

A CORRELATION FRAMEWORK FOR FUNCTIONAL MRI DATA ANALYSIS

Ola Friman, Magnus Borga, Peter Lundberg[†] and Hans Knutsson

Department of Biomedical Engineering
Depts. of Radiation Physics and Diagnostic Radiology[†]
Linköping University
Sweden
olafr@imt.liu.se

ABSTRACT

A correlation framework for detecting brain activity in functional MRI data is presented. In this framework, a novel method based on canonical correlation analysis follows as a natural extension of established analysis methods. The new method shows very good detection performance. This is demonstrated by localizing brain areas which control finger movements and areas which are involved in numerical mental calculation.

1. INTRODUCTION

The functional processes of the human brain are still poorly understood although much effort has been focussed on revealing its secrets. A relatively new and promising tool for this purpose is functional magnetic resonance imaging (fMRI). The purpose of fMRI is to map sensor, motor and cognitive functions to specific areas in the brain. For example, one might be interested in which brain areas that are activated by a simple motor task such as flexing the fingers, or in higher cognitive functions such as areas for language processing or mental mathematical calculations. The physical basis of the method is that oxygenated and deoxygenated blood have different magnetic properties, a difference that can be measured in an MR-scanner. More specifically, the signal intensity in a T2*-weighted MR image of the brain depends slightly on the local oxygenation level of the blood. This is called the blood oxygenation level dependent signal, commonly referred to as the BOLD signal. When neurons in the brain are active they consume oxygen. Blood with a higher level of oxygenation is supplied to the neurons to compensate for the increased oxygen consumption. However, the neurons can not utilize all supplied oxygen which results in an excess of oxygen in the venous vessels. Since T2*-weighted MR images partially reflect the blood oxygenation it is possible to analyze such images to detect areas of brain activity indirectly by localizing areas of elevated oxygen levels. To determine where elevations in oxygenation level occur during task performance baseline images acquired at a resting state are also required. For this reason

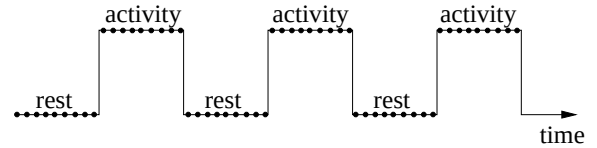


Fig. 1. A typical reference timecourse used in fMRI.

a reference timecourse is specified, where rest and task performance are alternated, see Fig. 1. A volunteer performs a task, such as flexing a finger, inside the MR-scanner according to the reference timecourse and brain images are acquired simultaneously. The resulting data is a number of image slices of the brain where a timecourse of intensity values is obtained in each pixel, see Fig. 2. In active brain regions the intensity timecourses have a component that follows the reference timecourse due to the BOLD effect. The problem is to detect such pixels in the MR images. It is essential to capture the state of the brain at a certain timepoint, and therefore a very fast imaging sequence called echo planar imaging (EPI) is used. Unfortunately the EPI images suffer from low signal to noise ratio which makes the detection of active brain areas difficult. In order to obtain useful images it is not possible to have a sampling period less than 2 s. With a typical number of acquisitions 200, the effective time for an experiment becomes about 7 minutes.

In this paper a correlation analysis framework for this particular detection problem is described. As a starting point we use an *ordinary correlation* method in order to detect active pixels. Then a method based on *multiple correlation* is introduced, and finally a newly developed *canonical correlation* method [4] is presented.

2. THEORY

2.1. Ordinary correlation analysis

We begin by describing an ordinary correlation analysis approach. At present time this is the most widely used method to detect active pixels in fMRI images. Assume that N acquisitions of each image slice are taken at subsequent time-

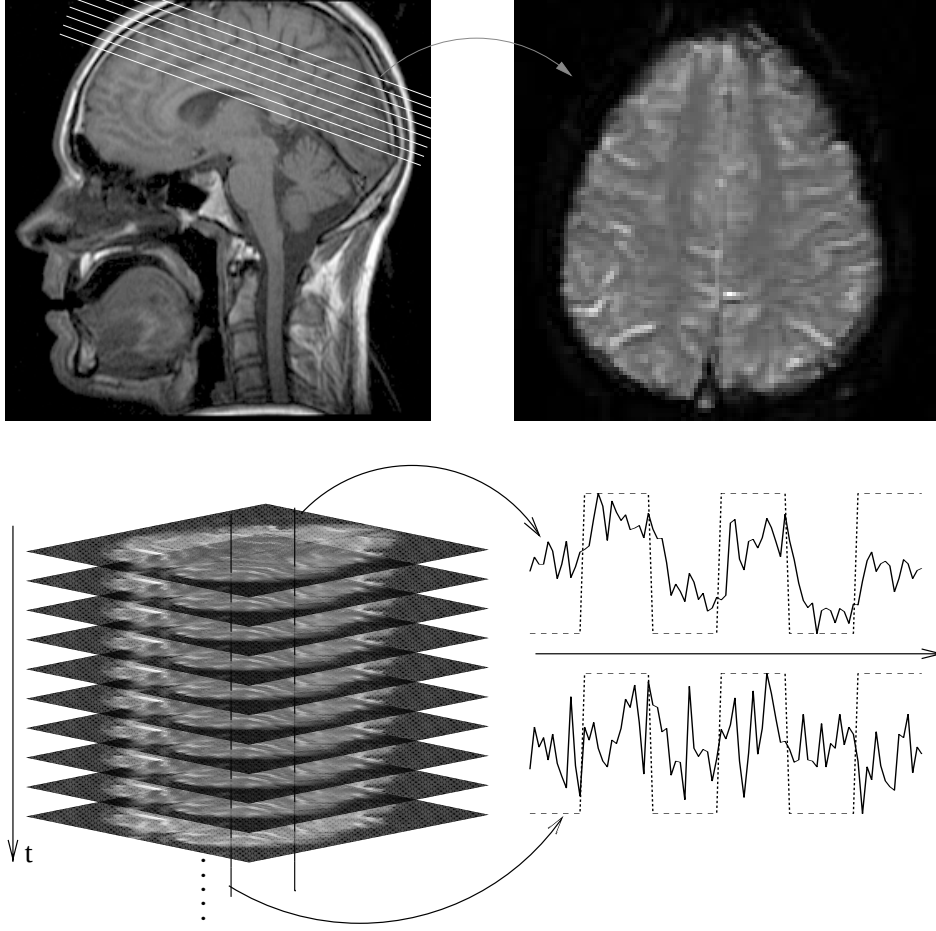


Fig. 2. *Upper left:* A number of image slices of a human brain. *Upper right:* An example of an EPI image. *Lower:* Repeated acquisitions of an image slice over time. The intensity in an activated pixel follows the reference timecourse due to the BOLD effect while a nonactivated pixel is not affected of the task performance.

points. First we define a model timecourse $y(t)$ which is believed to represent the true BOLD response well, i.e. the oxygenation changes in the blood due to the task performance. One possible choice of $y(t)$ is simply the square-wave used as reference timecourse, Fig. 2. In each pixel a timecourse of intensity values $x(t)$ is obtained and we calculate the sample correlation $\tilde{\rho}$ between our model timecourse $y(t)$ and $x(t)$, Fig. 3. For zero mean random variables x and y , Pearson's correlation coefficient is defined as

$$\rho = \frac{E[xy]}{\sqrt{E[x^2]E[y^2]}}, \quad (1)$$

and the sample correlation is calculated by

$$\tilde{\rho} = \frac{\sum_{t=1}^N x(t)y(t)}{\sqrt{\sum_{t=1}^N x(t)^2 \sum_{t=1}^N y(t)^2}}. \quad (2)$$

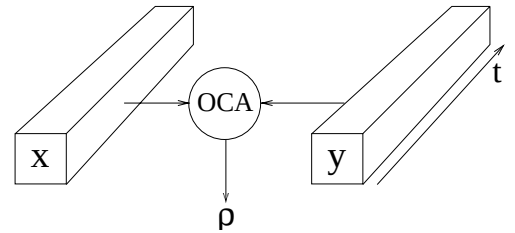


Fig. 3. An ordinary correlation analysis between an experimental pixel timecourse $x(t)$ and a model timecourse $y(t)$ for the BOLD response.

The result is an image or a map of sample correlation coefficients, see Fig. 4. A large sample correlation coefficient indicates that the pixel timecourse $x(t)$ is similar to the modelled timecourse $y(t)$, thus this pixel can be declared active.

To define a correlation threshold above which we consider a pixel as being active we turn to statistical theory.

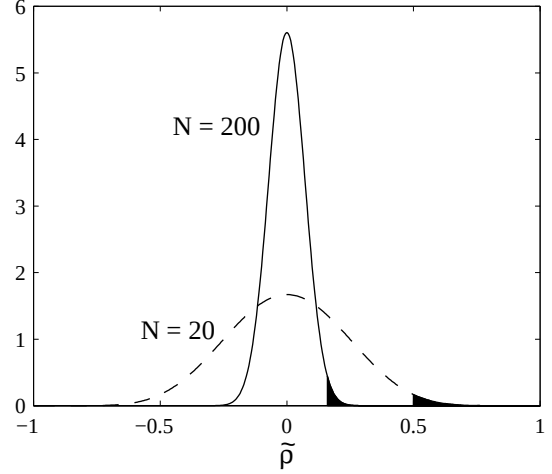
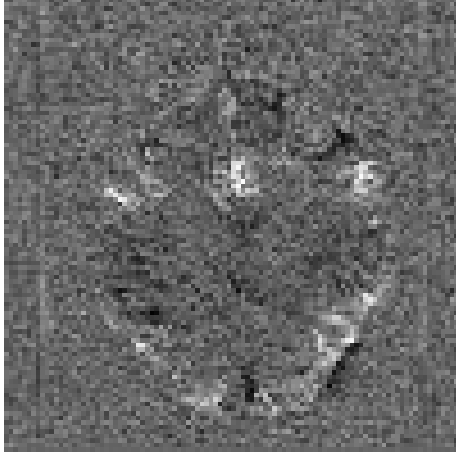


Fig. 4. *Left:* A map of sample correlation coefficients resulting from an ordinary correlation analysis. Bright areas correspond to activity. *Right:* The distribution of a sample correlation coefficient between two uncorrelated random variables. Note that the distribution only depends on the number of observations N . A threshold for the correlation map to the left is found by determining the correlation value for which the right tail area equals some predefined small probability.

Suppose that a pixel is not activated by the task, i.e. for this pixel $x(t)$ and $y(t)$ are uncorrelated. What is the probability that these two timecourses still by pure chance give a sample correlation above a chosen threshold and the pixel thereby falsely is declared as active? Of course we would like this probability to be small, e.g. 10^{-3} . If the noise in the pixel timecourse $x(t)$ is considered to be white and Gaussian distributed, Fig. 4 shows the probability density function for the sample correlation coefficient for a nonactivated pixel. From this distribution function it is possible to determine a correlation threshold for which the right tail area is equal to e.g. 10^{-3} .

A simple way to find such a threshold is to transform the sample correlation coefficient to a t -value [1], which follows Student's t -distribution with $N - 2$ degrees of freedom,

$$\sqrt{N-2} \frac{\tilde{\rho}}{\sqrt{1-\tilde{\rho}^2}} \in t(N-2). \quad (3)$$

Tables of t -values are found in most elementary books in statistics and we can easily find a threshold which fulfils the desired low probability for declaring a pixel as active when in fact it is not.

2.2. Multiple correlation analysis

There are some deficiencies in the ordinary correlation analysis method described above. One drawback is that we model the BOLD response by a single timecourse $y(t)$. The BOLD response has been shown to vary both between persons and between brain regions. For example, there is a delay in the BOLD response which varies between 3 to 8 seconds. Clearly, a single timecourse cannot model such variations. Therefore we try to find a set of basis functions

$$\mathbf{y}(t) = [y_1(t), y_2(t), \dots, y_n(t)]^T \quad (4)$$

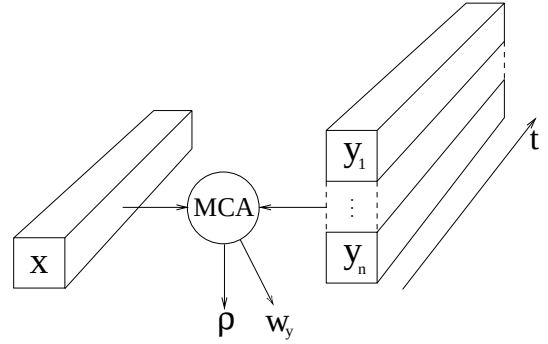


Fig. 5. A multiple correlation analysis between an experimental fMRI timecourse and a set of basis functions.

which are able to represent the possible variations believed to occur. For each pixel a specific model timecourse can be constructed by a linear combination of these basis functions

$$y(t) = \mathbf{w}_y^T \mathbf{y}(t) = w_{y_1} y_1(t) + \dots + w_{y_n} y_n(t). \quad (5)$$

An example of a set of basis functions is pairs of sine and cosine functions. The frequencies are chosen to the fundamental frequency of the specified reference timecourse and a few harmonics, i.e.

$$\mathbf{y}(t) = \begin{pmatrix} \sin(\omega t) \\ \cos(\omega t) \\ \vdots \\ \sin(k\omega t) \\ \cos(k\omega t) \end{pmatrix} \quad \omega = \frac{2\pi}{T}, \quad t = 1 \dots N, \quad (6)$$

where T is the period of the reference timecourse. In Fig. 6 four such sine/cosine pairs are shown. An advantage of this set of basis functions is that we can construct a signal with

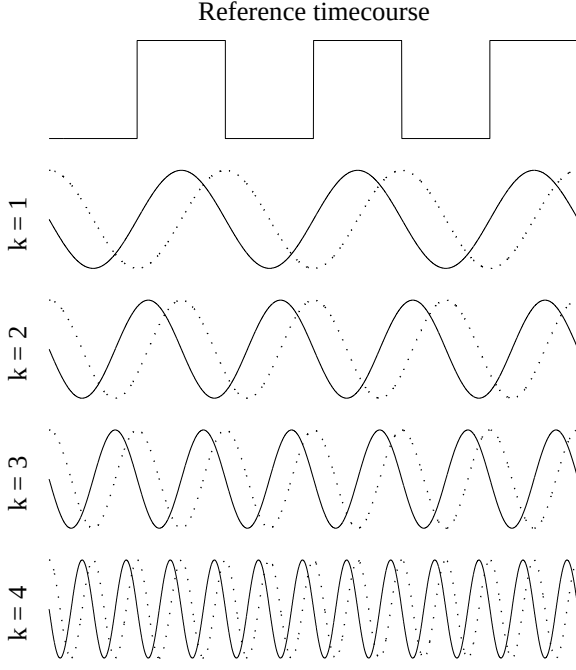


Fig. 6. Sine/cosine pairs which are used as basis functions instead of the reference timecourse in the top panel.

arbitrary phase, i.e. it is able to model a BOLD response with any delay. For each pixel, the problem is to find the coefficients $w_{y_1}, \dots, w_{y_n}$ in Eq. (5) so that the constructed timecourse $y(t)$ correlates the most with the experimental pixel timecourse $x(t)$. This is achieved by a multiple correlation analysis, Fig. 5.

Consider a zero mean random variable x and a zero mean random vector $\mathbf{y} = [y_1, \dots, y_n]^T$. The multiple correlation coefficient is defined as

$$\rho = \max_{\mathbf{w}_y} \frac{E[\mathbf{w}_y^T \mathbf{y} x]}{\sqrt{E[x^2] E[(\mathbf{w}_y^T \mathbf{y})^2]}} = \max_{\mathbf{w}_y} \frac{\mathbf{w}_y^T \mathbf{c}_{yx}}{\sigma_x \sqrt{\mathbf{w}_y^T \mathbf{C}_{yy} \mathbf{w}_y}} \quad (7)$$

where $\mathbf{c}_{yx}$ is a vector containing the covariances between the pixel timecourse and the basis functions. $\mathbf{C}_{yy}$ is the covariance matrix between the basis functions. It is not difficult to solve this maximization problem [1]. However, we can simplify further by observing that our basis functions in Eq. (6) are uncorrelated for a whole number of periods of the reference timecourse and that they all have the same variance $\sigma_y^2 = \frac{1}{2}$. Thus, for this case the covariance matrix is diagonal, $\mathbf{C}_{yy} = \frac{1}{2} \mathbf{I}$. Introducing this simplification and setting the derivative of Eq. (7) with respect to $\mathbf{w}_y$ to zero gives the following equation,

$$\rho \hat{\mathbf{w}}_y = \frac{1}{\sigma_x \sigma_y} \mathbf{c}_{yx} = \frac{\sqrt{2}}{\sigma_x} \mathbf{c}_{yx}. \quad (8)$$

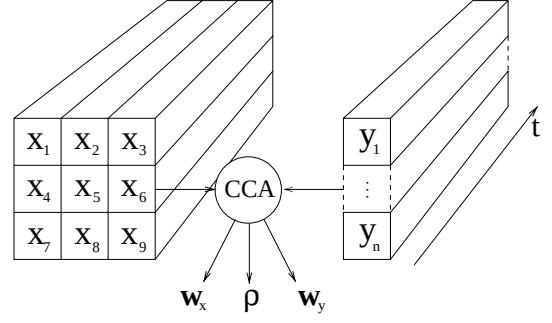


Fig. 7. A canonical correlation analysis between a set of fMRI timecourses and a set of basis functions.

Hence, the unit vector $\hat{\mathbf{w}}_y$ and ρ are found as the direction and length respectively of the vector at the right hand side in Eq. (8). The sample multiple correlation coefficient $\tilde{\rho}$ is then given by the length of an estimate of this vector,

$$\tilde{\rho} \hat{\mathbf{w}}_y = \frac{\sqrt{2}}{\sqrt{N}} \frac{\sum_{t=1}^N \mathbf{y}(t)x(t)}{\sqrt{\sum_{t=1}^N x(t)^2}}. \quad (9)$$

As in the ordinary correlation case, for each image slice a map of sample multiple correlation coefficients is obtained and we apply a transformation in order to find a threshold in a simple manner,

$$\frac{N - n - 1}{n} \frac{\tilde{\rho}^2}{1 - \tilde{\rho}^2} \in F(n, N - n - 1) \quad (10)$$

As above, N is the number of observations i.e. the length of the timecourses and n is the number of basis functions. For a nonactivated voxel the statistic in Eq. (10) follows an F -distribution with n and $N - n - 1$ degrees of freedom, under the assumption of Gaussian white noise in the timecourses.

2.3. Canonical correlation analysis

The previous section described how the ordinary correlation analysis method can be generalized into a multiple correlation method by increasing the dimensionality of the right hand side in Fig. 5. A question that naturally arises is how to generalize further by introducing multidimensional variables on both sides. In 1936 H. Hotelling developed a general solution to this problem which is called canonical correlation analysis [5]. Figure 7 shows how it can be applied in the context of functional MRI. Instead of analyzing single pixels separately at the left hand side, a region of pixels is considered. Here we choose a 3×3 region. Analogous to the multiple correlation approach we now wish to construct two timecourses as linear combinations of pixel timecourses and basis functions respectively,

$$x(t) = \mathbf{w}_x^T \mathbf{x}(t) = w_{x_1} x_1(t) + \dots + w_{x_m} x_m(t), \quad (11)$$

$$y(t) = \mathbf{w}_y^T \mathbf{y}(t) = w_{y_1} y_1(t) + \dots + w_{y_n} y_n(t). \quad (12)$$

Just as in the previous section, $y(t)$ is a timecourse constructed using the basis functions. The timecourse $x(t)$ can be viewed as the output from a linear filter applied to the 3×3 region chosen in the image. The canonical correlation analysis finds the linear combination coefficients $w_{x_1}, \dots, w_{x_m}$ and $w_{y_1}, \dots, w_{y_n}$ so that $x(t)$ and $y(t)$ correlates the most. Thus the canonical correlation analysis will for each region adaptively find a filter which reduces the noise and extracts a signal in the region to obtain good correlation.

To find the sample canonical correlation, first consider two zero mean random vectors $\mathbf{x} = [x_1, \dots, x_m]^T$ and $\mathbf{y} = [y_1, \dots, y_n]^T$. The canonical correlation is defined by

$$\rho = \max_{\mathbf{w}_x, \mathbf{w}_y} \frac{E[\mathbf{w}_x^T \mathbf{x} \mathbf{y}^T \mathbf{w}_y]}{\sqrt{E[(\mathbf{w}_x^T \mathbf{x})^2] E[(\mathbf{w}_y^T \mathbf{y})^2]}} = \max_{\mathbf{w}_x, \mathbf{w}_y} \frac{\mathbf{w}_x^T \mathbf{C}_{xy} \mathbf{w}_y}{\sqrt{\mathbf{w}_x^T \mathbf{C}_{xx} \mathbf{w}_x \mathbf{w}_y^T \mathbf{C}_{yy} \mathbf{w}_y}} \quad (13)$$

where $\mathbf{C}_{xx}$, $\mathbf{C}_{yy}$ and $\mathbf{C}_{xy}$ are the within and between sets covariance matrices. It can be shown [1, 2], that the solution can be obtained from the following eigenvalue problems

$$\begin{cases} \mathbf{C}_{xx}^{-1} \mathbf{C}_{xy} \mathbf{C}_{yy}^{-1} \mathbf{C}_{yx} \hat{\mathbf{w}}_x = \rho^2 \hat{\mathbf{w}}_x \\ \mathbf{C}_{yy}^{-1} \mathbf{C}_{yx} \mathbf{C}_{xx}^{-1} \mathbf{C}_{xy} \hat{\mathbf{w}}_y = \rho^2 \hat{\mathbf{w}}_y \end{cases} \quad (14)$$

The eigenvalues of $\mathbf{C}_{xx}^{-1} \mathbf{C}_{xy} \mathbf{C}_{yy}^{-1} \mathbf{C}_{yx}$ and $\mathbf{C}_{yy}^{-1} \mathbf{C}_{yx} \mathbf{C}_{xx}^{-1} \mathbf{C}_{xy}$ coincide and are called (squared) canonical correlations. The square root of the largest eigenvalue ρ_1 , referred to as the largest canonical correlation, is the solution to the maximization problem in Eq. (13). In practice, the sample canonical correlations are found by substituting $\mathbf{C}_{xx}$, $\mathbf{C}_{xy}$ and $\mathbf{C}_{yx}$ with the estimates

$$\mathbf{S}_{xx} = \frac{1}{N} \sum_{t=1}^N \mathbf{x}(t) \mathbf{x}^T(t) \quad (15)$$

$$\mathbf{S}_{xy} = \frac{1}{N} \sum_{t=1}^N \mathbf{x}(t) \mathbf{y}^T(t) \quad (16)$$

$$\mathbf{S}_{yx} = \mathbf{S}_{xy}^T \quad (17)$$

and due to our choice of basis functions, $\mathbf{C}_{yy} = \sigma_y^2 \mathbf{I} = \frac{1}{2} \mathbf{I}$. The sample canonical correlation coefficient is assigned to the center pixel and the 3×3 region is slid over the image to produce a map of sample canonical correlations.

The distribution of the sample canonical correlations for two independent sets of data is given in [3], but this distribution is very complex. An approximation based on a sum of incomplete beta functions [6], offers a possible way to find a sample canonical correlation threshold. However, the adaptive filtering procedure enlarges the detected active areas and more sophisticated methods for finding a proper threshold are required. Such methods are currently under investigation.

3. RESULTS & DISCUSSION

We use two different fMRI experiments to demonstrate the performance of the three correlation methods. In the first experiment the task was simply to flex the index finger of the right hand. A volunteer flexed his finger inside the MR-scanner while image slices of the brain were acquired. The reference timecourse was: 20 s rest, 20 s flexing, 20 s rest, etc. Totally 200 acquisitions of each slice were obtained. In the second experiment we attempted to locate areas activated in mental calculation. The task was to sum two digit numbers which were projected onto a screen in the scanner room. In this experiment 180 acquisitions of each slice were obtained.

In the ordinary correlation method a delayed (4 s) reference timecourse was used as a model timecourse $y(t)$ in order to account for the delay in the BOLD response. In the multiple and canonical correlation methods the sine/cosine functions in Fig. 6 were used to model the response. Figure 8 shows two adjacent image slices from each experiment where the detected activation is overlayed on anatomical background images. Reversed right/left orientation is a well established convention in Radiology, and therefore also adopted here. In order to detect activation, thresholds for the ordinary and multiple correlation maps were selected at a significance level of 10^{-3} . For the maps of canonical correlations, thresholds which approximately detect the same area of activation were selected. The legends in Fig. 8 show the ranges of correlation coefficients which indicate active pixels in each method. The lower bound of this range is given by the threshold and the upper bound of the most activated pixel.

In the finger flexing experiment, strong activation is detected in the left hemisphere in areas known to control motor tasks. The mental calculation experiment results in a number of activated areas, which is expected due to the higher complexity of the task. The next step in the analysis is to identify these areas.

In these experiments, the multiple correlation method does not perform significantly better than the ordinary correlation method. However, note that the multiple correlation for the most activated pixel has increased compared to the ordinary correlation. This indicates that the square-wave reference timecourse is not optimal for detecting activation. Another advantage of the multiple correlation method is that no delay in the BOLD response needs to be specified. A characteristic for both these methods is the large number of spurious activated pixels, which is clearly seen in Fig. 8. In contrast, the canonical correlation method detects homogeneous areas of activity and few spurious activations. The lower panels of Fig. 8 show timecourses for an activated pixel using the ordinary correlation method and the canonical correlation method respectively. For the ordinary correlation analysis, the blue timecourse shows the experimental intensity values and the red is the square-wave model of the BOLD response. The correlation coefficient between

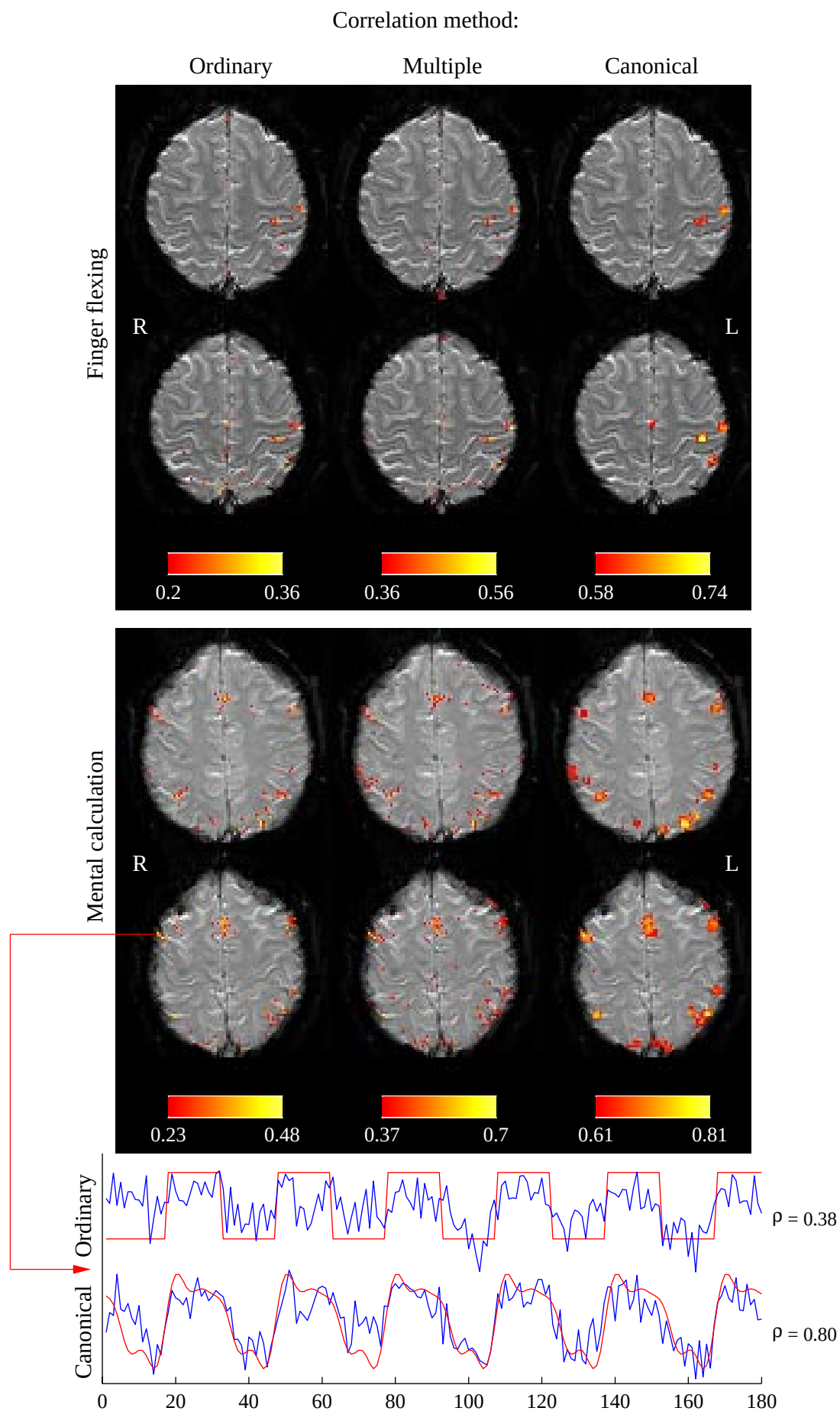


Fig. 8. The result of the three correlation methods applied to the finger flexing and mental calculation experiments. See the text for details.

these timecourses is 0.38. The lower timecourses were obtained using the canonical correlation method. The blue timecourse shows the signal that is extracted from the 3×3 region, i.e. a linear combination of the 9 timecourses constituting the region. The red timecourse shows the combination of the sine/cosine functions which is found to model the BOLD response most adequately in this region. The correlation coefficient between these two timecourses is 0.8, a significant increase compared to 0.38 from the ordinary correlation method. The price we have to pay for the increased sensitivity and robustness of the canonical correlation method is spatial resolution due to the filtering of the data.

It should be stressed that the ordinary correlation method and the multiple correlation method are established methods for fMRI analysis, though they are generally presented as a t-test and an F-test. The canonical correlation method is novel and a natural extension of the established methods when they are presented in a correlation analysis framework.

4. ACKNOWLEDGEMENTS

The authors thank Jonny Cedefamn for assistance. The financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

5. REFERENCES

- [1] T. W. Anderson. *An Introduction to Multivariate Statistical Analysis*. John Wiley & Sons, second edition, 1984.
- [2] M. Borga. *Learning Multidimensional Signal Processing*. PhD thesis, Linköping University, Sweden, SE-581 83 Linköping, Sweden, 1998. Dissertation No 531, ISBN 91-7219-202-X, <http://people.imt.liu.se/~magnus/>.
- [3] A.G. Constantine. Some non-central distribution problems in multivariate analysis. *Ann. Math. Stat.*, pages 1270–1285, 1963.
- [4] O Friman, J Carlsson, P Lundberg, M. Borga, and H. Knutsson. Detection of neural activity in functional MRI using canonical correlation analysis. *Magn. Reson. Med.*, 45(2):323–330, February 2001.
- [5] H. Hotelling. Relations between two sets of variates. *Biometrika*, 28:321–377, 1936.
- [6] S. Pillai. On the distribution of the largest characteristic root of a matrix in multivariate analysis. *Biometrika*, (52):405–414, 1965.