A novel method for spatio-temporal pattern analysis of brain fMRI data

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Received November 11, 2003; revised September 6, 2004

Abstract A novel data processing procedure for fMRI was suggested in this paper, by which spatial and temporal characteristics of stimuli-induced signal dynamic responses can be investigated simultaneously. First the multitaper spectral estimation was utilized to estimate the spectrum of each voxel; the significance of the line frequency components at the interested frequency was tested to detect the task-related cortex areas; the temporal independent component analysis (tICA) was then applied to the activated voxels to obtain stimuli-induced signal dynamic responses. The advantages of this procedure are: few assumptions are needed for the cerebral hemodynamics and spatial distribution of task-related areas, problems which often appear in tICA analysis of fMRI data, such as the lack of stability, reliability and robustness, are overcome by the suggested method.

Keywords: functional magnetic resonance imaging (fMRI), temporal independent component analysis (tICA), multitaper spectral analysis (MTM).

DOI: 10.1360/03yf0530

1 Introduction

Functional magnetic resonance imaging (fMRI) is a non-invasive brain imaging technique which has been utilized in brain function researches since the early 1990s[1]. However, it is often difficult to do analysis in fMRI data because of the low signal to noise ratio (SNR) (about 2%—4% with 1.5T magnetic field strength) and the delay within the true neural activity and the stimuli-induced signal dynamic responses.

The prevalent methods applied to fMRI data could be divided into two main categories: the hypothesis-driven techniques (such as statistical parameter mapping[2,3], correlation analysis, univariable *t*-test, etc.) and the data-driven techniques (such as independent component analysis, principal component analysis, etc.). When the former techniques are utilized, the model of the stimuli-induced signal responses must be specified and the results are usually highly related to the satisfaction to these assumptions. The assumptions about neural system model are not needed in data-driven multivariable statistical techniques, which utilize the statistical information of the data and are more adaptive and powerful than the model-driven techniques. Among data-driven techniques, independent component analysis (ICA), first suggested by Jutten and Hérault et al.[4], is a promising one. In applications ICA can be classified into spatial independent component analysis (sICA) and temporal independent component analysis (tICA) according to the assumptions about the actual physical model[5, 6]. sICA was first applied to fMRI data by Makeig[7] and McKeown et al.[8] and was prevalent from then on[9, 10]. sICA assumes that the spatial distribution of independent functional voxels in brain is sub-Gaussian while that of background noises is super-Gaussian. The generalizability of this assumption in different cortex areas is still in dispute[11,12]. Results have indicated that task-related cortex areas detected by sICA tend to confuse with the cortex areas where high density of capillaries are contained[12]. When tICA is utilized, no assumption is needed about the spatial distribution of functional brain areas and background noises, the physiological meaning of the model is clear and the results can be readily explained[5,6,10]. However, because of the high spatial dimension of the fMRI data, tICA algorithm is time-consuming, sensitive to SNR, and the convergence can hardly be assured even applied to single scan data. tICA alone as applied in brain function research is effective primarily in analyzing EEG data whose temporal dimension is much higher than its spatial dimension. tICA has been successfully utilized in spatial-temporal pattern analysis of human auditory cortical EEG data by Seifritz[13] and some unexpected hemodynamic characteristics of the cortical responses were discovered. At present there are two primary strategies to improve the tICA as applied in fMRI data analysis: one is to select some areas according to the prior knowledge to enhance SNR before tICA is applied[7]. In the other strategy, the cerebral cortex is partitioned into spatially non-overlapped areas to which tICA is applied separately, and task-related voxels are picked out with a low threshold then analyzed by tICA to detect task-related cortex areas[14]. In both strategies task-related voxels are pre-selected locally and subjectively; thus the objectivity and reliability of the results are suspectable to some extent. Better results are expected if the task-related voxels are pre-selected more objectively from the whole cerebral cortex.

This paper will suggest a novel procedure in which tICA and multitaper spectral analysis method (MTM) are unified to detect the spatio-temporal stimuli-induced responses of task-related brain areas reliably. The main idea of this procedure is: if the paradigm of fMRI experiment is block designed and some cortex areas are task-related, then the time courses of voxels in these areas will have a significant periodic component at the same frequency of task, which can be used as a criterion to pick up the task-related voxels. MTM suggested by Thomson[15, 16] was successfully used to investigate the long-term climate change[17] in 1995, and was first applied to fMRI data by Mitra[18] in 1999. MTM is utilized in this paper as the tool of spectrum estimation because of its robustness[17—19]. It can obtain the cerebral cortex activation maps and the corresponding significant values simultaneously. The characteristics of stimuli-induced responses can be obtained by applying tICA to the task-related cortex areas detected by MTM. Simulated data are generated to test the validity of the procedure suggested. Eight sets of fMRI data are analyzed by the procedure, and the spatio-temporal stimuli-induced responses of the task-related brain areas are successfully separated.

2 Description of procedure

The procedure consists of three steps. The first step is preprocessing, in which datasets were registered to eliminate the head movement artifacts, and then spatially smoothed with a $5\times5\times10$ mm full-width at half maximum (FWHM) Gaussian kernel[2,3]. In the second step, the spectrum of each voxels' time courses was estimated by MTM, and the significance of a task frequency component's existence was tested, task-related cortex areas were then detected with a proper threshold. In the third step, the stimuli-induced responses were separated by tICA from task-related cortex areas along with the relative activation maps at the same time.

Denote f_0 as the task frequency in the paradigm, T as number of scans, L as the number of slices, and let the resolution of each slice be $M\times N$. The time course of voxel at [m, n] of the lth slice is denoted as:

$$X_{l,m,n}=\left\{x_{l,m,n}(1),x_{l,m,n}(2),\cdots,x_{l,m,n}(T)\right\} \quad 1\leqslant l\leqslant L,\quad 1\leqslant m\leqslant M,\quad 1\leqslant n\leqslant N. \quad (1)$$

The spectrum estimated by MTM is 1)

$$Y^{(k)}{}_{l,m,n}(f)=\left|\sum_{t=1}^{T}v^{(k)}(t)x_{l,m,n}(t)e^{-i2\pi ft}\right|^2,\quad k=0,\cdots,K-1, \quad (2)$$

where the tapers $v^{(k)}(t)$ are the kth discrete prolate spheroidal sequences (DPSS, which can be generated by *dpss* function in Matlab), the number of the tapers is taken as $K=\lfloor 2T\omega\rfloor$. The last taper is eliminated in practice because it has worse spectral concentration properties.

If the sequences $X_{l,m,n}$ are assumed to contain a sinusoid of complex amplitude $\mu_{l,m,n}$ at frequency, then (2) can be written as

$$Y^{(k)}{}_{l,m,n}(f)=\mu_{l,m,n}V_k(f-f_0)+n_k(f),\quad k=0,\cdots,K-2, \quad (3)$$

1) Hu, D.W., Multiple-window statistical technique—from theory to applications, AIVRU memo, University of Sheffield, 1996, 15.

where $V_k(f)$ is the Fourier transform of the kth DPSS; $n_k(f)$ is the spectrum of noises, and can be assumed to be white in $[f_0-\omega,\ f_0+\omega]$. Thus, μ can be estimated by linear regression method at $f = f_0$,

$$\hat{\mu}_{l,m,n}(f_0)=\frac{\sum_k Y^{(k)}{}_{l,m,n}(f_0)V_k^*(0)}{\sum_k \left|V_k(0)\right|^2}. \tag{4}$$

In order to test the significance of a line frequency component, both the absolute value of $\hat{\mu}_{l,m,n}(f_0)$ and the ratio $\hat{\mu}_{l,m,n}(f_0)/n_k(f)$ need to be taken into account. A line frequency component at frequency f_0 would be considered to exist only when the absolute value of $\hat{\mu}_{l,m,n}(f_0)$ is significant compared to that of $n_k(f)$. If there is no more than one line frequency component in the short interval $[f_0-\omega,\ f_0+\omega]$, the significance of a non-zero $\hat{\mu}_{l,m,n}(f_0)$ can be tested by Fisher's statistic which are written as follows:

$$F_{l,m,n}(f_0)=\frac{(2K-\upsilon)\left|\hat{\mu}_{l,m,n}(f_0)\right|^2\left\|V(0)\right\|^2}{\upsilon\left\|Y(f_0)-\hat{\mu}_{l,m,n}(f_0)V(0)\right\|^2}, \tag{5}$$

where $V(0)=\{V_0(0),\cdots,V_{K-2}(0)\}$, $Y(f_0)=\{Y^{(0)}{}_{l,m,n}(f_0),\cdots,Y^{(K-2)}{}_{l,m,n}(f_0)\}$. For testing at a known frequency υ is 2, degree of freedom for this F-test is $(2, 2K-2)$[17,18]. $\left\{F_{l,m,n}(f_0)\right\}_{L\times M\times N}$ is a $L\times M\times N$ matrix to which a proper threshold (the significance is selected as 99% in our calculation) is set to detect the task-related cortex areas. Let P denote the number of voxels that have passed the test, a matrix X with $P\times T$ dimensions is constructed with the rows containing the time courses of these voxels. tICA algorithm is used to do analysis on X.

As is known, a voxel's hemodynamic signals measured by fMRI can be influenced by several factors such as respiration-induced and pulse-induced fluctuations, α- and β-rhythm, background noise and head movement artifact, etc. If a voxel belongs to a task-related cortex area, its hemodynamic signals also contain the stimuli-induced signal responses. It has been suggested that physiological noise is the dominant factor in fMRI studies[20]. Signal sources of all the factors can be effectively separated by tICA if they are independent of each other, referred to as $S=\{s_1,s_2,\cdots,s_Q\}^T$. If the voxels' hemodynamic signals are assumed to be linear mixtures of independent sources, then X can be written as $X = AS$, where A is a $P\times Q$ matrix modeling the linear mixture, and its inverse matrix, $W = A^{-1}$, is often called the unmixing matrix. In this paper tICA algorithm based on maximum likelihood estimation[21] with tanh(•) as the nonlinearity is applied to X.

By investigating the temporal architecture of each independent component, task-related components which reflect the characteristic of task-related cortex areas' dynamic responses can be picked out. The ith column of matrix A reflects the spatial distribution of the ith independent component, elements of the column indicate how strongly the corresponding voxels' hemodynamic signals are influenced by the independent component, the relative spatial distribution maps of an independent component can be obtained by transforming the corresponding column of matrix A into an image.

3 Simulated experiments

Simulated data is generated to test the validity of the procedure. Brain BOLD signal of a normal subject in rest is scanned, 100 fMRI images with resolution of 64×64 are collected and used as the background process. As is shown in fig. 1, two simulated activated areas (black and gray) are generated. A toothed and a square waves are added to the hemodynamic signals of voxels in black area, while in the gray area, only the square wave is added, the amplitudes of these waves are both 2% of mean baseline.

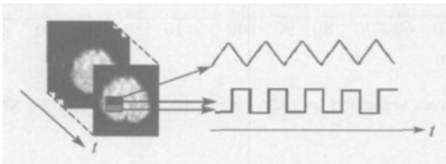

Fig. 1. Illustrative figure for simulated data generation.

An image picked out from the simulated data is shown in fig. 2(a). The absolute values of estimated spectrum at the task frequency (f_0) calculated by (4) are used to form an image shown in fig. 2(b). As can be seen, the spectral values of voxels in brain border area are approximate with those in simulated activated area, thus the activation maps cannot be obtained by simply thresholding this image. The image in fig. 2(c) is obtained by (5), which indicates the significance of a line frequency component's existence. Activation map shown in fig. 2(d) is obtained with significance of 99%, the activated excursion size is a little larger than the real one because the spatial resolution is reduced by the Gaussian smooth performed on the simulated data.

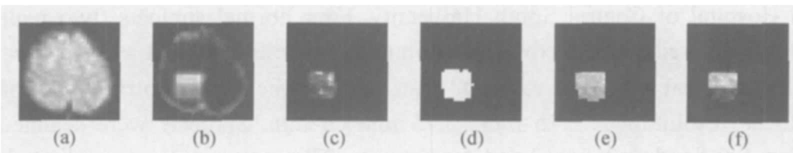

Fig. 2. Simulated data and the results. (a) is an image picked out from the simulated data, (b) is formed by the absolute values of estimated spectrum at the interested frequency calculated by (4), (c) is formed by the values calculated by (5), (d) is the 0-1 image by thresholding (significance of 99%) (c), (e) is the relative spatial distribution map for square wave, and (f) is the relative spatial distribution map for toothed wave.

When the SNR of the simulated data is 2%, the toothed and square waves separated by the suggested procedure are shown in fig. 3(a), and results under SNR of 4% are shown in fig. 3(b). As can be seen, when the SNR is enhanced, improvement of results is obvious. The relative spatial distribution maps of square and toothed waves detected under SNR of 2% are shown in fig. 2(e) and (f). If a voxel did not pass the *F*-test, the corresponding value in the relative spatial distribution map is set to 0. The relative spatial distribution map indicates not only the location of activation areas but also the strength of hemodynamic signal influenced by the independent component. The spatial distribution and temporal architecture of stimuli-induced signal responses then can be obtained by investigating the relative spatial distribution map and the independent components.

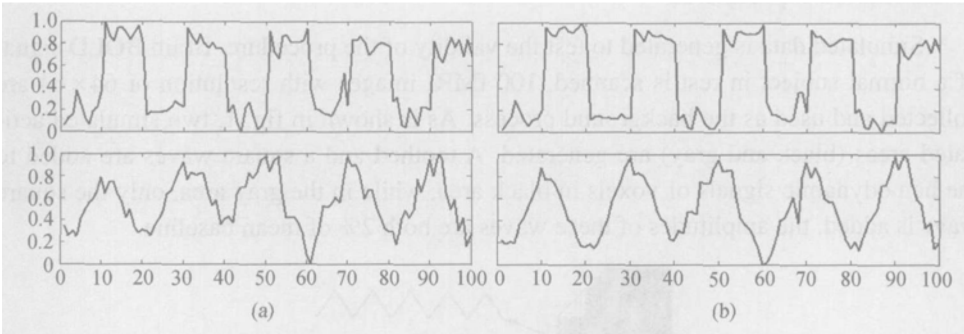

Fig. 3. Square and toothed waves separated by tICA. (a) is the results when the SNR is 2%, and (b) is the results when the SNR is 4%.

Simulated activation areas with the two artificial waves have been accurately detected by the suggested procedure. Although the results were influenced by the noises to some extent, the procedure is valid and stable when the SNR is between 2%—4% which is usual in real fMRI data. Simulation also indicates that if there are several independent signal dynamic responses in the same activation area, they can still be separated by the procedure. Because the spatial distributions of the toothed and square waves are partially overlapped, which violated the spatial independent assumption for sICA, they cannot be separated accurately either by sICA or by tICA individually.

4 fMRI experiment

Data were acquired in a GE Signa System operating at 1.5 Tesla at the Second Xiangya Hospital of Central South University. Four normal subjects (two males, two females) participated in the study. MR scanning parameters are: TR = 3 s, TE = 60 ms, gap = 1.5 mm. Total 8 datasets with 100 scans (16 oblique slices, matrix = 64×64) were acquired, the resolution is 3.75 mm$\times$3.75 mm$\times$5 mm. Subjects were scanned while performing left-hand and right-hand movements. The movements were elicited with a periodic design consisting of 5 blocks of 20 scans. Each block consisted of 30 seconds of baseline followed by 30 seconds of movement under visual cue. The whole experiment lasted 312 s. All the data were processed off line with the same set of parameters.

The results of 8 datasets are consistent with physiological knowledge. The result of one subject test is taken as an example. Two normalized responses induced by left hand movement are shown in fig. 4, the corresponding relative spatial distribution maps are shown in fig. 5. Signal dynamic responses shown in fig. 4(a) is generally called consistent task-related (CTR) component, and the corresponding cortex areas were constantly activated when task was performed, and returned to baseline when subject was in rest. The activated cortex areas shown in fig. 5(b) which contained the signal dynamic response shown in fig. 4(b) were remarkably activated at the beginning of the hand movement task and then returned to the baseline although the task was still going on, i.e. this kind of cortex area was only correlated with the beginning of tasks, and the corresponding signal dynamic response shown in fig. 4(b) was called transiently task-related (TTR) component. The CTR cortex areas include ipsilateral (activated in 6 datasets) and contralateral (activated in 8 datasets) sensorimotor cortex (M/S), supplementary motor area (SMA) (activated in 6 datasets), ipsilateral (activated in 6 datasets) and contralateral (activated in 4 datasets) cerebellum. Among all the CTR cortex areas, the contralateral M/S was the most activated areas measured either by size or by intensity. These results are consistent with the existing physiological experiments.

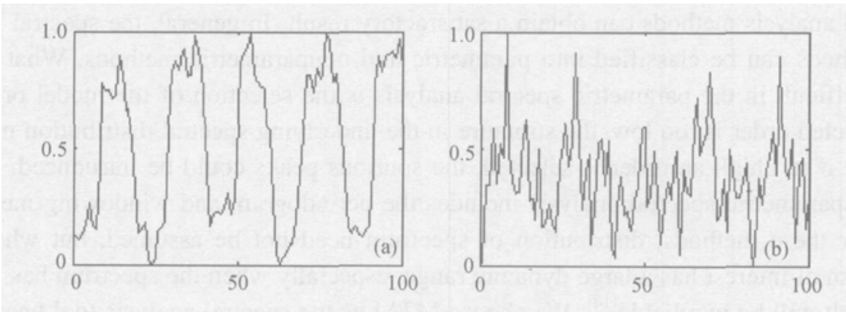

Fig. 4. The unit magnitude stimuli-induced signal dynamic responses of task-related cortex areas separated from one subject data. (a) The consistently task-related component; (b) the transiently task-related component.

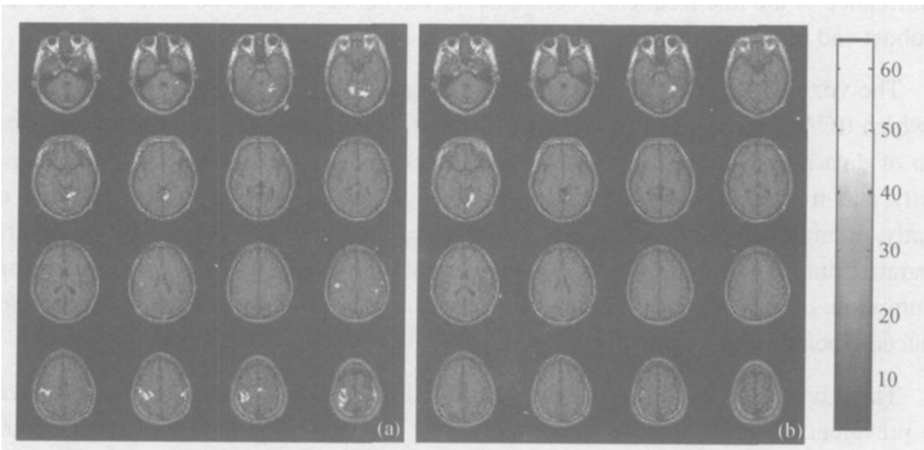

Fig. 5. Task-related cortex areas separated by the suggested procedure from one trail when the subject did a left hand movement task. The areas were marked by white in the brain images. (a) is the CTR cortex areas, and (b) is the TTR cortex areas.

TTR area, the ipsilateral cerebellum (activated in 3 datasets) is partially overlapped with CTR areas. Ipsilateral cerebellum participates in the accurate movement orientation, and the stimuli-induced signal response suggested that it may participate in preparation and startup of movement. SMA, as has been demonstrated by Roland[22], also participates in the preparation and startup of movement. The different characteristics of two areas' stimuli-induced signal responses suggested that the underlying mechanisms of movement's preparation and startup are different, on which further studies are necessary.

Except the contralateral M/S, the task-related cortex areas were not constantly activated in all the datasets, which may be relative to subject's physiological state, autecological difference and the SNR of experimental data[23,24].

5 Discussion

When the spectral analysis was used to detect the task-related cortex areas, the results would not be influenced by the delay of the signal response to the onset of task and the responses' concrete temporal architecture, so the hemodynamics need not to be assumed a prior, and the results would be more objective. As is well known, not all the spectral analysis methods can obtain a satisfactory result. In general, the spectral analysis methods can be classified into parametric and nonparametric methods. What is the most difficult in the parametric spectral analysis is the selection of the model order. If the selected order is too low, the structure in the underlying spectral distribution may be missed; if too high an order is selected, the spurious peaks could be introduced. While the nonparametric spectral analysis includes the periodogram and windowing methods, etc. For these methods, distribution of spectrum need not be assumed, but when the spectrum of interest has a large dynamic range, especially when the spectrum has peaks, the result will be unreliable[18]. We choose MTM as the spectral analysis tool because it is a good choice for capturing the "peaks" in the interested spectrum, furthermore the significance of the line frequency components' existence can also be tested and the result is robust and reliable.

The voxels picked out by the MTM are significantly activated, so the SNR of data to which tICA is applied is much higher than that of the raw data, and the spatial dimension of data is reduced greatly. This approach eliminates the illness of the data significantly and makes the stimuli-induced signal dynamic responses to be separated efficiently. It must be pointed out that the task-related cortex areas can be successfully separated only if their responses satisfied the temporal independent and non-Gaussian assumption, or the results will be unreliable. Temporal correlation of the tasks should be reduced when the paradigm is designed.

The advantages of the procedure suggested in this paper are obvious compared to the prevalent methods such as SPM[2, 3], sICA, tICA. For SPM, the cerebral hemodynamics, the architecture of stimuli-induced signal dynamic responses and distribution of background noises must be assumed, and the result is usually highly related to how well these assumptions are satisfied. The results obtained by sICA are difficult to be explained, tICA is time-consuming and sensitive to SNR. The task-related independent components could not be separated when tICA was directly applied to raw data. What is more, the spatial distribution, signal dynamic responses of the task-related cortex areas and the noises' distribution must be assumed when univariable *t*-test method, wavelet analysis etc. were utilized, and the stimuli-induced signal dynamic responses cannot be obtained by these methods. Stimuli-induced signal dynamic responses are important in the brain function research because it suggests the differences of underlying information processing mechanism of cortex areas. Unifying the temporal and spatial information of cortex areas' signal response is helpful for finding new cerebral information processing mechanism. The procedure suggested in this paper is robust and less time-consuming. Task-related cortex areas can be detected with significance, together with the stimuli-induced signal dynamic responses, so more information can be obtained by the proposed procedure. The procedure will be a helpful tool for studying the temporal-spatial information processing mechanism of neural networks in brain. The procedure can also be used to investigate the brain rhythm[25], and good results are expected if it is applied to EEG[13] and functional optical imaging (OI) data.

Acknowledgements This work was supported by the National Science Fund for Distinguished Young Scholars (Grant No. 60225015), the National Natural Science Foundation of China (Grant Nos. 30370416, 30100054), the Ministry of Science and Technology of China (Grant No. 2001CCA04100), and the Ministry of Education of China (TRAPOYT).

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