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Recent developments in computer methods for fMRI data processing

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1. Introduction

Functional Magnetic Resonance Imaging (fMRI) is a relatively new procedure which uses magnetic resonance imaging to measure tiny metabolic changes which take place in an active part of the brain. It is becoming a diagnostic method for learnng how a normal, disease or injured brain performs, as well as, for assessing the potential risks of surgery or other invasive treatments on the brain. Physicians perfom fMRI to examine the anatomy of the brain, to determine precisely which part of the brain is handling critical functions, such as thinking, speech, motion and sensation, to assess the effects of stroke, trauma or degenerative diseases (such as Alzheimer's Disease) on brain function, to monitor the growth and function of brain tumors and to plan surgery, radio therapy or other surgical treatments of the brain.

After an fMRI paradigm has been designed and carried out, the resulting data must be passed through various analysis steps before the physician can obtain answers to questions about experimentally-related activations at the individual or multi-subject level and address the above matters. The goal of a computer-based fMRI analysis is to detect automaticaly, in a robust, sensitive and valid way, those parts of the brain which show increased intensity at the points in time where stimulation was applied. The fMRI analysis methods consist of three basic stages: preprocessing, signal detection – description, and extraction of the brain connectivity.

The purpose of preprocessing is to remove various kinds of artefacts and condition the data, in order to maximize the sensitivity of the next stage of analysis. Preprocessing includes spatial or temporal filtering of fMRI data and image restoration. After preprocessing, signal detection is accomplished. It aims to determine which voxels are activated by the stimulation. This can be performed by simple correlation analysis or more advanced methods. The main output of this step is an activation map which indicates those points in the image where the brain has been activated in response to the stimulus. Signal description aims at modeling the response shape by several parameters and relating these parameters to variables of the the stimulation context. Finally, connectivity analysis attempts to estimate brain networks.

The aim of this chapter is to provide an overview of the computer methods which have been developed to accomplish the above stages of the computer-based fMRI data analysis. The

chapter is organised as follows: first (Section 2), some fundamental features of the fMRI modality (including what is fMRI, how does fMRI work, what does fMRI measure, what are the advantages and disadvantages of fMRI, what are the sources of noise in fMRI, what are the spatial and temporal characteristics of fMRI, etc.) are described. The next section (Section 3) provides an overview of the preprocessing methods used in fMRI analysis. Then (Section 4), a summary of the main ideas that have been proposed to model and detect the fMRI signal is presented. In the fifth section, a description of connectivity analysis mehtods is given. Finally (Section 6), the importance of fMRI studies in understanding brain function and the applications of fMRI are exposed.

2. Description of the fMRI modality

Functional Magnetic Resonance Imaging (fMRI) is a neuroimaging technique which uses the physical phenomenon of Nuclear Magnetic Resonance (NMR) and the associated technology of MRI to detect regional changes in cerebral metabolism or in blood flow, volume or oxygenation in response to task activation. It utilizes Blood Oxygen Level Dependent (BOLD) constrast which is based on the differentiation of the magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) blood. These magnetic susceptibility differences lead to small but detectable changes in susceptibility weighted MR image intensity (Jezzard et al., 2001, Lazar, 2008).

2.1 fMRI image formation

When the human brain receives a stimulus an increase in neuronal activation takes place. When neurons are activated require energy. This energy is supplied in the form of glucose and oxygen (the oxygen is carried in hemoglobin). The resulting increased need for oxygen is overcompensated by a large incerease in perfusion. As a result, the venous oxyhemoglobin concentration increases and the deoxyhemoglobin concentration decreases. As the later has paramagnetic properties, it alters the T2* weighted magnetic resonance image signal (deoxyhemoglobin is sometimes referred to as an endogenous contrast enhancing agent, and serves as the source of fMRI signal) (Jezzard & Clare, 2001). More specifically, the intensity of the fMRI image increases in the activated areas. As the conditions are alternated, the signal in the activated voxels increases and decreases according to the paradigm (Figure 1).

2.2 BOLD response

As mentioned above neural activity requires increased local blood flow to supply additional oxygen. The increased need for oxygen leads to increase in perfusion. Increasing the prefusion rate in a tissue volume element generally leads to the dilution of the venous deoxyhemoglobin, reducing the tendency of the blood to decrease the magnetic resonance signal. This incease in signal intensity is referred as the BOLD.

A schematic representation of the common features of the fMRI BOLD response to a period of neural stimulation is given in Figure 2. fMRI BOLD response is divided into three epochs: a) initial dip, b) positive BOLD response, and c) post stimulus undershoot. Immediately after electrical activity commences there may be a brief period of approximately 0.5-1sec during which the fMRI signal decreases slightly below the baseline (~0.5%). This is known

as initial dip. Subsequently, the BOLD response increases, yielding a robust positive BOLD response whose peak is located 5-8sec after the stimulus is applied. Finally, upon cessation of the stimulus, there is a return of the BOLD response to baseline, often accompanied by a post stimulus undershoot, during which the response passes through baseline and remains negative for several seconds. Eventually, the response returns to baseline (Hoge & Pike, 2001).

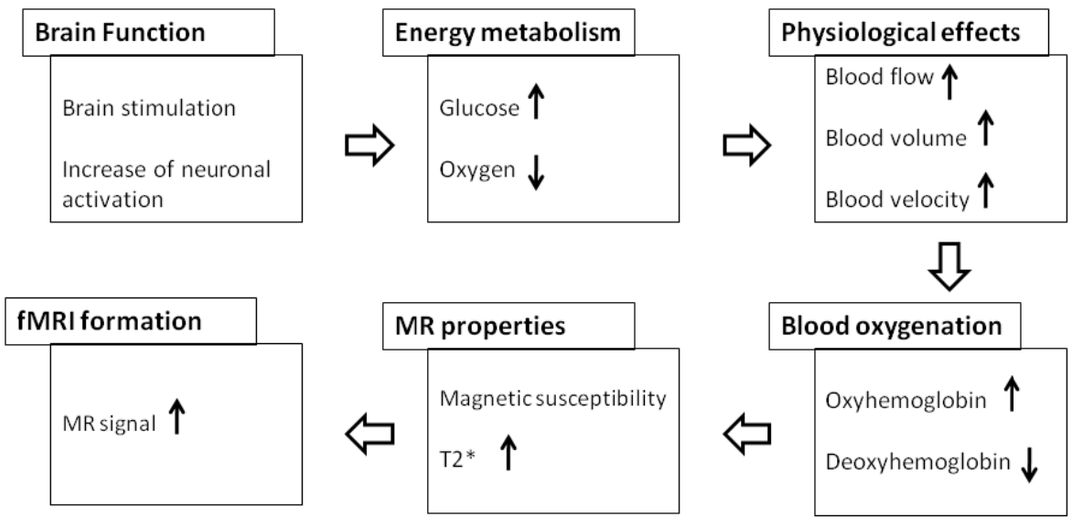

Fig. 1. Schematic representation of the fMRI formation.

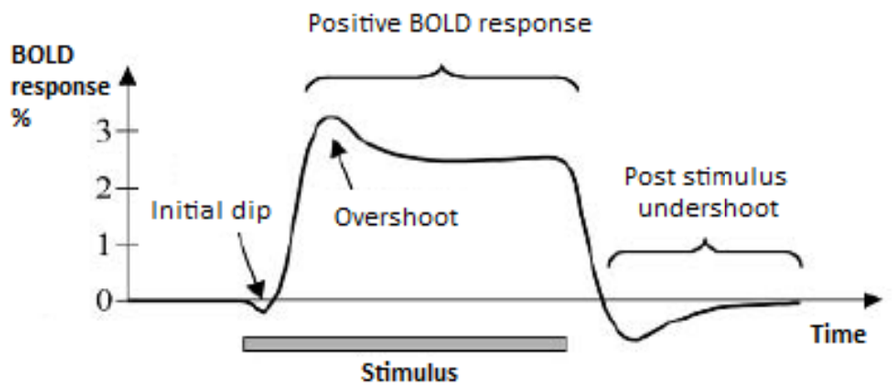

Fig. 2. Schematic representation of the BOLD response.

2.3 fMRI paradigm

During the fMRI paradigm the subject is positioned in the scanner and asked to alternatively perform several tasks or is stimulated to trigger several processes or emotions. Tne stimuli are usually audio, visual and motor, but can involve more complex functions such as memory and thought. Each of the above conditions is repeated several times and can be separated by rest periods. More specifically, there are two types of fMRI designs: a) event related designs in which stimuli of different types are intermixed, and b) block

designs in which stimuli of the the same type are presented in blocks. The brain of the subject is scanned repeatedly, using Echo Planar Imaging (EPI) technique. EPI is a fast magnetic resonance imaging sequence which allows the acquisition of a brain volume in less than 3 seconds (Figure 3) (Jezzard & Clare, 2001).

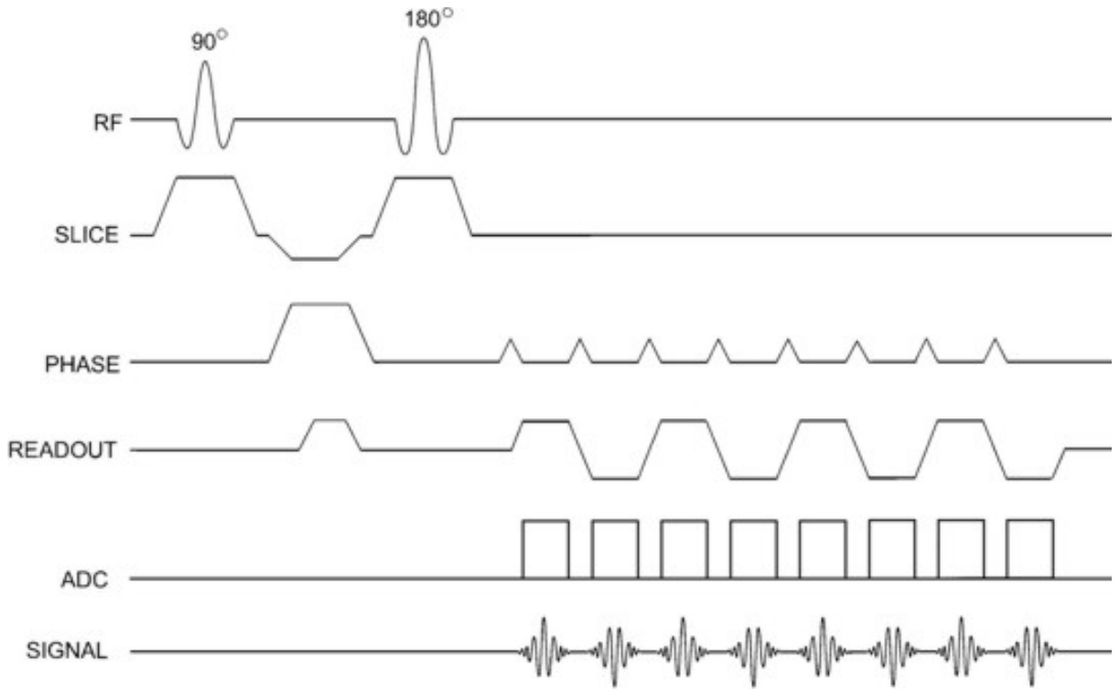

Fig. 3. Echo Planar Imaging (EPI) technique.

2.4 Advantages and disadvantages of the fMRI modality

The fMRI image volume offers several distinct advantages over other functional image modalities, such as PET and SPECT. These advantages are: a) it is considerably safer since no contrast agent is needed in order the signal to be administrated, b) the total scan time is very short, and c) it has high spatial and temporal resolution. The disadvantages of the fMRI are the following: a) it is very expensive, and b) it captures a clear image only if the patient does not move.

2.5 Spatial and temporal resolution in fMRI

One reason for the popularity of fMRI is its good spatial and temporal resolution. Spatial resolution in fMRI means the smallest activated area that can be reliably detected. It is basically limited by imaging time and by reasonable signal to noise ratio (SNR). Smaller voxels indicate smaller SNR but also improve spatial resolution by enabling the detection of smaller structures and smaller activated areas. Temporal resolution is defined as the shortest time between two stimuli in the same cortical area which produce distinguishable responses. Due to short acquisition time high temporal resolution of fMRI is possible in principle. However, it is limited by a blurred intrinsic hemodynamic response and a finite SNR (Menon & Goodyear, 2001).

2.6 fMRI time series

The functional images, as already mentioned, are T2* weighted images with lower spatial resolution than anatomical images. However, functional images are not considered as anatomical images of the object and they are not examined as those. The collection of them in a certain time rate consitutes a set of images. Each voxel's intensity value in each image of the set is called time series of the specific voxel (Figure 4).

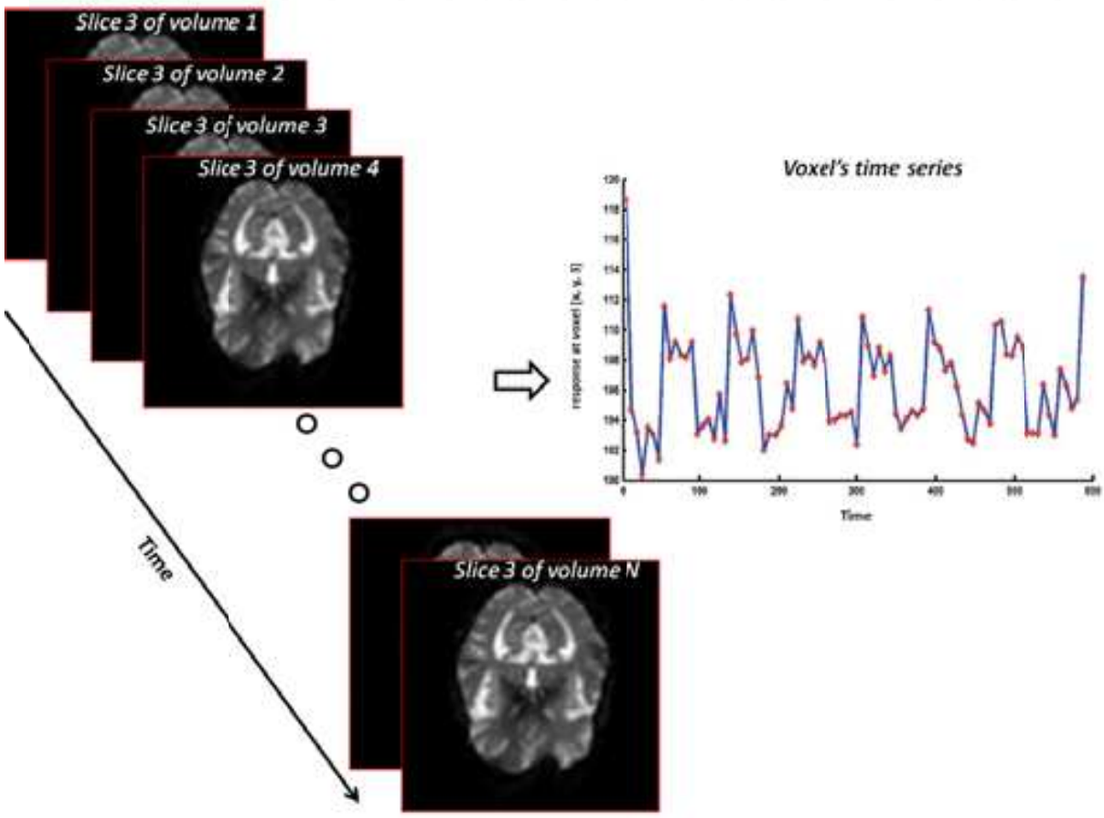

Fig. 4. fMRI time series.

2.7 Sources of noise in fMRI

fMRI time series contain not only the activity evoked by the experiment (effects of interest) but also structured and random noise. Noise in fMRI has several sources. These are: a) thermal noise arising from the subject, the receiver coil and the amplifiers, b) systematic noise arising from subject motion, c) systematic noise arising from tissue pulsation related to cardiac and respiratory cycles, and d) noise due to slow fluctuations in blood oxygenation (Lazar, 2008).

3. fMRI analysis – preprocessing stage

A successful fMRI paradigm is the one that ensures that the evoked neural activity generated by the stimulus or task constitutes a signal which can pass through all transformations which are necessary for the preprocessing and statistical analysis stages.
Preprocessing is performed to remove extraneous sources of variation and isolate the fMRI signal. There are six preprocessing steps that are needed in order the confounding effects of artefacts to be removed and the SNR to be enhanced. These are: slice timing, motion correction, intensity normalization, spatial normalization, spatial and temporal filtering.

3.1 Slice timing

Functional MRI volumes are formed one slice at a time. The scan time of individual slice differs within a repetition time (TR) depending on the acquisition order. More specifically, in ascending or descending sequential acquisition, the last slice is collected almost one TR after the first slice. In interleaved acquisition (all odd slices are collected first followed by all even slices) adjacent slices are collected a TR/2 apart. A problem is that later analysis steps assume that every voxel is sampled at exactly the same time. It is desirable to correct for this time shift. Slice timing correction makes the data in each slice to correspond to the same time instant. It is achieved by phase shifting of the sines that make up the signal. Each voxles time series is transformed to the frequency domain, phase shift is applied to the data and then the inverse Fourier transform is applied to recover the corrected time series (Smith, 2001, Strother, 2006).

3.2 Motion correction

One of the strongest fMRI artefacts are the movement related ones. If the subjects move their head during the fMRI paradigm, the position of the brain within the functional images will vary over time. Consequently any voxel's time series does not refer to the same anatomical point in the brain. Since the head movement cannot completely eliminated by scanner enviromental manipulation, it is corrected afterwards through mathematical transformations. Motion correction is achieved by the spatial alignment of the voxels across the sequentially collected fMRI image volumes. Spatial alignment is perfromed by registering the whole time series of the images to a target image (usually image picked first or middle image volume). Registration is based on the fact that only rigid body movement occurs. Thus, rigid body transformation is applied where six parameters (three translations and three ratotions) are needed. For the determination of the optimal value of parameters a cost function is used. Many of the differences between registration algorithms concern the choice of the cost function and the optimization strategies which are used (Smith, 2001, Strother, 2006).

3.3 Intensity normalization

In fMRI experiment there is additional scan-to-scan variance at very low spatial frequencies that cannot be readilly accounted for by the experimental stimulus. One possible cause of changes is the scanner itself (scanner drift). Several global normalization approaches have been developed to model and control this variation. Intensity normalization refers to the rescaling of all intensities in an fMRI volume by the same amount. It is applied to each

functional volume separately. A common approach for intensity normalization is the following. For each fMRI volume, the mean intensity across all voxels, which have been an intensity above a predetermined threshold, is calculated. Then all intensity values are rescaled by a constant value, so that the new mean intensity becomes a preset value. An alternative procedure is to use mean intensity value of each volume as confounding variables in later statistical analysis. Such methods present the following probelm. If the activation is strong then the activation itself will increase the mean intensity, thus, after normalization the "non-activated" parts of the volume will be negatively correlated with the stimulation, and will show up as "deactivation" in the final statistical image. Solutions to this problem, as well as, a comparison of detrending methods can be found in (Smith, 2001, Strother, 2006).

3.4 Spatial normalization

It is performed for two reasons. First, it enables to report the locations of activation according to a well know coordinate space, and second, it enables group comparisons. It is performed by a two step procedure: a) determination of an optimum 12 affine transformation (3 translations, 3 rotations, 3 zooms and 3 shears) between the template image and the image to be normalized, and b) estimation of nonlinear deformations defined by a linear combination of 3D Discrete Cosine Transform (DCT) basis functions (Smith, 2001, Strother, 2006).

3.5 Spatial smoothing

The importance of measuring and manipulating the spatial correlations of fMRI has been studied in (Poline & Mazoyer, 1995, Friston et al., 1993a, Worsley et al. 1996). Additionaly, the impact of spatial smoothing, as a preprocessing step, on signal detection of fMRI signal has been mentioned in (Skudlaski et al., 1999, Parrish et al., 2000, Lowe & Sorenson, 1997, Strother et al., 2004). There are two reasons for applying spatial filtering: a) blurring can increase SNR, and b) certain statistical theory, which may be used in later processing, requires the fMRI images to be spatially smoothed. A variety of methods for spatial filtering and a comparison of such methods have been reported in the literature (Smith, 2001, Nandy & Cordes, 2004, Sole et al., 2001, Long et al., 2004, Wink & Roerdink, 2004). The most common method for carrying out spatial smoothing is to convolve each volume with a Gaussian kernel. The width of the kernel lies between 3mm and 10mm of full width half maximum (FWHM) for fMRI. The recommended FWHM for fMRI is 2-3 times the voxel size. The convolution is performed in all three directions of the fMRI volume.

As far as it concerns temporal filtering, works on each voxel's time series instead on each spatial volume image. It aims to remove low and high frequency components without damaging the signal of interest. High pass filtering removes slow varying unwanted signals such as physiological effects (heartbeat, breathing) or scanner related drifts. High pass filtering is often achieved using finite impulse linear filters or alternatively using non linear high pass filtering procedures. Another approach is to model low frequencies in late statistical procedures instead of removing them at the preprocessing stage. Lowpass filtering attempts to reduce high frequency noise. A common way to carry out low pass filtering is the linear convolution with a Gaussian kernel (Smith, 2001, Strother, 2006). Other

more sophisticated approaches use wavelet filtering, Markov random fields and local neighborhood smoothing (Kruggel et al., 1999).

4. fMRI analysis – modeling and inference stage

After the improvement of the quality of the fMR images, statistical analysis is carried out to determine which voxels are activated by the stimulation. The current section presents an overview of the methods reported in the literature concering modeling and detection of fMRI signal.

Most functional MRI studies are based on the correlation of hemodynamic response function with stimulation. Activation is then defined as stimulus-linked and time-dependent local intensity changes in the image. Strategies for fMRI data analysis, in terms of signal analysis, consist of two steps: signal description and signal detection. Signal description aims at modeling the BOLD response by parameters which describe the stimulation context. Signal detection aims to detect significantly activated areas and it is commonly achieved by applying a test statistic. A statistical parametric map is created. The value of each voxel in this map express how closely the voxel's time series is from the expected time course. Voxels with high correlation values are given high activation score while voxels with low or no correlation have low score. In case of negative activation (deactivation) voxels are given a negative score.

The fMRI analysis has generated an abundant literature. The methods can be grouped into two broad categories: a) univariate methods (hypothesis testing methods), and b) multivariate methods (exploratory methods). Univariate methods try to define which voxels can be characterized as activated given one single model. This allows the parameterization of the response and then the estimation of the model parameters. This is followed by a statistical test which assesses the signal estimation and concludes to the presence or the absence of activation. The methodological variations can be related to the estimation procedure used or the statistical method employed to assess the presence of activation. Multivariate methods extract information from the dataset, often with any prior knowledge of the experimental conditions. They generally, extract a set of meaningful patterns from the dataset. In order to achieve this, they use some structural properties, such as decorrelation, independence, similarity measures, that can discriminate between features of interest present in the data. The gap between the two families of methods tried to bridge methods which use multivariate linear models. According to the description of the two groups of methods, methods such as Generalized Linear Model and some extensions of it, Wavelet basis functions, Bayesian framework, Principal Component Analysis (PCA), Independent Component Analysis, Canonical Correlation Analysis (CCA), Clustering techniques can be used for the analysis of fMRI data.

4.1 Generalized Linear Model

One of the most common approach in fMRI statistical analysis is the construction of a model that describes the way in which the BOLD response depends on the stimulus. A widely used mathematical model for this purpose is the Generalized Linear Model (GLM) (Friston et al., 1995a). It consists of two parts: fixed effects and random error. The fixed effects are the part of the model that do not vary if the experiment is repeated. The ranodm error is the part

which explains how the observations vary even if the experiments is repeated on the same subject and under the same conditions. The mathematical formula of GLM is given as:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}, \tag{1}$$

where $\mathbf{Y}$ is a matrix representing the time series of all the voxels, $\mathbf{X}$ is the design matrix of the predictors, $\boldsymbol{\beta}$ are the unknown coefficients of the predictors, and $\mathbf{e}$ is the error, usually assumed to be normally distributed with zero mean and variance σ^2 (independent and identically distributed). The error $\mathbf{e}$ may have a constant or a non constant variance, as well as, nonzero covariance. The columns of the design matrix $\mathbf{X}$ reflecting how the signal is varying in active areas (stimuli presented at each time point) and can contain different types of covariates of interest including: factors which describe the experimental design, predicted hemodynamic responses and categorical covariates, such as demographics of the subject group membership and so forth.
The basic GLM is usually used under the following assumptions: a) voxels are independent, b) time points are independent, c) the error variance at each time point is the same, and d) the same model, as given by the design matrix, is appropriate for every voxel in the brain (Lazar, 2008). Under these assumptions, the estimates of $\boldsymbol{\beta}$ can be obtained through the ordinary least squares (OLS). Thus, the estimated parameters are given as:

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^T\mathbf{X})^{-1}\mathbf{X}^T\mathbf{Y}. \tag{2}$$

The estimated parameters define how well the model, described in the design matrix, fits the time series of each voxel. However, the assumptions reported previously do not hold in practice. Thus, statistical research in fMRI has focused on ways of improving and extending the generalized linear model, or it has centered on alternative analysis methods.

4.2 Extensions of the Generalized Linear Model

A great part of the fMRI literature has concentrated on the improvement of the GLM described above in order to take into account temporal correlations, spatial correlations or both.

4.2.1 Temporal correlations

The basic GLM model described above assumes that the error term has zero mean and variance $\sigma^2\mathbf{I}$. This means that the error term is independent and identically distributed. However, fMRI errors are not independent. Temporal correlations exist due to physiological effects and scanner instability. In order temporal correlations to be addressed three general methods are proposed in the literature: a) ignoring temporal correlation, b) prewhitening, and c) precolouring. Ignoring temporal correlations leads to under estimation of variance, over estimation of significance and to many false positives. Prewhitening is assumed to be a statistical optimal approach but requires the precise estimation of autocorrelation structure. Precolouring has the advantage that autocorrelation structure estimation is avoided but on the other hand is statistically insufficient.

The autocorrelation models used in the literature extend the basic GLM by modeling the error term as a stochastic process. This can be achieved using an autoregressive model (AR(1), AR(p), AR(1) + white noise model) (Friston et al., 2000a, Marchini and Ripley, 2000, Kershaw et al., 1999, Burock & Dale, 2000, Purdon et al., 2001, Purdon & Weisskoff, 1998, Worsley et al., 2002). Thus, the error term is replaced with zero mean and unknown covariance structure. The variance is given as $\sigma^2\mathbf{V}$, where $\mathbf{V}$ is a matrix whose elements depend on the autocovariance function between two time points. The matrix V is the autocorrelation matrix for the intrinsic and assumed correlations. The intrinsic correlations are described by:

$$\mathbf{V_i} = \mathbf{K_i}\mathbf{K_i^T}. \tag{3}$$

The assumed correlations are described by:

$$\mathbf{V_a} = \mathbf{K_a}\mathbf{K_a^T}. \tag{4}$$

The matrices $\mathbf{K_i}$ and $\mathbf{K_a}$ correspond to convolution matrices.

Based on this modeling of error term, a general class of procedures is obtained by multiplying the GLM by matrix $\mathbf{S}$ (Friston et al., 2000a). This yields a model of the following form:

$$\mathbf{SY} = \mathbf{SX}\beta + \mathbf{Se}, \tag{5}$$

where $\mathbf{S}$ is the applied temporal filter matrix. A variety of methods have been reported in the literature concerning the estimation of the matrix $\mathbf{S}$. These methods were developed either in the time or frequency domain. Generally, if $\mathbf{S}$ has a Toeplitz form then it can be considered as an applied (de)convolution. However, $\mathbf{S}$ can take any one of the following forms:

$$\mathbf{S} = \begin{cases} \mathbf{K_i^{-1}} & \text{"whitening"} \\ \mathbf{K_{AR(1)}^{-1}} & \text{AR(1) model} \\ \mathbf{K_{AR(p)}^{-1}} & \text{AR(p) model.} \\ \mathbf{K_{1/f}^{-1}} & \text{1/f model} \\ \mathbf{I} & \text{"none"} \end{cases} \tag{6}$$

A comparison of the methods for selecting the matrix $\mathbf{S}$ can be found in (Friston et al., 2000a).
Until know it is assumed that the correlation structure is known. However, in practice $\mathbf{V}$ is unknown and thus must be estimated. Getting the correct correlation structure is important for three reasons: a) it leads to the best estimator, b) it guides us to the best design of the experiment, and c) it leads to the correct estimator of the variance, vital for getting the

correct statistics. A variety of methods have been proposed for the estimation of **V**. It must be mentioned that no simple methods exist that give best unbiased answers. The best methods all involve costly iterative calculations which are expensive to compute.

4.2.2 Spatial correlations

So far no information has been used from neighboring voxels, and all the models have been fitted independently at each voxel. If the signal extends over a certain region in space then it can be shown that signal detection is optimal if the data is simply averaged over all voxels in that region. Since the location of the region of interest is not known it is reasonable to smooth the data (spatial smoothing) with a kernel. The shape of the kernel models the assumed spatial activation patterns. Smoothing the data has been criticized because it sacrifices resolvability for detection ability. Moreover, the width of the signal to be detected should be known in advance.

Instead of smoothing the data or ignoring the spatial correlations, spatial modeling is another approach. Spatial modeling aims to analyze statistical parametric maps in order to detect those areas of the brain that were activated by the stimulus. A variety of methods has been proposed in the fMRI literature (Marchini & Presanis, 2004, Hartvig & Jensen, 2000). The most widely used methods are based on the thresholding of statistical parametric maps. The threshold value is determined using the classical approach where a null hypothesis of no activation at each voxel is postulated and then tested. The core unit of this approach is to choose a significance level for each test such that the family-wise error rate (FWE) is controlled at some pre specified level. This induces a multiple-comparisons problem which is addressed by using random field theory. Another way of spatial modeling is though Bayesian framework, more specifically spatial mixture models, or clustering techniques. These models explicitly model activated voxels in addition to the ''null'' distribution of non activated voxels. Benjamini & Hochberg (1995), Genovese et al. (2002) suggested that thresholds can be defined by controlling the false discovery rate (FDR). A different Bayesian analysis is described by Smith et al. (2003) and Smith & Fahrmeir (2007). Their approach is based on the basic linear model but the voxel time series is modeled as the sum of a baseline trend, an activation profile and an error. Their analysis is concentrated on the second term of the model. The application of the method to simulated and real data detected more isolated voxels than a comparable linear model-based analysis. Also the use of anatomical prior information increased the sensitivity of preserving details of activated structures.

As far as it concerns the use of clustering techniques for localization and characterization of spatial patterns of activation blurs the distinction between purely spatial and spatiotemporal models. Bowman & Patel (2004) tried to build a spatial model that does not have a temporal component. Although, their method was developed for PET images they indicate that the statistical issues are the same and the analysis can be used for fMRI as well.

4.2.3 Spatio-temporal correlations

A more natural way to handle functional neuro-imaging data is to build models that incorporate both spatial and temporal correlations. The most straightforward approach to achieve this is to apply clustering techniques to the time series data or spatial regularized approach, the so called "direct modeling". Time series clustering is a non model approach since no parametric model is specified for the spatial relations. These are clarified by the

detected clusters. With direct modeling spatial models are fitted, often with an aid of prior information provided by neuro-scientific reasoning or previous experiments.
Application of clustering techniques prerequisites an answer to the following questions: a) what should be clustered, b) what clustering algorithms should be used, c) which is the number of clusters, and d) how is the number of clusters decided. A variety of methods have been proposed in the fMRI literature to address those issues. As far as it concerns the first question there are two perspectives: a) clustering fMRI time series proposed by Baumgartner et al. (1998) and b) clustering features of fMRI time series proposed by Goutte et al. (1999). After the determination of the nature of the dataset, clustering algorithms (hierarchical clustering, k-means, fuzzy clustering) are utilized. A basic input of the clustering algorithms is the number of clusters. Methods described in (Filzmoser et al., 1999, Baumgartner et al., 1998, Balslev et al., 2002, Fadili et al., 2000) are trying to address this issue. However, the problem remains inherently difficult.
In direct modeling both temporal and spatial components are modeled explicitly (Lazar, 2008). Some authors (Solo et al., 2001, Purdon et al., 2001, Katanoda et al., 2000, Worsley et al. 2002) use a spatial regularization of the noise estimate. A potential disadvantage of these models is the adequacy of the spatial model, which is usually isotropic. Another way of spatial regularization is the use of Markov random fields (Descombes et al., 1998). The inference based on Markov random fields can be interpreted within the Bayesian framework where the prior probabilities is given by the voxel time course, while the posterior probability takes into account the contextual information carried by the neighboring voxels.

4.2.4 Estimation of parameters

An important concern in model based fMRI analysis is the ability to find unbiased estimators of the parameters. In the previous sections the least square estimation procedure is reported. Another attractive approach is the maximum likelihood framework. Least squares estimation approach yields maximum likelihood estimators under the assumption that the noise is Gaussian. This idea has been generalized in (Nan & Nowak, 1999) to deal with complex data.
In the previous sections, Bayesian framework is reported as a method for spatial or spatiotemporal modeling. However, another application of this framework in fMRI analysis is in the estimation of parameters. The main difference between maximum likelihood and the Bayesian framework is the introduction of priors in the statistical model of the data. The introduction of Bayesian concepts is in fact a way to optimize parameters in an expectation – maximization fashion. Genovese (2000) and Worsley (2000) proposed a Bayesian model for the estimation of parameters. A similar approach is previously described by Kershaw et al. (1999). They use informative priors for all parameters, avoiding in this way the computational issues. An advantage of this approach is that it allows researchers to give answers to questions beyond those of localization and also the parameters of the model can interpreted in terms of physiology of hemodynamic response. In 2004 Woolrich et al. proposed a model that not only models the hemodynamic response but also introduces a spatiotemporal noise component. The advantages of this approach is that allows for model comparison and the formulation of the HRF is not restricted by the experimental design. A different perspective on the Bayesian analysis is presented in Hartvig (2002), where marked point processes are used to describe the spatial activation pattern. Although, Bayesian framework is widely applied in fMRI analysis the potential of this framework is not fully

exploited. A comparison of classical and Bayesian framework is given in (Friston and Penny, 2002).

4.3 Multivariate analysis

In this section we give a short description of multivariate or model free approaches such as component, correlation and clustering analysis of fMRI data. Component analysis includes principal and independent component analysis while correlation analysis includes canonical and maximum correlation analysis. Clustering include methods such as k-means or fuzzy k-means. In contrast to the methods described in previous sections which were voxel based, the techniques which are presented aim to finding or characterizing the multivariate nature of the data, looking in subspaces or higher dimensional directions of common behavior. These directions may be in space, time or both depending on how the analysis is performed.

4.3.1 Component analysis

A classical multivariate statistical analysis technique is the Principal Component Analysis (PCA). The goal of PCA is to explain the variance-covariance structure of the data through linear combinations of the original data. It aims in: a) data reduction and b) interpretation. Although, the original dataset contains p variables, often much of the variability can be accounted for by a smaller number, m, of principal components. Hence, data reduction is necessary. A PCA can show relationships that were not previously suspected, and it allows interpretations that would not ordinarily result. PCA of fMRI data is often performed through a Singular Value Decomposition (SVD) technique after centering the dataset. The SVD simply decomposes the dataset into mutually orthogonal spatio-temporal components. On the contrary, Independent Component Analysis (ICA) aims to derive statistically independent components either in the spatial or in the temporal domain but not in both. This is justified since the independence of the random variables is a much more constrained problem than their correlation. The ICA uses information available in higher moments; hence it does not assume normality. Application of ICA involves two main preprocessing steps, data reduction and whitening. PCA is often used for the data reduction step. It is used in such a way that the majority of the variability in the data is captured. The innovative characteristic is that even if the number of required components is large, it will still be smaller than either the number of time points or the number of voxels in a typical fMRI study. PCA is also used to prewhiten the data. Whitening transforms the search space to an orthogonal one. A variety of algorithms, which constrain the results to be correlated and take advantage of the higher order features of the data are available to actually perform the ICA.

Comparison of PCA and ICA reveals the following differences. First, the frame of reference into which one projects the multivariate data with ICA is no more inevitably orthogonal. Second, the direction of the axes in ICA is not only computed from the second order statistics like in PCA but also from higher orders statistics. A third difference is the ordering of the components. More specifically, in PCA, the first principal component accounts for as much of the variability in the data as possible, and each successive orthogonal component accounts for as much of the residual variability as possible. The PCA can be used to decrease the dimension of the problem by considering only the first components which explain most of the variance in the data. With ICA, the number of sources to be computed must be

selected first. By changing the dimensions of the unmixing matrix to be estimated, the number of independent sources is computed by the algorithm. The obtained independent sources depend on the postulated number of sources, which is not the case in PCA (Lazar, 2008, Bugli & Lambert, 2007).

4.3.2 Extensions of PCA and ICA

An extension of PCA is its nonlinear version (Friston et al., 1999, Friston et al., 2000b). The motivation for this extension is the observation that the conventional analysis imposes biologically implausible constraints on the solutions. These constraints are: a) the components are orthogonal and account successively for the greatest amount of remaining variance, b) the decomposition is into linearly separable components. The last constraint precludes the possibility of interactions among brain systems. However, neuroscientists believe that brain systems interact with each other in a complex way.

Another form of PCA is functional PCA (Viviani et al., 2005). The data delivered by the functional magnetic resonance imaging (fMRI) scans are considered as continuous functions of time sampled at the inter scan interval and subject to observational noise. These functions may be estimated by fitting a set of basis functions to each voxel time series. Collectively, the functions replace the voxels of a series of images with a single "functional image." In functional PCA, the eigenanalysis is carried out directly on these functions. It requires two steps: a) smoothing time series and b) application of PCA on the estimated functions. As an explorative tool, functional PCA can be used as an alternative to other multivariate methods. This is justified in (Viviani et al., 2005).

Kernel PCA is a modification of the original PCA using techniques of kernel methods (Thirion & Faugeras, 2003). It does not assume that underlying structures of interest are uncorrelated spatially and temporally. The reason for this modification is that the assumption reported previously does not always hold for fMRI data. Kernel PCA is a two step procedure. In the first step each voxel time series is analyzed univariately, resulting in a temporal characterization of that voxel's behavior. Then, the voxel based models are subjected to a multivariate analysis. The aim of the kernel PCA is to preserve temporal patterns extracted in the first modeling step, something that is not attainable with ordinary PCA because of the assumption that components are uncorrelated.

As far as it concerns modification of the basic ICA approach these are spatial ICA, temporal ICA, spatiotemporal ICA, skew ICA and combination of spatiotemporal and skew ICA (Biswal & Ulmer, 1999, Calhoun et al., 2001, Calhoun et al., 2003a, McKeown et al., 1998, Calhoun et al., 2003b, Stone et al., 2002). Spatial ICA seeks a set of mutuall independnent source images, temporal seeks a set of independent source time courses, while spatiotemporal ICA decomposes an image sequence into a set of spatial images and a corresponding set of time courses such that signals in both sets are maximally independent. It is based on the observation that the underlying source images and time courses associated with brain tissue tend towards statistical independence, but neither source images nor time courses are independent in such cases. These approaches are based on the assumption that the probability density function (PDF) of the independent sources is highly kyrtotic and symmetric. Skew ICA is based on the assumption that images are characterized by the skewness (rather than the kurtosis) of their PDF's. This assumption is consistent with spatially localized regions of activity. Spatiotemporal skew ICA combines the ideas of

spatiotemporal ICA and skew ICA and produces better results both spatially and temporally.

4.3.3 Correlation analysis

Correlation analysis includes canonical and maximum correlation analysis methods. Canonical Correlation Analysis (CCA) (Friman et al., 2001, Nandy & Cordes, 2003, Lazar, 2008) is a way of quantifying the correlation between sets of variables. More specifically, it is a mean to detect the subcomponents of two multivariate datasets that are maximally correlated. It has been proposed as a way of investigating fMRI datasets with two possible applications: a) the derivation of temporal components that are maximally correlated and b) the derivation of the most spatially smooth maps of the dataset. An advantage of this approach is that the transformation of the original variables into the new scale reveals the correlation structure between the sets. This would not always be apparent if the simple pairwise correlations between components of the two sets were calculated instead.

Maximum correlation analysis of maximum correlation modeling (MCM) (Friman et al., 2002a, Friman et al., 2002b, Lazar, 2008) is a technique related to CCA. It works as follows: it considers the eight neighbors around each voxel. From this neighborhood five new time series are created. These are: a) time series of the center voxel, b) the average of the voxels to the immediate left and right of the center, c) the average of the voxels above and below the center, d) the average of the voxels in the upper left and low corners, and e) the average of the voxels in the upper right and lower left corners. The five new time series are combined linearly via weights ($w1$, $w2$, $w3$, $w4$, $w5$) which are positive numbers and sum to one. Also the weight applied to the center voxel is greater than the others. The correlation of this spatially smoothed time courses with the convolution of the stimulus and the hemodynamic response function is calculated. The aim is to find the values of the weights and the parameters of the model such that the correlation is maximized.

4.3.4 Clustering

Clustering is another exploratory method based on the following statistical viewpoint. The dataset X is a set of N features (the temporal time series) that belong to a given signal manifold or feature space F. The literature on fMRI data clustering deals with the following problems: a) the method for constructing the final clusters, b) the definition of the feature space F, c) the assessment of the quality of clustering results, and d) the determination of the number of clusters. Clustering algorithms also try to isolate patterns of no interest since the lack of prior knowledge. Flandin et al. (2003) suggest that introducing anatomical and functional information improves the generality and the precision of the method. Unlike PCA and ICA they do not decompose the data into components, and thus, do not benefit from the associated denoising effect.

4.4 Wavelets and fMRI

Wavelet analysis of fMRI data has gained the attraction of researchers due to the numerous advantages of wavelet basis functions. These advantages are: a) wavelets are multi-resolutional, b) they are adaptive to nonstationary or local features, c) wavelet transform has a whitening effect and this may be statistically convenient for modeling purposes, d) the wavelet transform is useful for data compression and denoising, e) the discrete wavelet

transform is very fast computationally, even compared to the fast Fourier transform, and f) the brain has a fractal nature, and wavelets are an effective way of modeling such processes. Thus, wavelet analysis has three main uses: a) creation of activation maps (Fadili & Bullmore, 2004), b) modeling, and c) resampling. The most traditional application of wavelets is the last one.

Wavelet resampling has been proposed to assess the presence of activation with colored noise. It was introduced by Bullmore et al. (2001) and it is remarkably simple. First, the discrete wavelet transform of fMRI time series is applied. It is adjusted to have zero mean. Second, the coefficients are resampled at each level of detail. Finally, the inverse wavelet transform of the permuted coefficients is applied to obtain a reconstructed time series that has the same variance and covariance as the original. Breakspear et al. (2004) proposed a two step procedure that aims to preserve both spatial and temporal second-order structure which is presented in the original data. Also, issues such as which is the best way to resample coefficients in each direction at each level are addressed. As far as it concerns the choice of wavelet family, the order of the wavelet, the number of vanishing moments, the way of resampling in multiple directions (jointly or independently), the management of edge effects are discussed in (Bullmore et al., 2001, Breakspear et al., 2004). Resampling can also be achieved in the frequency domain. At each frequency the components are approximately independent and so the same rationale, as for wavelet resampling, holds. A comparison of these two methods is given in (Laird et al., 2004), while a detailed comparison of prewhitening with an autoregressive mode, wavelet and Fourier resampling is presented in (Friman and Westin, 2005).

As already mentioned above, wavelet has also been used in fMRI analysis for data compression and modeling. The latter is of specific interest because attempts are presented to directly use prior anatomical information, and hence, to derive a set of functions that have intrinsic physiological meaning and interpretation. Fadili & Bullmore, (2002) propose a wavelet generalized least squares algorithm. The advantage of transforming the data into the wavelet domain is that the variance-covariance matrix of the error is approximately diagonal, which facilitates inference. The novel characteristic of this procedure is that the parameters of the long-range dependency process are estimated simultaneously with the parameters of the linear model.

5. Connectivity analysis

So far only the estimation of sites of activation and their relationship to stimulation or cognitive activity were discussed. No special reference to the relationships between different sites in the brain has been made. Connectivity analysis attempts to estimate such networks, in order to build up a more shopisticated picture of the functioning of the brain. Connectivity analysis is carried out on the basis of either similarities in time seires or relationships between final activation levels. There are two types of connectivity, functional and effective connectivity. Functional connectivity is defined as the temporal correlations between spatially remote neurophysiological events (Friston et al., 1993b). This definition provides a simple characterization of functional interactions, and it does not comment on how these interactions are mediated. Effective connectivity is the influence one neuronal system exerts over another (Friston et al., 1993c). Effective connectivity depends on two models: a mathematical model describing how are connected and a neuroanatomical model

describing which areas are connected. From the definitions given above it is understood that functional and effective connectivity differ fundamentally at a practical level. This is because the time scale and the nature of neurophysiological measurements are very different.

Functional connectivity is a statistical concept since it can be defined as the extent of correlation in brain activity measured across a number of spatially distinct brain regions. Studies regarding the presence or the absence of functional connectivity between a set of brain regions depend on: a) the type of measurement (e.g. EEG, fMRI, MEG), b) the type of the analysis, and c) the state of the subject during the recording of brain activity (e.g. rest, stimulation or cognitive task). However, the majority of the studies have employed only two approaches: a) coherence of EEG signals, and b) inter-regional correlation in fMRI time series. Studies of patterns of functional connectivity (based on coherence or correlation) among cortical regions have demonstrated that functional brain networks exhibit small-world attributes possibly reflecting the underlying structural organization of anatomical connections. More detailed graph theoretical analysis of functional brain connectivity helped to identify functional hubs, which are highly connected and central to information flow and integration. It should be noted that functional connectivity does not make any explicit reference to specific directional effects or to an underlying structural model (Friston, 2003, David et al., 2004, Achard et al., 2006).

The methods for measuring functional connectivity can be categorized according to the mathematical domain in which they are implemented (time, frequency). Functional connectivity is highly time-dependent. Statistical patterns between neuronal elements fluctuate on multiple time scales, some as short as tens or hundreds of milliseconds. While the majority of the methods have been developed in the time domain, considerable fewer methods have been developed in Fourier or wavelet domain. The motivation is that associations between brain regions may not be equally subtended by all frequencies. Some frequency bands may be of special importance in mediating functional connectivity. Functional connectivity studies in the frequency domain have provided evidence for a fractal organization of functional brain networks (Friston, 2003, David et al., 2004, Achard et al., 2006).

As far as it concerns effective connectivity its computation is more challenging than the computation of functional connectivity. More specifically, there are linear and nonlinear models for effective connectivity such as multiple linear regression, covariance structural equation modeling and variable parameter regression. Multiple linear regressions (Friston et al. 1995b, Buchel & Friston, 2001) demonstrated that nonlinear interactions can be characterized using simple extensions of the linear models. Structural equation modeling (Penny et al., 2004, Buchel & Friston, 2001, Buchel & Friston, 1997a, McIntosh & Gonzalez-Lima, 1994) was introduced as a technique that allows combining observed changes in cortical activity and anatomical models. Variable parameters regerssion (Buchel & Friston, 2001, Buchel & Friston, 1998) was introduced as a flexible regression technique, allowing the regression coefficients to smoothly vary over time. Multiple linear regression models are sufficient to analyze effective connectivity to one region at a time. Structural equation modeling allows for more complicated models compromising many regions and demonstrates how nonlinear interaction are dealt withing this context. The basic idea behind this approach differs from the usual statistical approach of modeling individual observations. In muliple linear regression models the regression coefficients derive from the minimisation of the sum of squared differences of the predicted and observed dependent

variable. Structural equation modeling approaches the data from a different perspective. The emphasis lies on the variance-covariance structure. Thus, the models are solved by minimizing the difference between the observed variance-covariance structure and the one implied by a structural or path model. An important issue in structural equation modeling is the determination of the participating regions and the underlying anatomical model. Several approaches can be adopted. Those include categorical comparisons between different conditions, statistical images highlighting structures of functional connectivity and non-human electrophysiological and anatomical studies. Due to the fact that the goal of some experiments is not to compute effective connectivity but to demonstrate changes in effective connectivity, variational parameter regression is proposed. Variational parameter regression allows the characterization of the variance of regression coefficients by using the framework of state space models and the Kalman filter (Buchel & Friston, 1997b).

6. Applications of fMRI

Functional neuroimaging has revolutionized the way that cognitive neuroscientists investigate the relationship between brain and behavior. Functional MRI is contributing to that revolution by providing a widely available, non-invasive technique which combines high spatial resolution with critical information about the temporal dynamics of the cortical and sub-cortical signal changes observed. It is widely accepted as a tool for identifying brain regions that are associated with certain perceptual, cognitive, emotional, and behavioral functions, such as visual, sensorimotor, language, and memory. It is suitable for accessing many aspects of human cognition and plays an important role in assisting presurgical planning in neurosurgery and in providing additional diagnostic information in the clinical management of patients who have functional disorders due to neurological diseases and mental illness. Some other fundamental application of fMRI is the management of pain, the improved assessment of risk, and the improved seizure localization.

The ability of fMRI to depict brain activity *in vivo* makes it a promising tool for the diagnosis, interpretation, and treatment evaluation of clinical disorders involving brain function. Presurgical planning is an area of clinical importance where fMRI plays an active role. When surgeons are going to remove a part of a patient's brain, it is critical to know exactly where various motor and sensory functions are mapped in that individual's brain. Functional MRI is a non-surgical technique for obtaining critical information before any surgical intervention starts.

Other areas of obvious clinical potential, such as psychopharmacology, neurology, stroke treatment and recovery, drug addiction, and psychiatric disorders, are under research. As already mentioned in previous sections fMRI allows for the creation of maps of brain activity corresponding to the performance of a specific task. A way to exploit these maps is to identify areas of the brain which are functionally important and therefore should be carefully avoided during neurosurgery. An important characteristic of these maps is that they are specific to the individual patient and they do not based on averages across many subjects.

Pharmacology is another area where fMRI has great potential. Although, fMRI is not recommended for the identification of the binding sites of a drug, due to its good spatial and temporal resolution, it can be utilized for the indication of brain areas that a drug influences.

A better understanding of the anatomy and physiology of addiction may eventually lead to more effective treatment.
As far as it concerns the application of fMRI to neurological and psychiatric disorders is still under development. Also fMRI has great potential in the area of medical diagnosis, since the analysis of this modality reveals a great variety of differences between healthy and diseased subjects. Many such studies have been conducted already concerning various diseases. In the future the fusion of fMRI with other medical image modalities will offer a significant amount of valuable information for the better understanding of human brain anatomy and function (Owen et al., 2001, Thulborn & Gisbet, 2001, Faro & Mohamed, 2006).

7. References

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