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Statistical Methods for Detecting Activated Regions in Functional MRI of the Brain

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６．要約

機能的磁気共鳴画像法（fMRI）の賦活領域特定に用いる統計解析法について２つの方法を提示する。最初の解析法（t test）は Gaussian ノイズ中に含まれる既知の賦活信号の特定に関し、その特徴を有した。また、この解析結果は、fMRI 領域で広く用いられている cross-correlation 法と同じであった。２つ目の解析法（F test）は Gaussian ノイズを附加した既知の低次元部分空間中に含まれる未知の賦活信号をモデル化することに関し、その特徴を有した。モデル化に際し周期的な賦活・安静パラダイムを用い、フーリエ級数を使用した。F test の特徴は、パラダイムが周期性を持つことが必要という条件以外には、hemodynamic 遅延に関して何らの仮定を必要としない点にある。両者を用いて実際の画像解析を行い、その結果を比較した。

７．研究目的

In a typical functional magnetic resonance imaging (fMRI) experiment, blocks of baseline and activation images are scaned periodically while the subject is at rest (or some other "baseline" condition), and while the subject is performing a specified motor or cognitive task or is receiving a given sensory stimulus. The image series must then be analysed in order to detect those picture elements (pixels) that show significant responses to the activation-baseline pattern. This paper presents two statistical tests that can be used to perform this task.

The first test is called the *t* test. This is the optimal solution to the problem of detecting a known activation signal in a time series when it is embedded in white Gaussian noise. The results of this test are known to be equivalent to the cross-correlation method that is widely used for activation detection in fMRI [1].

The second test is the optimal solution when the measured data is modeled as an unknown activation signal that lies in a known subspace of the measurement space and has additive white Gaussian noise. This is called the *F* test. Also, a model for the signal subspace based on a truncated Fourier series is proposed for periodic activation-baseline paradigms. The advantage of this second method is that it does not assume any information about the shape or delay of the activation signal except that it is periodic and has the same period as the activation-baseline pattern. This makes it easier to apply this test in comparison to the t test or cross-correlation methods.

These tests are not new and have been applied to areas as diverse as sonar and radar signal detection. This paper serves as a compact review of the methods in the context of fMRI brain mapping and should serve as a useful reference for researchers in this area. Both problems are special cases of the general linear model that has recently been applied to funtional brain mapping [2], [3].

８．材料と方法

In order to test the algorithms presented in the paper, the two models were applied to sets of fMRI motor activation data. The data was collected with a 1.5T whole body system (Siremens Magnetom Vision, Erlangen, Germany) with a standard head coil. All studies were approved by the institutional review board at the Research Institute for Brain and Blood Vessels, and proper informed consent was obtained from all subjects.

The activation task consisted of flexing and stretching digits 2-5 on a flat plastic surface within a fixed 2.5cm distance without moving the wrist. Subjects wore headphones so that the frequency of finger movement could be paced by the metronomic sounds created by software on a Macintosh computer. Functional imaging consisted of a single-shot, blipped, and echo-planar pulse sequence. The acquisition time for a 128 x 128 slice was 96ms. Each frame consisted of five axial slices with a slice thickness of 3mm and a slice gap of 0.75mm. A scan consisted of 120 sequential frames (600 slices in total) centred 5cm above the axial plane containing the anterior and posterior commissures line (AC-PC line). The echo time (TE) was 67ms, and the interframe interval (TR) was 3sec, yielding a total scan time of 6 minutes. Subjects were instructed to keep their eyes open throughout the studies. They were provided with instructions and were allowed to practice before the scanning session. After an initial 60sec rest period, the motor task was performed for 15sec (5 activation frames) followed by a 15sec rest (5 baseline frames). Thus, a total of 10 frames were acquired during each 30sec

period (T=10). The 20 frames that were acquired during the initial 60sec rest period were discarded in order to ensure that the level of net magnitisation had reached a sufficiently steady state. This left N=100 frames that contained 10 activation-baseline cycles. The average intensity image of the remaining 100 frames was computed and subtracted from each individual frame. In addition, a linear drift component was estimated using linear regression and subtracted from the data at each pixel. No motion correction was applied to the data before processing.

An activation map was computed for the *t* test by calculating the *t* statistic for the time-series collected at each pixel of the functional image. In computing the *t* values the known activation signal was taken to be a delayed version of the square-wave stimulus paradigm. The test was repeated 5 times with delays of 0, 1, 2, 3, and 4 frames. The activation map was thresholded at a significance level of 0.01 according to the Student *t* distribution. This final result is called a *t* map.
Similarly, an *F* map was obtained by calculating the *F* statistic for each time-series in the image and then thresholding at the *F* value corresponding to the 0.01 significance level of the *F* distribution.

９．結果

All subjects studied for this paper consistently showed activation in the motor cortex region of the brain. However, as the emphasis of this paper is on methodology, the physiological implications of the results are left as a subject for future writing.
Figures 1a-e show the results of the *t* test applied to a single slice from one of the subjects for each of the five different delays. The *t* map is clearly sensitive to the delay that is unknown and may vary from region to region. Additionally, the shape of the reference activation signal may not be the presumed square wave and it may also vary from region to region. Moreover, both the shape and delay of the activation signal may vary with the activation task. These shortcomings apply equally well to both the t test and the cross-correlation methods.

Figure 1f shows the activated pixels obtained using the *F* test. There seems to be little difference between this result and those obtained from the *t* test with delays of 1 and 2, although the *t* map appears to have slightly more spurious solitary activated pixels. These may be pixels where the test has incorrectly declared the pixel to be activated. The clear advantage of the *F* test is that it does not require the activation signal or delay to be explicitly specified.

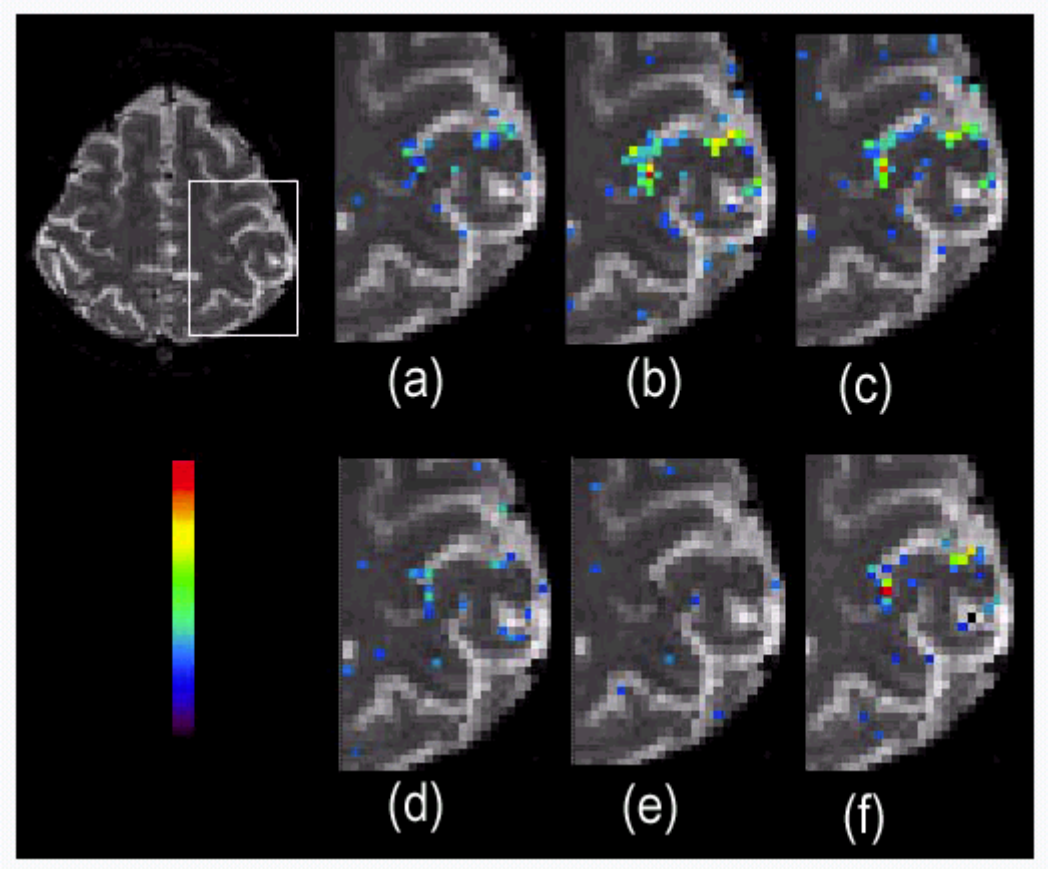

Fig. 1: (a)-(e) *t* maps (significance level 0.01) for delays of 0, 3, 6, 9, and 12 secs, respectively. (f) *F* maps (significance level 0.01) with a signal subspace dimension of 6.

In order to gain more insight into the *F* test, Figs. 2 a and b plot the time-series from an active and inactive pixel, respectively. Also included in the figures is the component of the time-series that is contained in the signal subspace. It can be seen that for the activated pixel, much of the total energy of the observed fMRI time-series is contained in the signal subspace. This is not the case for the inactive pixel. In other words, the trigonometric Fourier series model does a better job of explaining the variation in an active pixel than in an inactive pixel. In both cases, however, the variance of the residual is about the same.

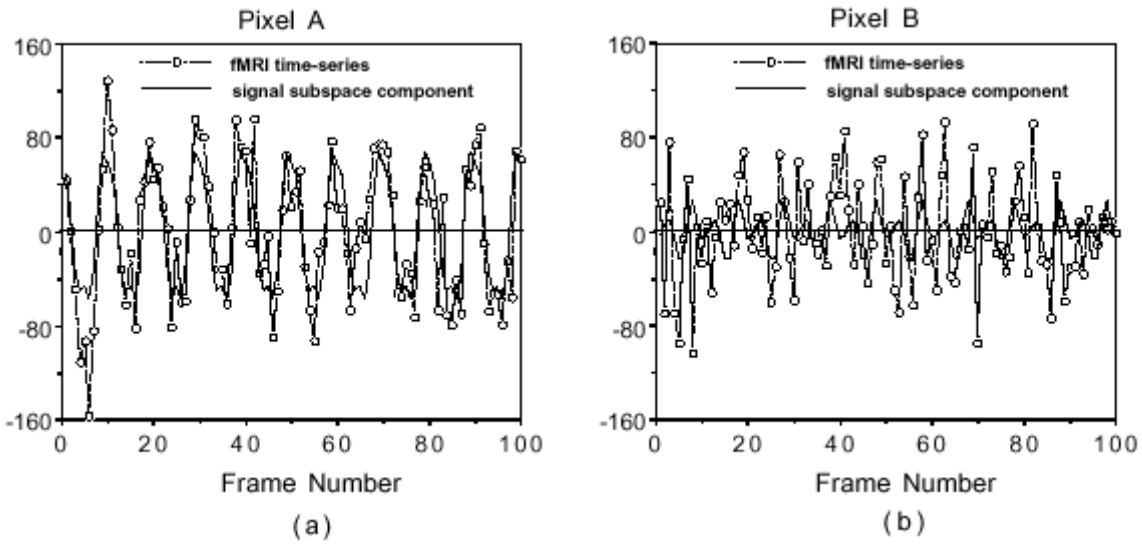

Fig. 2: Observed fMRI time series and its computed signal subspace component for (a) an activated pixel, and (b) an inactive pixel.

10. 考察

Two statistical tests for detecting activated pixels in fMRI brain activation studies were presented. The *t* test is equivalent to the cross-correlation method. The disadvantage of the *t* test and cross-correlation methods is that the shape and delay of the activation signal must be known a priori. On the other hand the *F* test does not require explicit knowledge of the activation signal. It only needs a subspace within which the signal is presumed to lie. In this paper such a subspace was specified for experiments that have a periodic stimulus paradigm.

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13. 研究業績

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13-2. 総説など：なし

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19. Abstract

Two statistical tests for detecting activated pixels in functional MRI (fMRI) data are presented. The first test (t test) is the optimal solution to the problem of detecting a known activation signal in Gaussian white noise. The results of this test are shown to be equivalent to the cross-correlation method which is widely used for activation detection in fMRI. The second test (F test) is the optimal solution when the measured data is modeled to consist of an unknown activation signal which lies in a known lower dimensional subspace of the measurement space with added Gaussian white noise. A model for the signal subspace based on a truncated trigonometric Fourier series is proposed for periodic activation-baseline imaging paradigms. The advantage of the second method is that it does not assume any information about the shape or delay of the activation signal, except that it is periodic with the same period as the activation-baseline pattern. The two models are applied to experimental echo-planar fMRI data sets and the results are compared.

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STATISTICAL METHODS FOR DETECTING ACTIVATED REGIONS IN FUNCTIONAL MRI OF THE BRAIN

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Two statistical tests for detecting activated pixels in functional MRI (fMRI) data are presented. The first test (*t*-test) is the optimal solution to the problem of detecting a known activation signal in Gaussian white noise. The results of this test are shown to be equivalent to the cross-correlation method that is widely used for activation detection in fMRI. The second test (*F* test) is the optimal solution when the measured data are modeled to consist of an unknown activation signal that lies in a known lower dimensional subspace of the measurement space with added Gaussian white noise. A model for the signal subspace based on a truncated trigonometric Fourier series is proposed for periodic activation–baseline imaging paradigms. The advantage of the second method is that it does not assume any information about the shape or delay of the activation signal, except that it is periodic with the same period as the activation–baseline pattern. The two models are applied to experimental echo-planar fMRI data sets and the results are compared. © 1998 Elsevier Science Inc.

Keywords: **Brain; Functional MRI; Statistical analysis; Detection theory.**

INTRODUCTION

Functional magnetic resonance imaging (fMRI) employs fast MRI techniques such as echo-planar imaging[1] (EPI) in order to detect changes in local cerebral blood flow and oxygenation levels elicited by neuronal activity. The technique hinges upon the sensitivity of the magnetization decay rates to changes in physiological conditions. For example, the decay rate T_2^* has a blood oxygenation level dependence (BOLD).[2] Apparently, the increase in blood flow in activated areas of the brain exceeds the corresponding increase in oxygen consumption. Thus, venous blood has an elevated oxygen content resulting in an increased T_2^* and a corresponding increase in the intensity of T_2^*-weighted MRI.

In a typical fMRI experiment, blocks of baseline and activation images are scanned periodically while the subject is at rest (or some other "baseline" condition) and when the subject is performing a specified motor or cognitive task or receiving a given sensory stimulus. The image series must then be analyzed in order to detect the picture elements (pixels) which show significant responses to the activation–baseline pattern. We present two statistical analysis methods that can be used for this purpose. Currently a widely used method for detecting activated pixels in fMRI data is the cross-correlation method.[3] In this method, one computes the cross-correlation between the measured time-series and a reference activation signal. Those pixels that show high correlations are declared to be activated. The main drawback of this method is that the cross-correlation coefficients depend on the shape of the activation signal (the hemodynamic response), which is unknown. One approach to overcoming this problem is to model the activation signal to be the output of a linear time-invariant (LTI) system whose input is the activation–baseline pattern.[4–6] The problem of estimating the unknown activation signal is therefore reduced to the problem of estimating the unknown parameters of the impulse response function of the LTI system. However, LTI systems may not be able to adequately model the dynamics of the activation signal. The reason for this statement is that when the activation–baseline pattern is a square wave (i.e., the num-

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ber of activation images equals to the number of baseline images during each activation–baseline cycle), its Fourier series only contains odd harmonics. Therefore, when this waveform is applied to the input of an LTI system, the output should not contain even harmonics. Nevertheless, published results in the literature show that hemodynamic responses to square wave activation–baseline patterns clearly contain strong second harmonic components.[3,5,7] These results appear to contradict the basic property of LTI systems mentioned above.

In this paper, we present and apply two statistical methods for detecting activated pixels in fMRI data. The first method assumes that the measured time-series at each pixel consists of a known activation signal in Gaussian white noise. The optimal solution to this problem is shown to be a *t*-test, which is shown to be equivalent to the cross-correlation method. In the second approach, the activation signal component is assumed to be unknown but to lie in a known signal subspace. The optimal solution for this model is given in terms of an *F* test. Another aim of this paper was to show that for periodic activation–baseline patterns, this method does not require explicit knowledge of the activation signal. Hence, it is easier to apply as compared to the first method or the cross-correlation method. These tests are of course not new and have been applied to areas as diverse as sonar and radar signal detection. This paper serves as a compact review of the methods in the context of fMRI brain mapping and should serve as a useful reference for researchers in this area. Both problems are special cases of the general linear model which has been applied to functional brain mapping by Friston et al.[8] They also derive an *F*-statistic but state that *F*-maps "are seldom employed as direct-tests of hypotheses. . . " Nevertheless, as stated above, the *F* test is the optimum test for detecting an unknown signal in Gaussian white noise when the signal lies in a known signal subspace. See chapter 4 of Scharf.[9] An example of the application of *F* statistics in functional brain mapping is given by Büchel et al.[10] for finding brain regions where significant relationships exist between regional cerebral blood flow and word presentation rate in positron emission tomography (PET).

THEORY

Let the discrete random sequence $x[n]$ ($n = 0,1,\ldots, N-1$) represent the "observed" fMRI measurements at a given pixel after estimating and removing the mean and a drift component and possibly applying preprocessing steps such as motion correction. The total number of samples in the sequence, N, is equal to the number of frames scanned during the fMRI experiment. The observed sequence is assumed to be of the form:

$$x[n] = \mu s[n] + e[n], \tag{1}$$

where $s[n]$ is a zero-mean deterministic (non-random) activation signal at the pixel under consideration, μ is a non-negative constant factor, and $e[n]$ represents added Gaussian white noise with variance σ^2 ($e[n]$: $N[0,\sigma^2]$). Eq (1) can be written in vector notation as follows:

$$\mathbf{x} = \mu\mathbf{s} + \mathbf{e}, \tag{2}$$

where $\mathbf{x}$, $\mathbf{s}$, and e are N-dimensional vectors that are represented by $N \times 1$ (column) matrices.

When $\mu = 0$, the pixel is not activated and the observed sequence is merely noise ($\mathbf{x} = \mathbf{e}$). When $\mu > 0$, the pixel is said to be activated. Therefore, given the observed sequence $x[n]$ and the model of Eq. (2) the problem of deciding whether or not the pixel under consideration is activated reduces to testing the null hypothesis $H_0{:}\mu = 0$ versus the alternative hypothesis $H_1{:}\mu > 0$.

This paper presents optimal threshold tests for the problem described above under two special cases: 1) when the activation signal $\mathbf{s}$ is assumed to be known and 2) when $\mathbf{s}$ is unknown but is assumed to lie in a known M-dimensional signal subspace of the N-dimensional measurement space ($M < N$).

Case 1a: Known Signal $\mathbf{s}$ *in Noise of Known Variance* σ^2

The signal model given in Eq. (2) implies that the random sequence $\mathbf{x}$ has a multivariate Gaussian density function with mean $\mu\mathbf{s}$ and covariance matrix $\sigma^2\mathbf{I}$, where $\mathbf{I}$ denotes the identity matrix. This probability density function (pdf) has the form:

$$f_{\mathbf{x}}(\mathbf{x}) = \frac{1}{(2\pi\sigma^2)^{(N/2)}} \exp\left[-\frac{1}{2\sigma^2}(\mathbf{x} - \mu\mathbf{s})^{\mathrm{T}}(\mathbf{x} - \mu\mathbf{s})\right]. \tag{3}$$

Assuming that the activation signal $\mathbf{s}$ and the noise variance σ^2 are known, $f_{\mathbf{x}}(\mathbf{x})$ is fully determined by the single parameter μ. Our objective is to decide between $H_0{:}\mu = 0$ and $H_1{:}\mu > 0$ based on the measured sequence $\mathbf{x}$. All the useful information that $\mathbf{x}$ carries about the parameter μ can be expressed in terms of a single random variable, a *sufficient statistic* for μ, given as follows:

$$z = \frac{\mathbf{s}^T\mathbf{x}}{\sigma\sqrt{\mathbf{s}^{\mathrm{T}}\mathbf{s}}} \tag{4}$$

Since z is obtained by a linear operation on $\mathbf{x}$, it also has a normal distribution with mean $\mu\sqrt{\mathbf{s}^{\mathrm{T}}\mathbf{s}}/\sigma$ and variance 1

(z:$N[\mu\sqrt{\mathbf{s}^T\mathbf{s}}/\sigma,1]$). Under the null hypothesis H_0 ($\mu = 0$), the z statistic has a standard normal distribution $N[0,1]$. Thus, assuming σ^2 is known, activated pixels can be detected by computing the statistic z from Eq. (4), and declaring a pixel activated if z is greater than a given threshold z_0. This may be denoted as the z test. For a given threshold level z_0, the probability of a false alarm or a type I error (the probability of declaring a pixel activated when it is in fact not) is given by:

$$\alpha = \frac{1}{\sqrt{2\pi}} \int_{z_0}^{\infty} \exp(-u^2/2)du. \tag{5}$$

In practice, the threshold value z_0 is chosen so that Eq. (5) gives a small probability of false alarm.

The *power* of the test, β, is defined as the probability of correctly rejecting H_0 when H_1 is in force. It is one minus the probability of a type II error. When H_1 is in force, z:$N[\mu\sqrt{\mathbf{s}^T\mathbf{s}}/\sigma,1]$ and for a given threshold z_0, the power of the test is given by:

$$\beta = \frac{1}{\sqrt{2\pi}} \int_{z_0}^{\infty} \exp[-(u - \mu\sqrt{\mathbf{s}^T\mathbf{s}}/\sigma)^2/2]du. \tag{6}$$

Unfortunately, since μ is not known, β cannot be determined. However, it can be shown that for a given fixed z_0 (or alternatively α) and for all $\mu > 0$, the z test has a power (β) greater than or equal to the power of any other threshold test whose type I error probability is less than or equal to α.[9] Such a test is said to be uniformly most powerful (UMP) of size α.

Case 1b: Known Signal **s** *in Noise of Unknown Variance*

In general, we do not know the noise variance σ^2 that may vary from pixel to pixel. Therefore, z cannot be computed using Eq. (4). To overcome this problem, one can substitute the following estimate $\hat{\sigma}^2$ for σ^2 in Eq. (4):

$$\hat{\sigma}^2 = \mathbf{x}^T(\mathbf{I} - \mathbf{P}_s)\mathbf{x}/(N - 3) \tag{7}$$

to obtain the new statistic t given as follows:

$$t = \frac{\mathbf{s}^T\mathbf{x}}{\hat{\sigma}\sqrt{\mathbf{s}^T\mathbf{s}}}. \tag{8}$$

$\mathbf{P}_s$ is the $N \times N$ projector matrix

$$\mathbf{P}_s = \frac{\mathbf{s}\mathbf{s}^T}{\mathbf{s}^T\mathbf{s}}. \tag{9}$$

The vector $\mathbf{P}_s\mathbf{x}$ gives the projection (component) of $\mathbf{x}$ in the direction of $\mathbf{s}$. Thus, $(\mathbf{x} - \mathbf{P}_s\mathbf{x})$ is the component of $\mathbf{x}$ which is orthogonal to $\mathbf{s}$. The sum of squares of elements of this vector is:

$$(\mathbf{x} - \mathbf{P}_s\mathbf{x})^T(\mathbf{x} - \mathbf{P}_s\mathbf{x}) = \mathbf{x}^T(\mathbf{I} - \mathbf{P}_s)\mathbf{x}, \tag{10}$$

where the right hand side is obtained using the fact that $\mathbf{P}_s$ is symmetric ($\mathbf{P}_s^T = \mathbf{P}_s$) and idempotent ($\mathbf{P}_s^2 = \mathbf{P}_s$). Dividing the right hand side of Eq. (10) by $N - 3$ yields the estimate $\hat{\sigma}^2$ given in Eq. (7). The divisor $N - 3$ is used because we are assuming that, in addition to the signal component $\mathbf{P}_s\mathbf{x}$, a mean and a drift component have been estimated and subtracted from the time-series. Therefore, the degrees of freedom are reduced by 3.

When the pixel is activated ($\mu > 0$), the statistic t defined in Eq. (8) will have a non-central t-distribution with $N - 3$ degrees of freedom and non-centrality parameter $\mu\sqrt{\mathbf{s}^T\mathbf{s}}/\sigma$. Under the null hypothesis H_0 ($\mu = 0$), the statistic t will have a central t-distribution with $N - 3$ degrees of freedom. It is important to realize that under H_0, the distribution of t is completely known even though σ^2 is unknown. That is, under H_0, t is invariant to σ^2. This allows us to define the following procedure for detecting activated pixels:

1. for each pixel, compute the statistic t from Eq. (8),
2. declare the pixel activated if t is greater than a given threshold t_0.

In this paper, the threshold test outlined above is denoted as the t-test. The probability of type I errors can be readily computed as follows:

$$\alpha = \int_{t_0}^{\infty} f_t(u)du, \tag{11}$$

where $f_t(u)$ is the Student's t pdf. In practice, t_0 is chosen in order to achieve a small probability of false alarm. The t-test outlined above can be shown to be UMP of size α which is invariant to the value of the noise variance σ^2.[9]

Case 2: Unknown Signal **s**

In this subsection, we consider the case when **s** is unknown but is assumed to lie in a known M-dimensional subspace of the measurement space. This subspace is denoted as the signal subspace. Let the signal subspace be spanned by the basis vectors $\mathbf{z}_k$ ($k = 1,2,\ldots,M$). Then, **s** can be written as follows:

$$\mathbf{s} = \sum_{k=1}^{M} a_k\mathbf{z}_k = \mathbf{Za}, \tag{12}$$

where $\mathbf{Z}$ is an $N \times M$ matrix with columns $\mathbf{z}_k$, and $\mathbf{a}$ is an $M \times 1$ vector with elements a_k which are said to be the coordinates of $\mathbf{s}$ with respect to the basis $\mathbf{Z}$. It is assumed that $\mathbf{Z}$ is known but $\mathbf{a}$ is unknown.

Let $\mathbf{P}_Z\mathbf{x}$ represent the projection of $\mathbf{x}$ into the signal subspace spanned by $\mathbf{z}_k$, where $\mathbf{P}_Z$ is the $N \times N$ projector matrix given as follows:

$$\mathbf{P}_z = \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T. \quad (13)$$

An efficient and robust numerical method for computing $\mathbf{P}_Z$ is to compute the left orthogonal matrix, $\mathbf{U}$, in the singular value decomposition of $\mathbf{Z}$,[11]

$$\mathbf{Z} = \mathbf{U}\mathbf{\Sigma}\mathbf{V}^T. \quad (14)$$

The projector matrix can then be expressed as $\mathbf{P}_Z = \mathbf{U}\mathbf{U}^T$.

The remaining component of $\mathbf{x}$ is $(\mathbf{I}-\mathbf{P}_Z)\mathbf{x}$ which is orthogonal to the signal subspace. The energy of $\mathbf{x}$ in the signal subspace is defined as:

$$\mathbf{x}^T\mathbf{P}_Z^T\mathbf{P}_Z\mathbf{x} = \mathbf{x}^T\mathbf{P}_Z\mathbf{x}, \quad (15)$$

where the right hand side of Eq. (15) is obtained using the fact that $\mathbf{P}_Z$ is symmetric and idempotent. The energy of $\mathbf{x}$ in the subspace orthogonal to the signal subspace is:

$$\mathbf{x}^T(\mathbf{I} - \mathbf{P}_z)^T(\mathbf{I} - \mathbf{P}_z)\mathbf{x} = \mathbf{x}^T(\mathbf{I} - \mathbf{P}_z)\mathbf{x}. \quad (16)$$

The ratio of energy in the signal subspace per dimension to the energy in the orthogonal subspace per dimension is given as follows:

$$F = \frac{\mathbf{x}^T\mathbf{P}_z\mathbf{x}/M}{\mathbf{x}^T(\mathbf{I} - \mathbf{P}_z)\mathbf{x}/(N - M - 2)}. \quad (17)$$

Intuitively, for activated pixels the energy per dimension in $\mathbf{P}_Z\mathbf{x}$ should be higher than the energy per dimension in $(\mathbf{I} - \mathbf{P}_Z)\mathbf{x}$. When the pixel is activated ($\mu > 0$), the statistic F would have a non-central F-distribution with M and $N - M - 2$ degrees of freedom and non-centrality parameter $\mu^2(\mathbf{Za})^T(\mathbf{Za})/\sigma^2$. Under the null hypothesis H_0 ($\mu = 0$), the statistic F would have a central F-distribution with M and $N - M - 2$ degrees of freedom. Again, the reason for subtracting the 2 extra degrees of freedom from the denominator is that we are assuming that a mean and a drift component have been estimated and subtracted from the time-series. It is important to realize that under H_0, the distribution of F is completely known even though σ^2 and $\mathbf{a}$ are unknown. That is, under H_0, F is invariant to σ^2 and $\mathbf{a}$. This allows us to define the following procedure for detecting activated pixels:

1. for each pixel, compute the statistic F from Eq. (17),
2. declare the pixel activated if F is greater than a given threshold F_0.

The above procedure is denoted as the F test. The probability of type I errors can be readily computed as follows:

$$\alpha = \int_{F_0}^{\infty} f_F(u)du, \quad (18)$$

where $f_F(u)$ is the F pdf. F_0 is chosen in order to achieve a small probability of false alarm. It can be shown that the F test outlined above is UMP of size α which is invariant to σ^2 and $\mathbf{a}$.[9]

Note that for the special case of the signal subspace dimension $M = 1$, $F = t^2$ and the F and t-tests are identical. The assumption of a one dimensional signal subspace is equivalent to assuming that the shape and delay of the activation signal are known. Therefore, in this case, the F test does not present any advantage over the t-test.

In order to apply the F test, we are required to model the signal subspace by specifying the basis vectors $\mathbf{z}_k$ ($k = 1,2,\ldots, M$). In this paper, a signal subspace is proposed that is suitable for those experiments in which the pattern of activation–baseline paradigm is periodic, say with a period of T scans. The fundamental assumption of the fMRI analysis model is that for such paradigms, the hemodynamic response is also periodic with the same frequency. This assumption is more relaxed than the LTI system model. That is, the "system" does not have to be an LTI system for this assumption to be true. Furthermore, the system is assumed to be low-pass (i.e., the activation signal does not contain high frequencies) which together with the periodicity assumption allows us to model the activation signal component as a truncated Fourier series with unknown Fourier coefficients. Thus, we obtain the following basis vectors $\mathbf{z}_k$ (assuming M is even):

$$\mathbf{z}_k = [1 \cos k\omega \cos 2k\omega \ldots \cos(N-1)k\omega]^T \cdot (k = 1, \ldots M/2) \quad (19)$$

$$\mathbf{z}_k = [0 \sin q\omega \sin 2q\omega \ldots \sin (N-1)q\omega]^T \cdot (k = M/2 + 1, \ldots M), \quad (20)$$

where $q = k - M/2$ and $\omega = 2\pi/T$. Note that in spite of their appearance, in general $\mathbf{z}_k$ are not mutually orthogonal. They are orthogonal if N is an integer multiple of T.

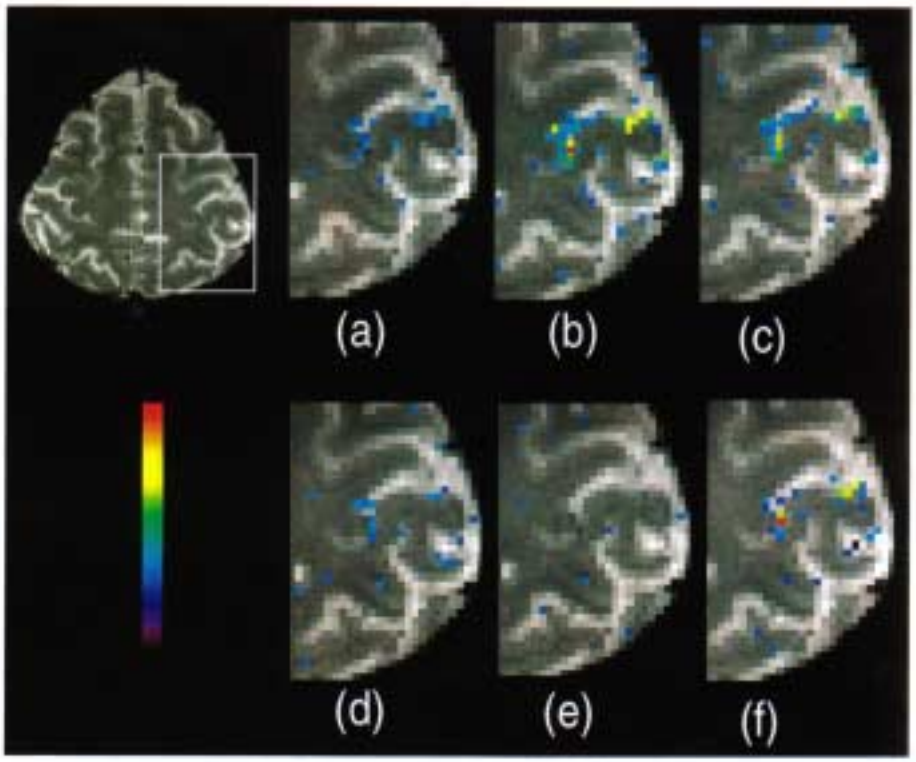

Fig. 1. (a)-(e) t-maps ($\alpha = 0.01$) for delays of 0, 3, 6, 9, and 12 s, respectively. (f) F-map ($\alpha = 0.01$; $M = 6$).

However, in this paper we do not make such an assumption.

This choice of the signal subspace has been previously applied to fMRI data analysis by Bullmore et al.[7] However, they suggested a non-parametric testing method for obtaining the significance of the activated pixels, as opposed to the F test proposed in this paper. The theory presented in this paper is valid for any model of the signal subspace. The success of the detection algorithm depends on how well the actual activation signal can be expressed as a linear combination of the selected basis functions. In general, one must choose a signal model that best represents the experimental conditions. See the work by Friston et al.[12] for an alternative set of basis vectors in terms of sine functions which ensure that the activation signal starts and ends with a value of 0 during each activation epoch.

MATERIALS AND METHODS

In order to test the algorithms presented in this paper, sets of fMRI motor activation data were utilized. The experiments were performed using a 1.5 T whole body system (Siemens Magnetom Vision, Erlangen, Germany) with a standard head coil. All studies were approved by the institutional review board at the Research Institute for Brain and Blood Vessels, and proper informed consent was obtained from all subjects.

The activation task consisted of flexing and stretching digits 2–5 on a flat plastic surface within a fixed 2.5-cm distance without moving the wrist. The frequency of finger movement was controlled by auditory pacing. Subjects wore headphones and were paced by metronome sounds created by software on a Macintosh computer. Functional imaging consisted of a single-shot, blipped, and echo-planar pulse sequence. The acquisition time for a 128 × 128 slice was 96 ms. Each frame consisted of five axial slices with a slice thickness of 3 mm and a slice gap of 0.25 mm. A scan consisted of 120 sequential frames (600 slices in total) centered 5 cm above the axial plane containing the anterior and posterior commissures line (AC-PC line). The echo time (TE) was 67 ms, and the interscan interval (TR) was 3 s, yielding a total scan time of 6 min. Subjects were instructed to keep their eyes open throughout the studies. They were provided with instructions and allowed to practice before the scanning session. After an initial 60 s rest period, the motor task was performed for 15 s (5 activation frames) followed by a 15 s rest (5 baseline

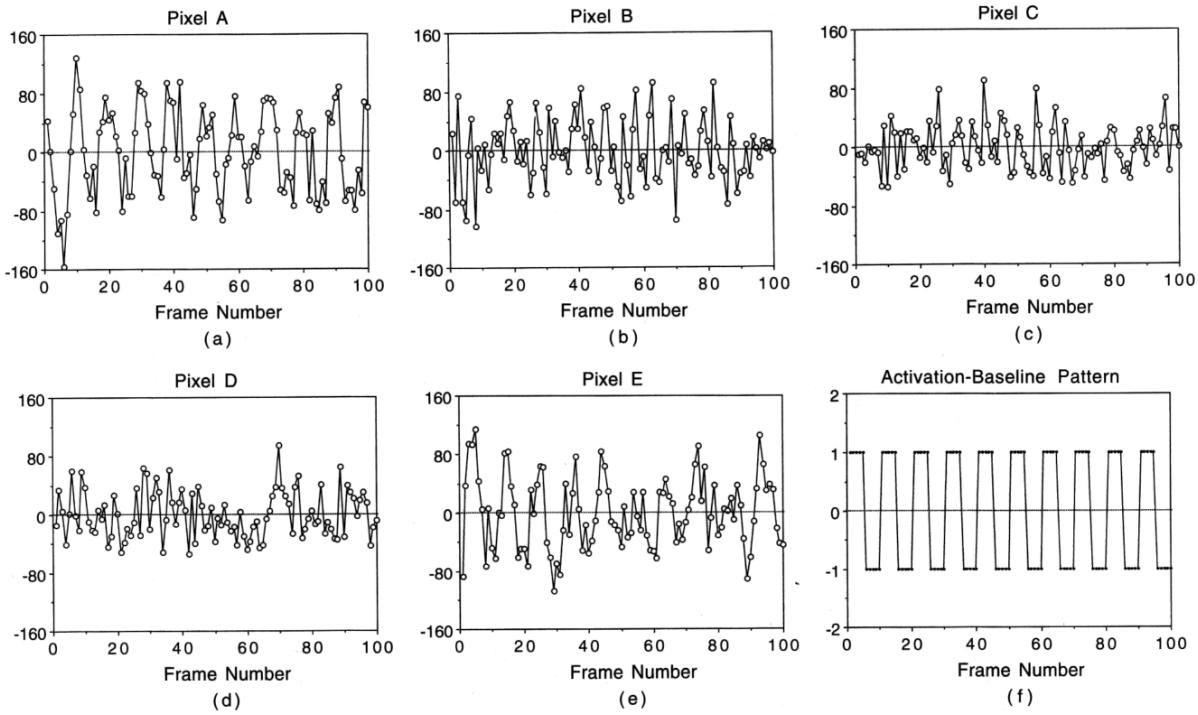

Fig. 2. (a)-(e) Observed fMRI time-series (x) for 5 different pixels. (f) Activation–baseline pattern ($T = 10$). Delayed versions of this pattern were used to model the activation signal s.

frames). Thus, a total of 10 activation and baseline frames ($T = 10$) were acquired during each 30 s period. The 20 frames that were acquired during the initial 60 s rest period were discarded in order ensure that the level of net magnetization had reached a sufficiently steady state. This left $N = 100$ frames that contained 10 activation–baseline cycles. The average intensity image of the remaining 100 frames was computed and subtracted from each individual frame. In addition, a linear drift component was estimated using linear regression and subtracted from the data at each pixel. No motion correction was applied to the data.

A "t-map" was obtained by computing the t statistic using Eq. (8) for all pixels. The t-map was thresholded to obtain the activated pixels. In computing the t values, the activation signal s was taken to be delayed versions of the square wave shown in Figure 2f. The t-test was repeated a total of five times using delays of $d = 0, 1, 2, 3$, and 4 frames with respect to x.

In the next step, we formed the $N \times M$ matrix $\mathbf{Z}$ with columns $\mathbf{z}_k$ and computed the projector matrix $\mathbf{P}_Z = \mathbf{U}\mathbf{U}^T$, where $\mathbf{U}$ is the left orthogonal matrix in the singular value decomposition of $\mathbf{Z}$. This computation need only be performed once, since the signal subspace is

Table 1. t and F values for time-series in Fig. 2

Pixel:	A	B	C	D	E
t ($d = 0$):	−2.02 (0.023)	−0.56 (0.287)	−0.86 (0.195)	−1.38 (0.086)	**3.6** (0.0002)
t ($d = 1$):	**−7.10** (10^{-10})	−1.88 (0.032)	0.55 (0.292)	0.13 (0.446)	**9.09** (10^{-14})
t ($d = 2$):	**−11.19** (10^{-19})	−1.39 (0.083)	−0.26 (0.399)	−0.68 (0.248)	**8.09** (10^{-11})
t ($d = 3$):	**−6.57** (10^{-9})	−0.96 (0.17)	−0.40 (0.345)	−1.84 (0.035)	**3.91** (10^{-4})
t ($d = 4$):	−1.45 (0.074)	0.01 (0.494)	0.29 (0.385)	1.05 (0.148)	0.13 (0.45)
F ($M = 6$):	**29.13** (10^{-19})	1.92 (0.085)	2.44 (0.031)	3.26 (0.006)	**20.26** (10^{-17})

Boldface font indicates significance at $\alpha = 0.001$ level.
Numbers in parentheses are significance levels.

taken to be the same for all pixels in the data set. Note that the dimension of the signal subspace, M, must always be less than or equal to T. Otherwise, $\mathbf{z}_k$ will not be linearly independent because the rank of $\mathbf{Z}$ is $\min(M,T)$.

Following the computation of $\mathbf{P}_Z$, we obtained an "F-map" by computing the F statistic using Eq. (17) for all pixels. The F-map was thresholded to obtain the activated pixels.

RESULTS AND DISCUSSION

Results from all subjects who were studied consistently showed activation in the motor cortex region of the brain. As the emphasis of this paper is on the methodology of obtaining the activation maps, we leave detailed interpretation of the results as a subject for future writing and concentrate here on methodological issues.

Figure 1a-e show the results of the t-test ($\alpha = 0.01$) in a single slice from one subject for the five different delays: $d = 0, 1, 2, 3, 4$. Clearly, the results are sensitive to the delay, which is unknown and may vary from region to region within the brain. Even if the most appropriate delay is known, it may not be possible to use it in computing the t values because we can only apply the delays in units of TR (3 s for the data presented in this paper). In addition to the unknown delay, the shape of the reference activation signal may not be the presumed square wave of Fig. 2f and it may also vary from region to region. Also, both the shape and delay of the activation signal may vary with the activation task. These shortcomings apply equally to both the cross-correlation method[3] or equivalently the t-test method presented in this paper.

Figure 1f shows the activated pixels obtained using the F test ($\alpha = 0.01$). There is little difference between the results obtained using the t-test at $d = 1,2$ (Fig. 1b and 1c) and the F test (Fig. 1f), although, the t-maps appear to be have slightly higher numbers of spurious single "activated" pixels. The clear advantage of the F test is that we do not have to specify the activation signal $\mathbf{s}$ or any delay. For periodic activation–baseline patterns, $\mathbf{s}$ is assumed to lie in the signal subspace $\mathbf{Z}$ defined by Eqs. (19) and (20). The value of M remains an option in our implementation of the algorithm. Its default value is set to $M = 6$ because there appears to be little power in the activation signal beyond the 3rd harmonic.[3,5,7] The maximum value that can be selected for M is T (in this Case 10) because the rank of $\mathbf{Z}$ equals to $\min(M,T)$ and if $M > T$, the matrix $\mathbf{Z}^T\mathbf{Z}$ will be singular and $\mathbf{P}_Z$ as defined in Eq. (13) cannot be computed. In the future, the use of model selection rules such as that based on the Akaike information criterion[13] (AIC) will be considered for selecting M.

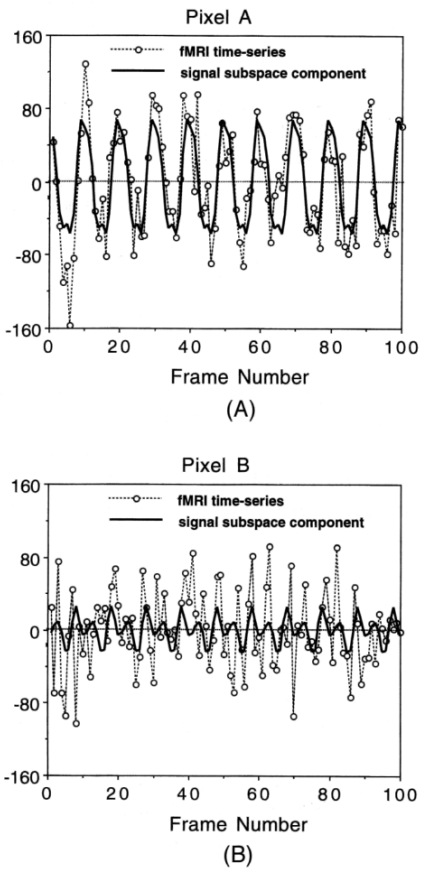

Fig. 3. Observed fMRI time-series ($\mathbf{x}$) and its computed signal subspace component for: (A) the activated pixel A in Fig. 2a; and (B) the non-activated pixel B in Fig. 2b.

In order to gain more insight into the algorithms, let us plot and examine the time-series of several selected pixels. The observed fMRI time-series ($\mathbf{x}$) are plotted for 5 different pixels (denoted as pixels A-E) in Fig. 2(a)-(e). Pixels B-D were chosen at random from the non-activated pixels (as declared by the F-test). Pixel A was chosen from the activated pixels (as detected by the F test) which showed opposite phase with respect to the activation–baseline pattern. Pixel E was chosen from the activated pixels which were in phase with the the activation–baseline pattern. The activated pixels were located in the primary motor area. The t values of these time-series are summarized in Table 1. The t values shown in boldface font pass the t-test at $\alpha = 0.001$ level ($t_0 = 3.18$). Pixels A and E pass the t-test at this level. These pixels, however, do not pass the test when the delay is $d = 4$ frames which corresponds to 12 s. Pixel A is also below the significance threshold when $d = 0$. The highest level of significance appears to be when the delay is between 3 to 6 s.

Table 2. *cc* values for time-series in Fig. 2

Pixel:	A	B	C	D	E
$d = 0$:	−0.2 (0.228)	−0.057 (0.286)	−0.087 (0.194)	−0.139 (0.085)	**0.347** (0.0002)
$d = 1$:	**−0.584** (10^{-11})	−0.188 (0.031)	0.056 (0.292)	0.014 (0.446)	**0.676** (10^{-16})
$d = 2$:	**−0.751** (10^{-21})	−0.142 (0.082)	−0.026 (0.398)	−0.07 (0.248)	**0.636** (10^{-13})
$d = 3$:	**−0.56** (10^{-10})	−0.099 (0.169)	−0.041 (0.345)	−0.186 (0.034)	**0.373** (10^{-4})
$d = 4$:	−0.149 (0.074)	0.002 (0.494)	0.03 (0.385)	0.108 (0.147)	0.013 (0.45)

Boldface font indicates significant *cc* ($\alpha = 0.001$).
Numbers in parentheses are significance levels.

To detect pixels that have highly significant negative t values (e.g., pixel A), we must use a two-tailed t-test. All our results remain valid for such a test, with the exception that now all pixels for which $\ldots t \ldots > t_0$ pass the test, and the threshold level is determined in a slightly different way as follows:

$$\alpha = 2 \int_{t_0}^{\infty} f_t(u)du. \tag{21}$$

This slightly increases the threshold to $t_0 = 3.39$ for $\alpha = 0.001$.

The F values of the time-series of Fig. 2 are also summarized in Table 1. The F values shown in boldface font are highly significant and easily pass the F test at $\alpha = 0.001$ level ($F_0 = 4.14$). The component of $\mathbf{x}$ in the signal subspace, $\mathbf{P}_Z\mathbf{x}$, is shown in Fig. 3 for the activated pixel A and the non-activated pixel B for $M = 6$. It can be seen that for the activated pixel, much of the total energy of the observed fMRI time-series is contained in the signal subspace. This is not the case for the non-activated pixel. In other words, the trigonometric Fourier series model does a better job of explaining the variation in an activated pixel than in a non-activated pixel. In both cases, however, the variance of the residual should be about the same.

Let us at this point compare the t-test outlined in the present paper with the cross-correlation method. There is a one-to-one correspondence between the cross-correlation coefficient *cc* given in Eq. (1) of Bandettini et al.[3] and our t statistic given in Eq. (8):

$$t = \mathrm{cc}\sqrt{N - N_o}/\sqrt{1 - \mathrm{cc}^2} \tag{22}$$

where N_0 is the reduction in degrees of freedom due to the number of free parameters in the model being employed (in our Case 3). This transformation can be obtained by using the relation $\mathbf{x}^T\mathbf{x} = \mathbf{x}^T\mathbf{P}_s\mathbf{x} + \mathbf{x}^T(\mathbf{I} - \mathbf{P}_s)\mathbf{x}$. The statistic *cc* is not normally distributed and strictly speaking, we cannot use Eq. (5) [or equivalently Eq. (13) of Bandettini et al.[3]] to obtain the significance threshold level. To test the significance of the *cc* values, they can be mapped using the *Fisher's Z* transformation[14] to

$$z = \frac{1}{2}\ln\frac{1 + \mathrm{cc}}{1 - \mathrm{cc}}. \tag{23}$$

The transformed statistic has an approximately normal distribution with mean 0 (under the null hypothesis) and variance $1/(N - 3)$.

The values of *cc* and their corresponding significance levels are compiled in Table 2 for the time-series in Fig. 2 and the five different delays. Comparison of Tables 1 and 2 reveals that the significance levels of *cc* and t values are almost identical for all pixels. Indeed for all practical purposes, the *cc* and t-tests can be considered equivalent.

In the present paper we have not considered spatial correlations in the image. The problem of how to make inferences based upon the t-maps and F-maps in the presence of spatial correlations has been addressed by Worsley.[15]

CONCLUSIONS

We have outlined two statistical tests for detecting activated pixels in fMRI brain activation studies. The t-test is equivalent to the cross-correlation method. The disadvantage of the t-test and cross-correlation methods is that, in order to apply them to fMRI activation detection, we must know the shape and delay of the activation signal $\mathbf{s}$. The F test does not require knowledge of s. On the other hand, the F test requires knowledge of a subspace in which $\mathbf{s}$ lies. In this paper, we proposed a subspace which is appropriate for experiments in which the activation–baseline imaging paradigm is periodic.

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