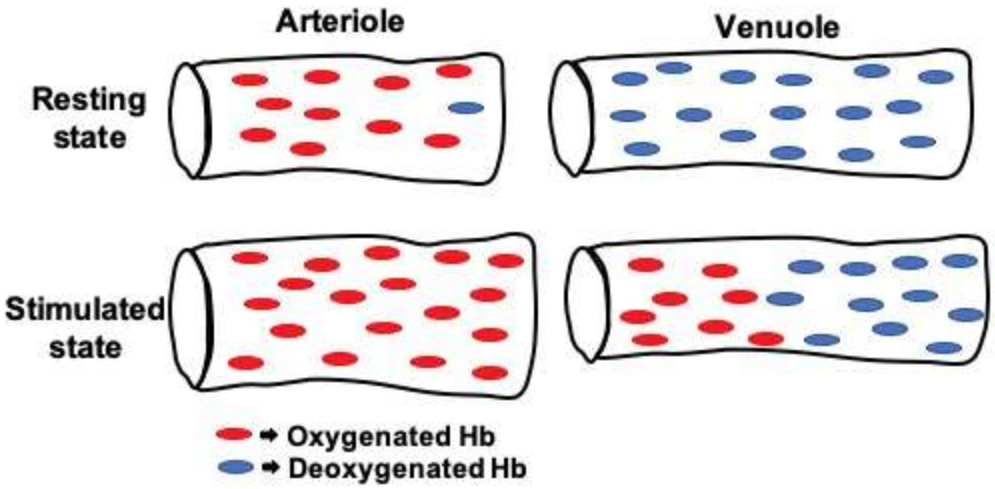

Figure 1: Picture depicting dynamic changes in oxygenated and deoxygenated Hemoglobin (Hb) ratio at the capillary level (arterial/ venous) during resting as well as stimulated state[8]

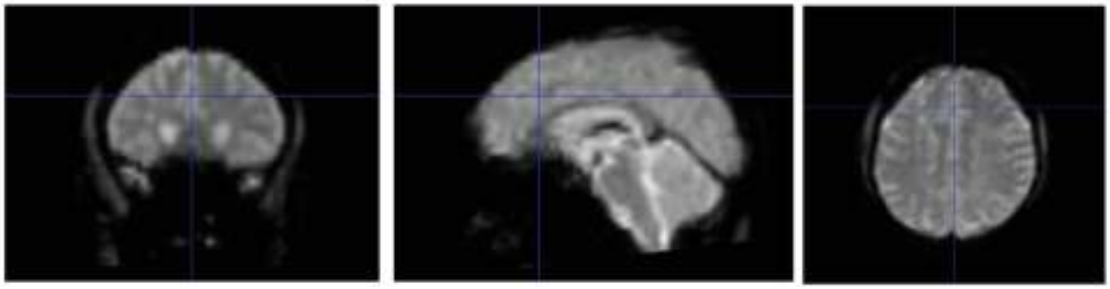

Figure 2: Representative BOLD contrast during fMRI with visual task

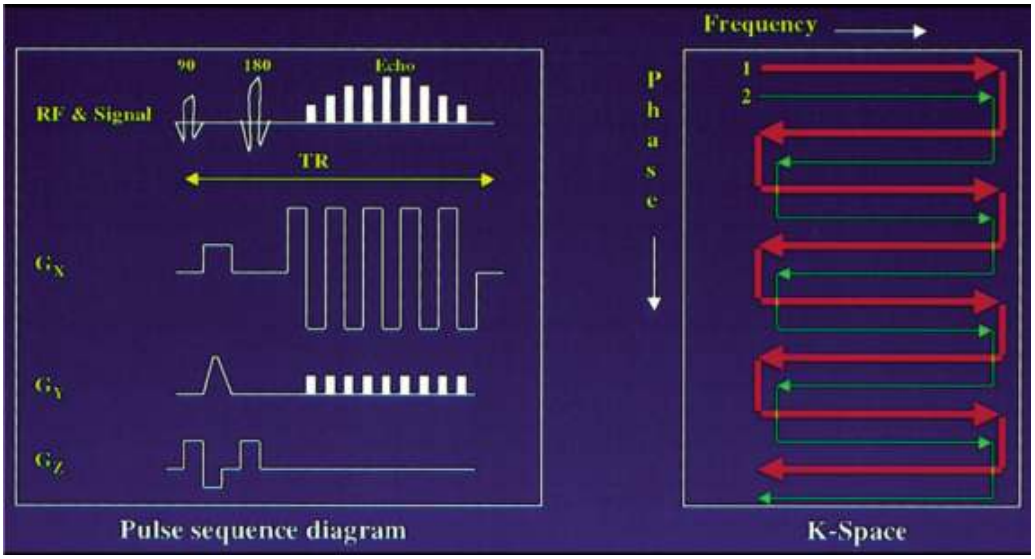

Figure 3: Echo-planar imaging. Within each TR period, multiple lines of imaging data are collected. Gx = frequency-encoding gradient, Gy = phase-encoding gradient, Gz = slice-selection gradient[9]

GRE sequences can introduce T2* weighting and GRE-EPI sequence is suitable for BOLD imaging as this fast imaging is less motion sensitive and allows greater multi-slice capability.[9] With the introduction of multislice imaging (SMS/ Multiband), the repetition times have been reduced by ~50%. Some vendors have combined Compressed Sense technique to reduce the TR further.

BOLD Data processing

Statistical Parametric Mapping (SPM, version 12) (https://www.fil.ion.ucl.ac.uk/spm/) is a open-source, freely available and widely used MATLAB based software for FMRI (BOLD) data analysis.[10] The software is based on mass univariate approach to fit a model at each voxel.

The preprocessing steps include image 'realignment' for motion correction, 'normalization' to spatially transform data from individual subjects into a common space [Montreal Neurological Institute (MNI) space in SPM] and enhancement of signal to noise ratio by the process of 'smoothing' (figure 4).

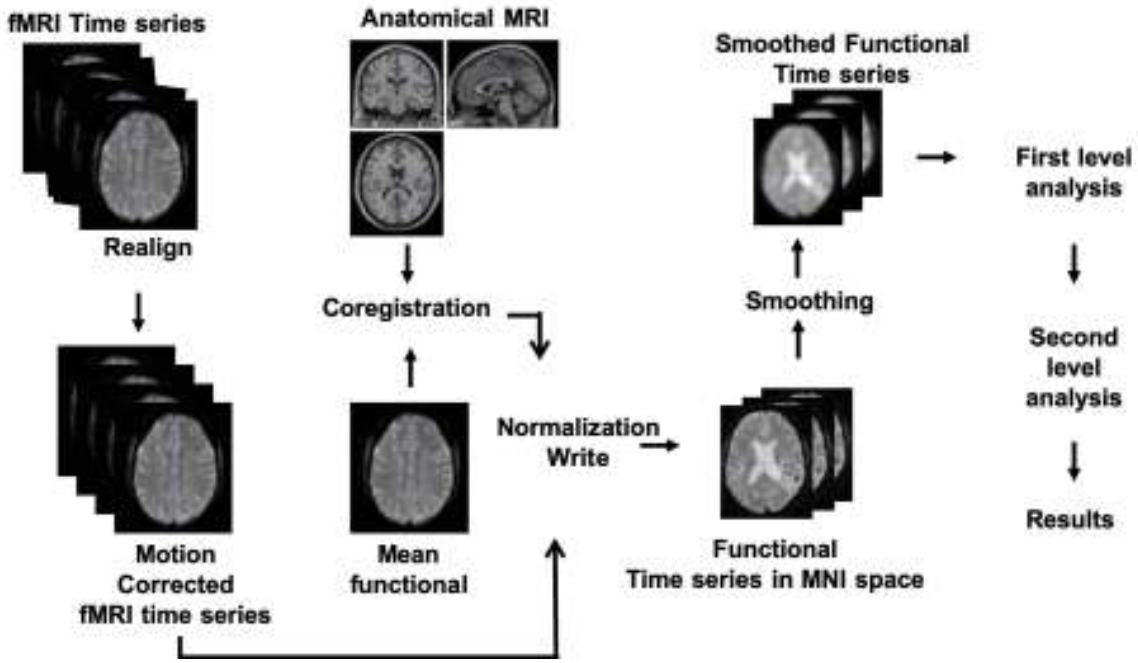

Figure 4: Overview of Statistical Parametric Mapping (SPM) based pre-processing pipeline of Blood Oxygen Level Dependent (BOLD) data[10]

During realignment, successive image volumes in a time series are co-registered to a target or reference volume (mean image or first image) using rigid body transformation in six directions. The process also estimates motion parameters that can be used during data post-processing to remove movement associated variance from the model.

Spatial transformation during normalization can be achieved in a number of ways. The simplest being affine transformation. During the process, image translation, rotation, skewing (shearing) and stretching (scaling) along each axis is performed to achieve transformation. This results in linear changes to the image coordinates and two points falling on the same line prior the transformation still falls on the same line post transformation. Piecewise linear transformation is another method and is the extension of affine transformation where entire image is broken into several sections and in each section linear transformation is applied. Nonlinear transformations with the use of 'basis-functions' allow greater flexibility and more accurate matching between two images.

The primary function of spatial smoothing is to suppress noise and enhance signal to noise ratio. It is achieved by applying three dimensional gaussian kernel. The process removes small scale changes in the image and reduces mismatch across individuals. With larger spatial scale, the process results in enhanced signal to noise ratio.

In many situations, another step termed 'slice time correction' precedes these steps that aids in correcting for mismatch between the acquisition timings of different slices.

During first level analysis, data from individual subject is tested for voxel time series (figure 5) corresponding to the applied task incorporated using general linear model (GLM) (figure 6).

In its simplest form, voxel time series forms the dependent variable and the expected BOLD stimulus response forms the independent variable. And, we want to evaluate the parameter estimate under the influence of residual error of each voxel. From the first level analysis, we get

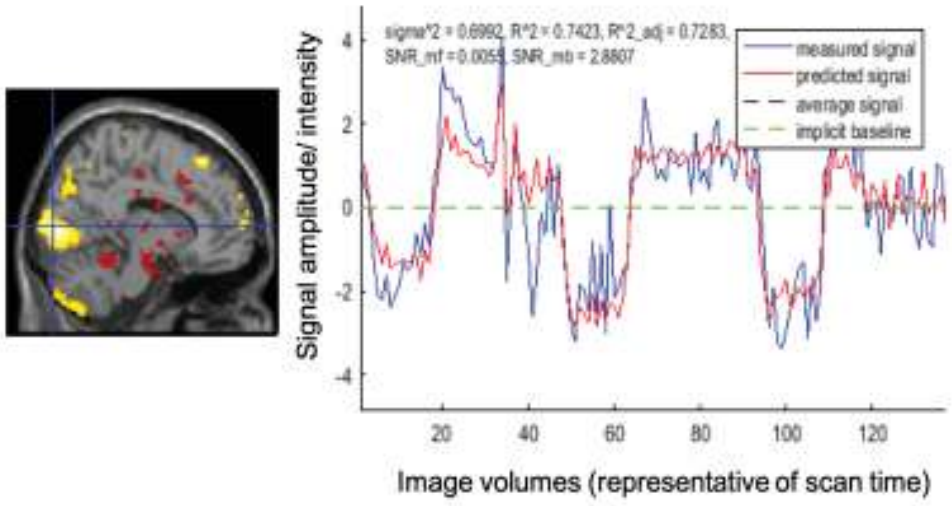

Figure 5: Picture depicting time course of signal change in right calcarine cortex with functional Magnetic Resonance Imaging (fMRI) task execution corresponding to visual task

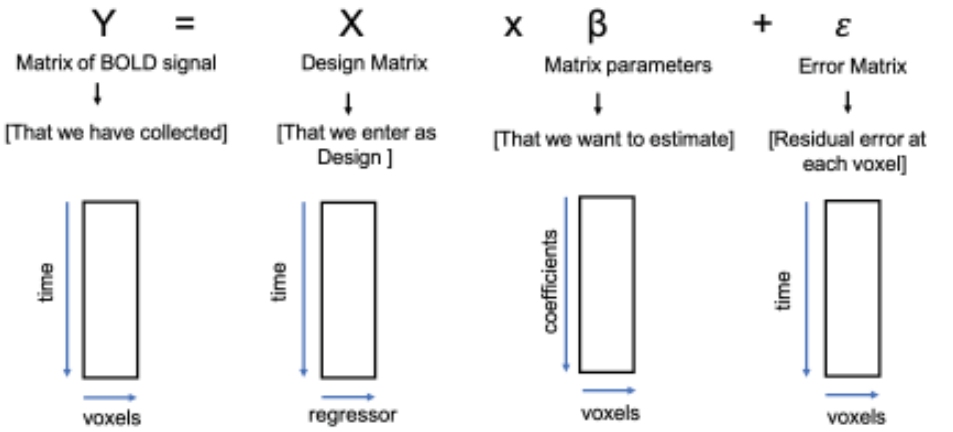

Figure 6: General linear model (GLM) variable in SPM analysis[11]

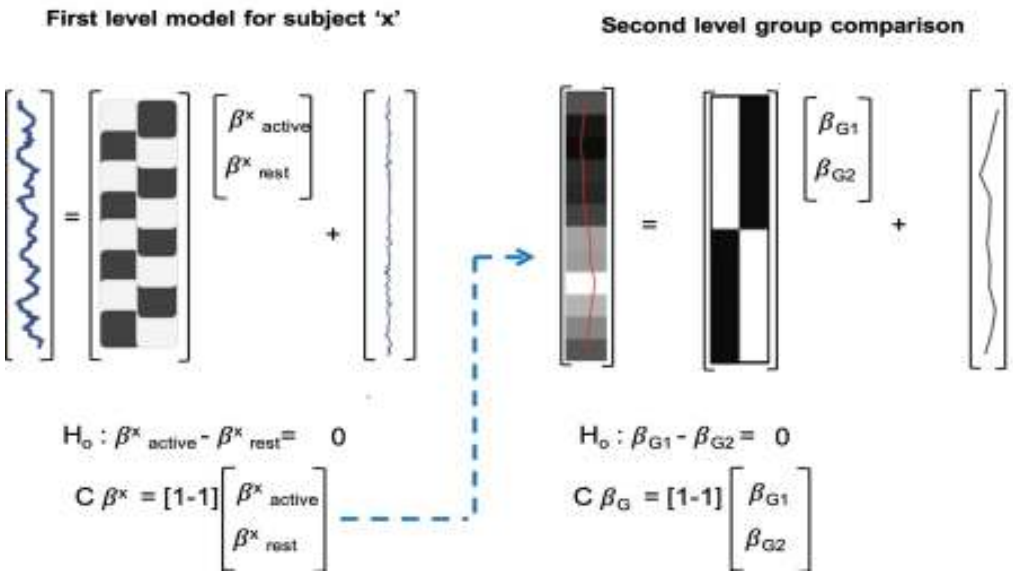

Figure 7: Illustration of two levels of modeling of fMRI data[11]

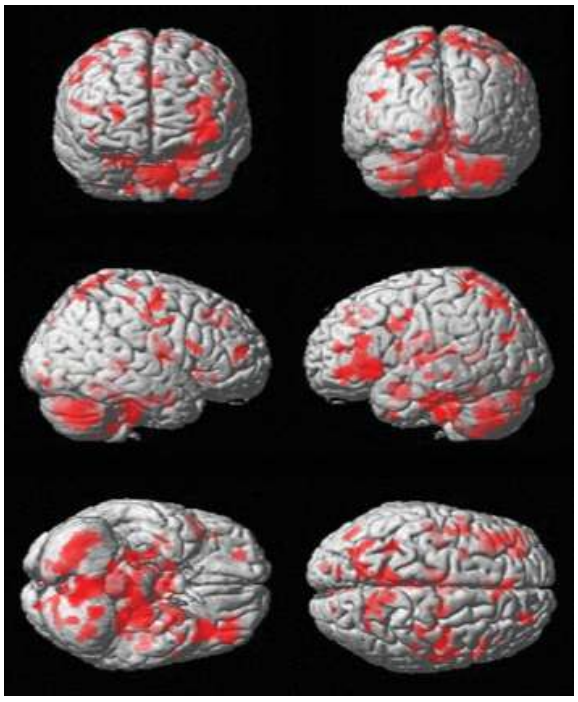

Figure 8: Rendered image of BOLD activations in Healthy participants during olfaction task represented at the significance level of p<0.001, uncorrected k=5

statistics estimates (effect of interest e.g. task>rest) for each of the brain voxels. In the second level analysis, statistical inference about the group/ groups is made using a number of suitable options as appropriate (figure 7).[11]

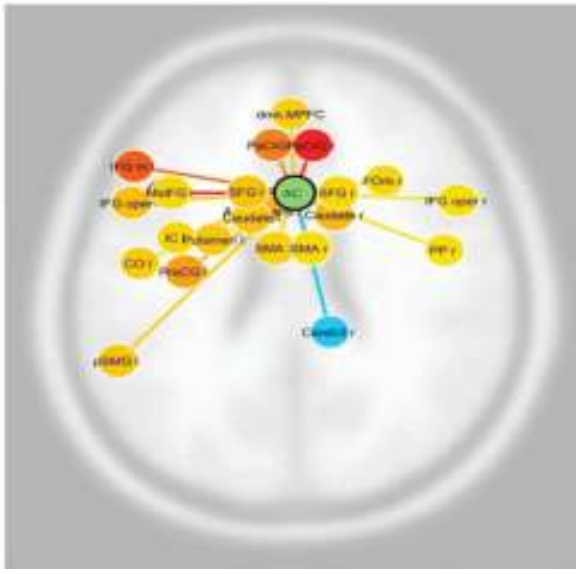

Figure 9: Olfaction task based functional connectivity in healthy participants with the seed Anterior Cingulate (seed: green; colour bar indicates T value, p<0.05, FDR corrected)

The result displays x, y, z co-ordinates (MNI) of the activated brain areas along-with peak statistics and are overlaid on standard brain template to get pictorial representation of the same.

Finally, inference of BOLD results is built based on these findings (figure 8). The same raw data can be used to estimate functional connectivity, using CONN (Connectivity analysis toolbox, SPM extension) analysis (figure 9).

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