Identifying multisubject cortical activation in functional MRI: a frequency domain approach

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Abstract

Functional magnetic resonance imaging (fMRI) has become a prominent technique in neuroscience. Activation brain maps are obtained by statistical analysis of fMRI time series, considering BOLD signal as dependent variable and expected haemodynamic response function (HRF) as regressor in a general linear model (GLM). However the results of GLM rely on the HRF specification. Considering periodic paradigm designs, we propose a multisubject frequency domain approach for activation brain mapping, which solely requires the stimulation frequency, avoiding subjective choices of HRF. We present some computational simulations, which evidence a good performance of the proposed approach. Further, is also presented an application of the new method in fMRI datasets, related to motor paradigm in periodic block and event related designs.

1 Introduction

Nowadays, several studies in neuroscience are based on neuroimaging techniques. Since the description of the blood oxygenation level dependent signal (BOLD) by Ogawa et al.[23], the number of studies based on functional magnetic resonance imaging (fMRI) has been increasing significantly. Tolias et al.[31], Logothetis[17] and Logothetis and Pfeuffer[18] showed that BOLD signal can be considered as an indirect measure of neuronal activity, due to local blood flow properties after spikes. In an fMRI session, several images are acquired during time, allowing the temporal monitoring of BOLD signal concurrently to the presentation of stimulus.

The main advantages of fMRI analysis compared to EEG and PET is its non-invasive properties and also the high spatial resolution. The images in an fMRI session are acquired in slices providing a 3-dimensional visualizations of the whole brain (volume), including non-cortical areas. In terms of data structure, each slice is a matrix composed by $X \times Y$ voxels, and each voxel represents a brain area. Hence, at each voxel there are T measurements, $\{y_t,\ t = 1, .., T\}$, which constitute the time series of BOLD signal related to that area.

The evaluation of BOLD temporal properties considering the paradigm design may be very useful to infer about neural dynamics. In general, the focus of most fMRI studies is the inferences about the effect of external stimulus in the BOLD signal. Considering parametric approaches, the general linear model (GLM, Graybill[13])is the most used method to identify brain activations, commonly named by SPM (statistical parametric mapping). A linear or non-linear regression is performed considering the observed BOLD signal as dependent variable and an expected haemodynamic response function (HRF) as regressor (Turner et al.[32], Buchel et al.[5], Friston et al.[10, 11]). As the dependent variable is obtained directly from the data, the first issue in this analysis is the determination of the HRF regressor. Assuming that the sequence and times of stimulus is known, there are many proposals to the HRF determination (Buchel et al.[6], Friston et al.[12]) based on haemodynamic delay, Volterra kernels, and non-parametric smoothing. The statistical significance of activation is obtained using a Wald statistics or a t-test.

In this paper, we propose a multisubject activation mapping in frequency domain, considering periodic paradigms. In this new proposed approach, hemodynamic response function specification is not necessary, hence subjective or incorrect determinations of HRF are avoided. Further, we have an extreme reduction in computational time, because the Fast Fourier Transform (fft) algorithm used is much faster than GLM estimation.

We also show some simulations focusing on power evaluation and asymptotic null distribution of no activation. An application to real fMRI dataset involving motor task is also presented.

2 Methods

2.1 Time Series Analysis

A time series is a set of observations y_t, each one being recorded at a specified time t. The obvious correlation introduced by the sampling of adjacent points in time can usually restrict the applicability of the many conventional statistical methods traditionally dependent on the assumption that these adjacent observations are independent and identically distributed. Time series analysis is the systematic approach by which one goes about answering the mathematical and statistical questions posed by these time correlations. In general, we observe one or more realizations $\{y_t, t = 1, \cdots, T\}$ of a stochastic process $\{Y_t\}$ and describe this process and make inferences about it. In time series analysis, there are two approaches commonly identified as the time domain approach and the frequency domain approach.

In the time domain, the correlation structure of a second order stationary process is described by the autocovariance function (acf) $\gamma_y(k)$ defined as

$$\gamma_y(k) = Cov(y_t, y_{t-k}) = E((y_t - \mu)(y_{t-k} - \mu)),$$

where μ is the mean of the process. This funtion measures the linear dependence between two points separated by a lag k on the same series observed.

In the frequency domain, the correlation structure is represented by the spectral density, $f(\lambda)$,

$\lambda \in [-1/2, 1/2]$, defined by

$$f(\lambda) = \sum_{k=-\infty}^{\infty} \gamma(k) exp(-2\pi i \lambda k), \qquad (1)$$

where λ is measured in cycles per unit of time. The spectral density describes the long-run properties of the process in terms of periodic components at different frequencies in any given realization.

2.2 Spectral Time Series Analysis of Periodic Stimulus Designs

In the analysis of fMRI voxel time series, considering the case of a event-related or block periodic designs, the stimulus oscillation frequency is defined as the fundamental frequency of activation. Thus, our aim is the identification of voxels which have BOLD signal oscillating in the stimulus frequency. Note that similar to GLM, this issue is performed in order to detect responses to the stimulus. We consider the model

$$y_t = \sum_{j=1}^{K} R_j \sin(2\pi\omega_j t + \psi) + \epsilon_t, \; t = 1, \cdots, T, \quad (2)$$

where y_t represents the BOLD signal, K is the number of components, R_j is the amplitude, ω_j is the frequencies of interest and ϵ_t is a gaussian white noise.

The variance of a voxel time series, $\{y_t, \; t = 1, \cdots, T\}$, attributable to an oscillation of frequency λ_j is obtained by the spectral density (1) with $\lambda = \lambda_j$, which can be estimated by the periodogram defined as

$$I(\lambda_j) = \mid d_y(\lambda_j) \mid^2, \qquad (3)$$

where $d_y(\lambda_j)$ is the discrete Fourier transform at the Fourier frequencies

$$\lambda_j = \frac{j}{T}, j = 1, 1, \cdots, [\frac{T}{2}],$$

of y_t and defined as

$$d_y(\lambda_j) = \frac{1}{T} \sum_{t=1}^{T} y_t exp(-i2\pi\lambda_j t). \qquad (4)$$

In practice, the discrete Fourier transform is obtained using the Fast Fourier Transform (fft) algorithm, which is computationally efficient. Most of the frequencies will contain information solely about the correlation structure of the underlying stochastic process at the voxel. Figure 1 shows some haemoresponse functions and their respective periodograms.

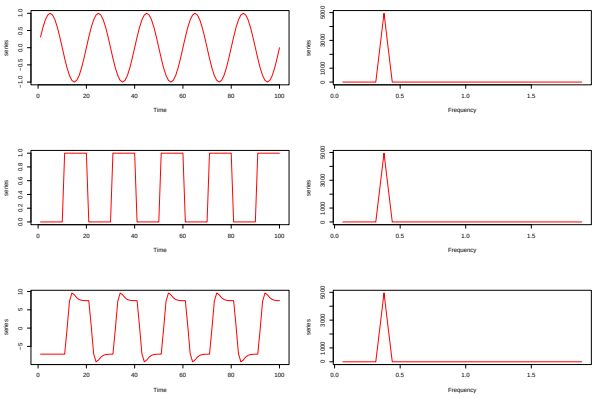

Figure 1: Some haemoresponse function and their respective periodograms.

The large value at the fundamental frequency is indicative of response to the stimulus. Hence, for a periodic design, we are only interested in the spectral density at a fourier frequency λ_a (the fundamental frequency of activation).

The asymptotic sampling properties of the periodogram are well-known. For stationary series,

(I) $I(\lambda_j)$ and $I(\lambda_k)$ are asymptotically independent, for all $j \neq k$;

(II) for $k = 1, \cdots, K$, $K << T$, $\frac{k}{T} \approx \lambda$ and $\frac{k}{T} \neq 0, \pm 1/2, \cdots$,

$$\frac{2I(\lambda_k)}{f(\lambda)} \xrightarrow{D} \chi^2_2, \tag{5}$$

independently, where χ^2_2 denotes a chi-squared random variable with 2 degrees of freedom [28, 3, 4].

2.3 Testing for a Response to the Stimulus

The periodogram (spectral density estimate) provides us with a baseline against which to test for significant departures from the underlying process. We define the ratio statistic at the fundamental frequency of activation, λ_a, for each voxel time series as

$$R_a = \frac{[T/2]I(\lambda_a)}{\sum_{j=1}^{[T/2]} I(\lambda_j)}, \tag{6}$$

to obtain a test statistic for significant activation. Large value of R_a indicates a large effect at the fundamental frequency.

From (I) and (II), under the hypothesis of no activation, the statistic

$$R_a \sim F(2, 2[T/2]),$$

asymptotically, where $F(2, 2[\frac{T}{2}])$ is a F-distribuition with 2 and $2[\frac{T}{2}]$ degrees of freedom [28, 3, 4]. Analogously, for N subjects, we have.

$$R^*_a = \frac{[T/2]\sum_{n=1}^{N} I_n(\lambda_a)}{\sum_{n=1}^{N}\sum_{j=1}^{[T/2]} I_n(\lambda_j)} \sim F(2N, 2N[T/2]). \tag{7}$$

Hence, we reject the null hypothesis of no activation for large power in the fundamental frequency of activation. Nevertheless, some fMRI time series are autocorrelated. In this cases, pre-whitening filters which preserve the time series periodicity should be applied.

3 Simulations

All simulations in this section were performed using the R Statistical Software (*www.r-project.org*). Firstly, consider the case of white noise time series. We simulated 10000 gaussian white noises of length 100 for 6 subjects in order to empirically estimate the F-statistics probability density function under the null hypothesis (frequency $\lambda = 0.05$). The histogram, theoretical and estimated density via kernel smoothing are presented in Figure 2. Note that the estimated and theoretical densities are really similar, indicating a good asymptotic approximation even for short length time series.

Focusing on the power evaluation, consider the following model:

$$x_{tn} = \beta \sin(2\pi\lambda t/T) + \epsilon_{tn},\ t = 1, ..., T \tag{8}$$

where T is the time series length, $n = 1, .., N$ is an index representing each subject, λ is the fundamental frequency of activation, β is a coeficient representing the energy in frequency λ and ϵ_t is a gaussian white noise. Ten thousand simulations were performed for each evaluation and the size of the tests is $\alpha = 0.05$. The effect in the power of the test by increasing the energy in the fundamental frequency of activation β for $N = 6$, $T = 100$ and $\lambda = 0.05$ is shown in Figure 3. On the other hand, the effects of sample length (T) and number of subjects (N) are presented in Figures 4 and 5, respectively.

The simulations evidence a good performance of the proposed statistical test. Figure 2 points toward a reasonable approximation of F-statistics null distribution for short length time series. This is a very important result, due to the length of BOLD time series. In many cases of periodic designs, the fMRI experiments have short sample length in order to avoid habituation effects. Further, Figure 3,4 and 5 show a fast increasing in the power of test, as the parameters N, T and β increase.

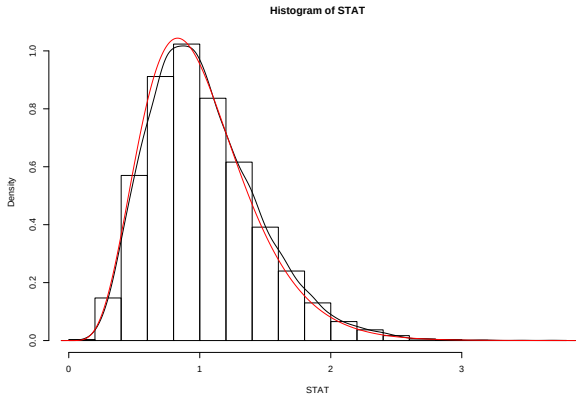

Figure 2: F-statistics empirically estimated probability density function (black line). The theoretical function is shown in the red line.

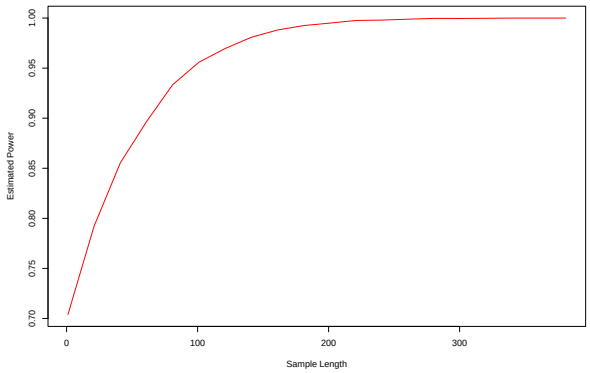

Figure 4: Test power as a function of time series length(T).

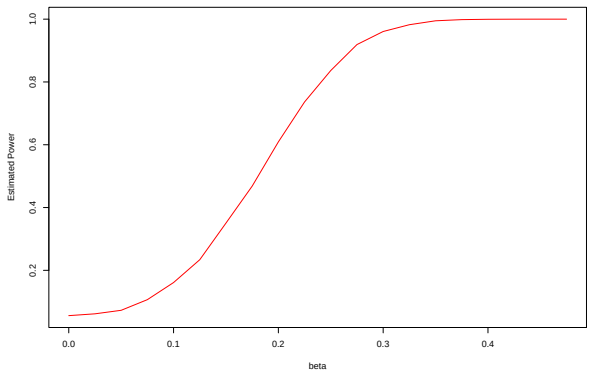

Figure 3: Test power as a function of energy in the fundamental frequency of activation(β).

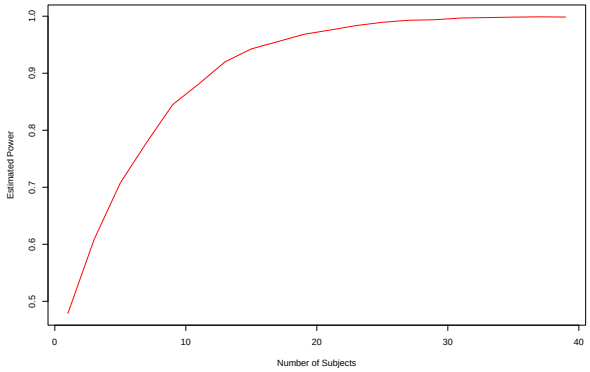

Figure 5: Test power as a function of the number of subjects(N).

4 Application to fMRI Data

In this section, we present the usefulness of the proposed method, illustrated with clinical application in an fMRI motor paradigm in both block and event-related designs.

Seven right handed [24] healthy volunteers, 4 male and 3 female, 36 to 75 yeas-old, were selected as controls for fMRI disease studies. They performed a simple motor task: self-paced finger tapping movement of dominant hand. The whole dataset have been acquired in the Radiology Institute of Clinical Hospital from University of S Paulo Medical School, in a 1.5T Signa LX scanner (GE, Milwaukee, USA), equipped with 23 mT/m gradients and echo-planar capability, with a head coil. The functional acquisitions were based on a 2D gradient eco EPI, TR 2000 / 3000ms, TE 40ms, FA 90, bandwidth 64 kHz, FOV 20cm, 64 x 64 pixels, 7 mm thick slices with 0.7mm gap between each of the 15 axial slices oriented according to the bicomissural plane. A total of 104 volumes were acquired (the first 4 were discarded later for T1 saturation effects).

Each block run consisted of 5 cycles with two epochs each (30 seconds of active movements and 30 seconds of rest) in response to a visual cue. In event related runs (10 trials), the subject was instructed to perform the task only once, in response to a verbal command, with an inter-stimulus interval of 20 seconds. The runs lasted 5min12sec for block runs (TR 3000 ms) and 3min8sec for event related runs (TR 2000 ms). The fundamental frequency of changes between the baseline and activation was 0.05TR for block design and 0.1TR for event-related.

The images were preprocessed considering motion realignment, slice time correction, and spatial normalization (SPM2, *http://www.fil.ion.ucl.ac.uk/spm/*) to the stereotatic space of Talairach and Tornoux[29], allowing multi subject analysis. The BOLD signal was detrended (polinomial of order 2) and also pre-whitened considering an AR(1) model in order to remove autocorrelation from the data [21, 33]. Note that this filter does not change the periodicity of the signal. Hence, 3D-brain activation maps were obtained considering the multisubject periodicity test.

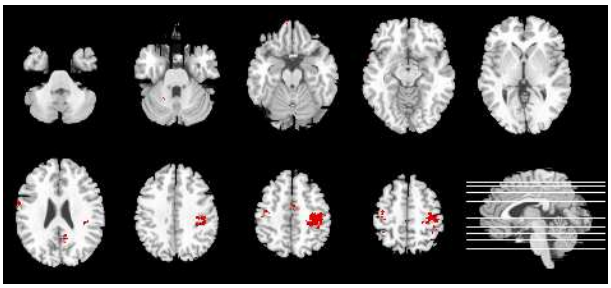

Figure 6: Block design: multi-slice activation maps (radiological notation).

According to block design activation map (Figures 6 and 7, voxel p-value=10^{-4}), we found more activated clusters in left primary sensorimotor cortex (SM1), followed by right SM1, and supplementary motor area (SMA). Smaller clusters were located in right cerebellar hemisphere (CER), and left inferior frontal and medial parietal secondary somatisensory areas (S2). In event related maps (Figures 9 and 10, voxel p-value=10^{-9}) there was a large number of activation clusters in left SM1, SMA, right CER, and left superior temporal gyrus. This pattern of activation was also found in classical fMRI motor studies with finger tapping, with is a simple task but with motor and sensory components [2, 15].

The primary motor cortex (M1, BA4) is located in the lateral pre-central gyrus and according to its somatotopic organization [25], hand is represented in the upper lateral segment. Its main function is to execute movements with the contralateral extremity muscles [22]. The primary sensitive cortex S1, BA 3a/b, BA 1 e BA 2) is posterior to M1, in the anterior boundary of post-central gyrus and paracentral

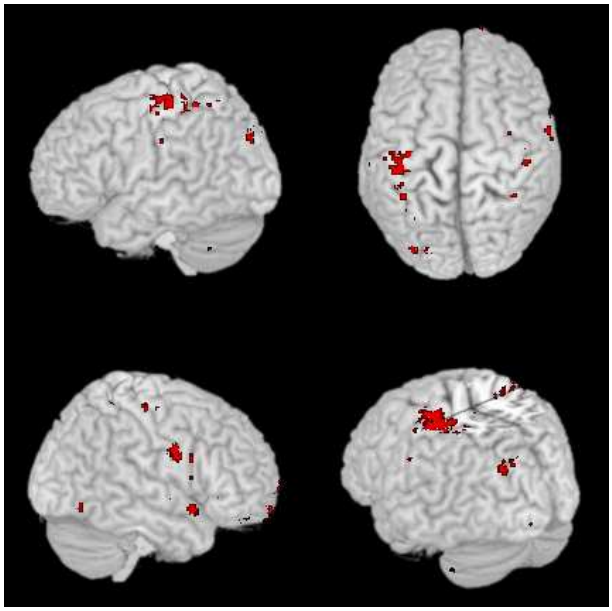

Figure 7: Block design: 3D-view activation maps.

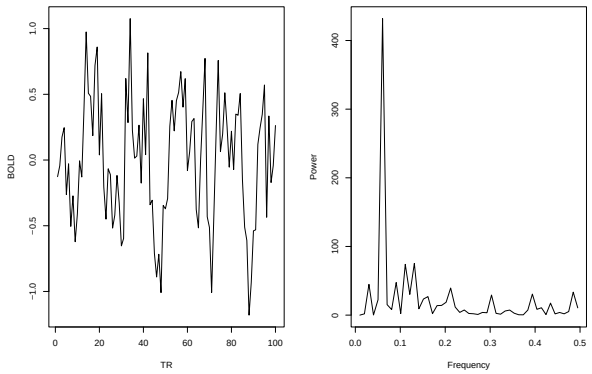

Figure 8: Block Design: Subjects mean time series corresponding to an active voxel in primary motor area and its periodogram.

lobule [22]. What we called SM1 comprises both primary motor and sensory area. In both designs, we had consistent activation in the SM1 contralateral to the movement. This was the main finding and highly correlated to the sensorymotor circuitry.

In block design we also found smaller clusters in the SM1 ipsilateral to the movement. The communication of hemispheres information is thought to be responsible for a reduction of the oxygenation, and consequently BOLD effect in this area, probably in order to give priority to the motor learning in the contralateral SM1 [16, 30, 1]. In our new method of analysis, the signal of BOLD change is not considered, just its periodicity along time, justifying the found activation.

The SMA (medial BA 6 aa) is located in the medial aspect of anterior paracentral lobule and superior frontal gyrus. It is related to the process of movement initiation, connecting moto-neurons, with a programming function [22]. It is activation in motor fMRI paradigm had already been established, and the extension of activation is related to the complexity of the task [26, 14]. We found this area activated in both paradigms, but with larger extension in the event related, what was expected since each movement required an individual programming, while in block design, only the first movement required, the following ones were automatically performed.

The cerebellum, in the posterior fossa, is a complex connectivity station, with holes in motor, somatosensory and cognitive tasks [27], with motor emphasis in the temporal and spatial extremity adjustment [34]. Activation in the anterior cerebellar hemisphere ipsilateral to the movement, similar to the ones found in this study, had been demonstrated with PET [9] and fMRI [1]. Also we found more cerebellar activation in event related than block design.

The S2 comprises the somatosensory association cortices: intramodal (anterior BA 7) in the superior

parietal lobule, and multimodal (posterior BA 7) in the pre-cuneus [22]. Some clusters were activated in these areas with block design, suggesting more sensory activity related to repetitive movements.

Finally, event related group map, we identify activation in left superior temporal gyrus, probably related to auditory task command [8]. In block group we found minimum amount of activation in medial occipital areas, probably related to visual command [7]. Figures 11 and 14 present the average time series of all subjects corresponding to an active voxel in primary motor area, respectively for block and event related designs.

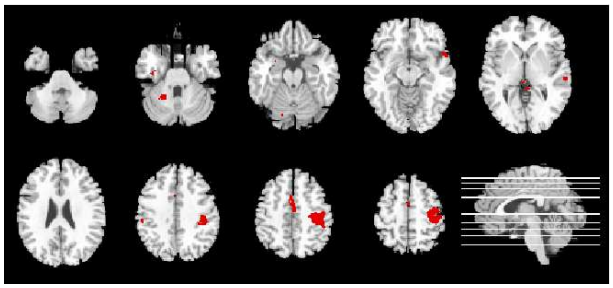

Figure 9: Event-related: multi-slice activation maps (radiological notation).

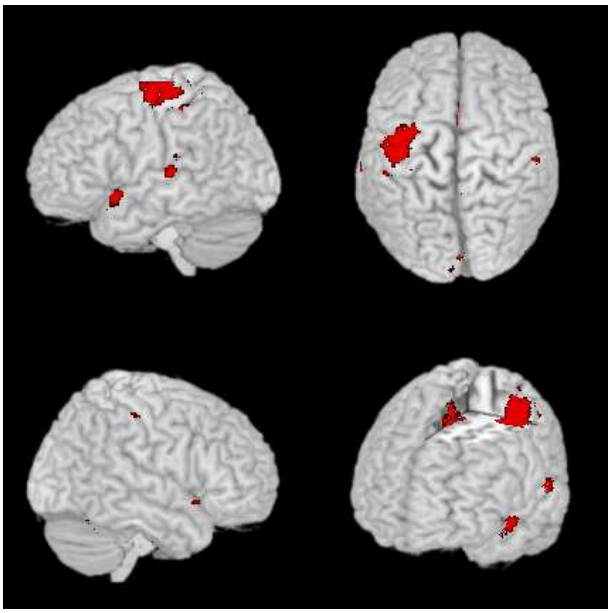

Figure 10: Event-related: 3D-view activation maps.

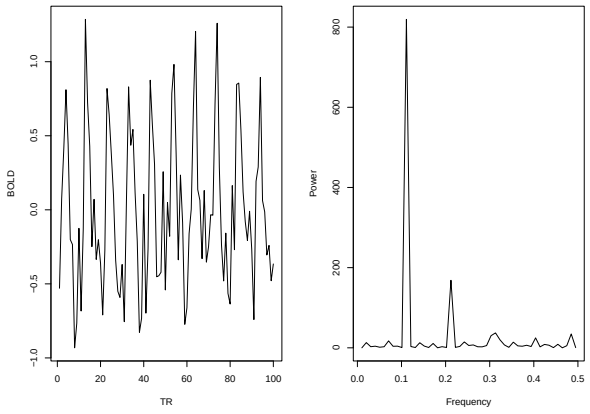

Figure 11: Event-related: Subjects mean time series corresponding to an active voxel in primary motor area and its periodogram.

5 Conclusion

Recently, the number of neuroscientific studies based on fMRI has been increasing fast. However, the quality of results relies on the choice of haemodynamic response function (HRF). In this paper, we propose a frequency domain multisubject approach, which is based solely in stimulus periodicities, avoiding subjective specification of HRF. The performance and usefulness of the new approach is evaluated by computing intensive simulations. We also present applications to fMRI datasets involving motor paradigm.

6 Acknowledgements

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