A COMPLETELY DATA-DRIVEN METHOD FOR DETECTING NEURONAL ACTIVATION IN FMRI

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is one of the most widely used methods to study neuronal activity in human brain in vivo. A data-driven method is proposed to detect both the temporal and spatial information in fMRI data acquired during the representation of stimuli, which may also be applied when the expected response cannot be estimated a priori. The method is built on the existing temporal clustering analysis technique with additional features of searching for the connected components in the temporal and spatial domains in the whole brain. Moreover, no pre-defined assumptions about the stimuli are required in comparison to the previous methods. The output contains the information on how long the activation sustains and where the corresponding voxels are. For validation, the method has been applied to four sets of data from an experiment involving visual stimuli. Our method is able to detect the response to the stimuli.

Index Terms— fMRI, image analysis, brain, signal analysis.

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI), among other functional imaging techniques such as PET, EEG, MEG, has been used for "brain mapping": these methods detect dynamic changes in a temporal series of images acquired during experiments which are designed to investigate specific questions or hypotheses [7] .

The methods for obtaining brain activation maps can be broadly divided into two categories: model-driven methods and data-driven methods. For the model-driven methods, the temporal information of the image intensity, i.e., the expected temporal location and duration of neuronal response, is known. The expected neuronal response is estimated by convolving the experimental design with the haemodynamic function and a general linear model (GLM) analysis is applied using the expected response, in order to find out which voxels exhibit activation patterns similar to the expected response [7]. However, such methods cannot be used when the expected response is not known a priori.

Data-driven fMRI analysis methods available include independent component analysis (ICA), e.g., [13] and temporal clustering analysis (TCA), e.g., [5, 9, 10, 11, 18]. In this paper, a new data-driven fMRI activation analysis method built on the modified TCA (MTCA) [18] is presented. The data are treated in a four-dimensional (4D) space ($X \times Y \times T \times S$, where X and Y are the number of voxels in x and y axis, T is the number of volumes acquired and S is the number of slices in each volume). The original TCA approach [5] located the temporal maximum in time series of each voxel in a single slice of fMRI data and the time point with the maximum number of voxels that reached their maxima is taken to be the response of interest.

In [8, 9, 10], a temporal averager [17] was applied to the fMRI data, therefore the temporal information of the detected responses was contained in a time bin instead of a time point. This additional step allowed the voxels activated by the same block of stimuli to be included in the analysis even though they did not reach the temporal maxima at exactly the same time point. However, the window size of the temporal averager was arbitrarily defined as there was no rule given to the most appropriate one for a given set of fMRI data. In addition, a bandpass filter was applied [8, 9, 10].

Instead of using a single slice of fMRI data, the MTCA method has been extended to whole brain data and an additional constraint from the voxels in a 3×3 neighbourhood two dimensional (2D) kernel of the detected maximum voxels was introduced, in order to take advantage of the observation that physiologically plausible brain activations seldom occur in single isolated voxels [9]. This idea was extended to the $3 \times 3 \times 3$ three dimensional (3D) neighbourhood kernel around the detected maximum voxels, i.e., the adjacent slices were also considered [10]. Both [9] and [10] used the same method to define the number of neighbouring voxels to be included in the activation analysis: (1) The number of neighbourbouring voxels in the defined neighbourhood that have also reached their maxima at the same time bin as the detected maximum voxel was computed. (2) A histogram of the number of occurrences against the number of neighbouring voxels that reached their maxima at the same time bin was generated using the results from (1). (3) A cut-off threshold for the minimum number of neighbouring voxels which also reached their maxima at the same bin for the detected voxels to be included in the final result was the 20%-th value from the tail of the histogram. The value was arbitrarily chosen.

An improved method is proposed in this paper so that the neuronal activation analysis can be carried out without having to determine the most appropriate frequencies for the bandpass filter, the most appropriate window width for temporal averaging and the threshold for the inclusive neighbouring voxels for the detected maximum. The bandpass filter and the temporal averaging are not included in the proposed method. Instead, the temporal maximum of each time series is found in the 4D data ($X \times Y \times T \times S$) and the connected components in both spatial and temporal domains

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are sought. The Otsu [14] algorithm is applied to classify the components according to their sum of percent signal change of all the detected maximum voxels in each component. Due to the nature of detecting the temporal maximum in the time series, this method is only suitable for experiments with a single event, i.e., involving an individual event [7] or a group of temporally continuous events. For validation, the fMRI data from four sets of visual experiments are used, since the brain regions activated in this kind of experiment have been long characterised, e.g., [2, 7].

2. METHOD

2.1. Pre-processing Steps

The acquired fMRI data are at first corrected for movement using in-house software [1], so that macroscopic head-motion can be corrected. The 4-D data $\underline{\boldsymbol{D}}$ ($X \times Y \times S \times T$) are used for analysis. A brain mask is obtained using [16], so that only the voxels inside the brain are included in the analysis. The signal intensity of each voxel inside the brain mask is transformed to percent signal change. A 5-point moving-average filter is applied to the time series to eliminate the spikes from high frequency noise.

2.2. Temporal Maximum Detection and Four Dimensional Connected Components Labelling

The registered images are read into Matlab using MRI Toolbox [4, 12]. A binary matrix, $\underline{\boldsymbol{D}}_{binary}$, of size $X \times Y \times S \times T$ with zeros, is created. The maximum value of all the time series in $\underline{\boldsymbol{D}}$ is found and wherever their percent signal change is greater than or equal to 1.5% the entry at the corresponding voxel and time in $\underline{\boldsymbol{D}}_{binary}$ is set to be '1'. 1.5 percent signal change is set to be the threshold, because the percent signal change of fMRI acquired in 1.5 Tesla scanners due to stimulation is in order of 2-3% [7] and the limit was lowered by 0.5%, in order to include all the possible voxels that might have been activated.

The activation of interest in fMRI is connected spatially and temporally, therefore the 4-D matrix, $\underline{\boldsymbol{D}}_{binary}$ undergoes a connected components labelling process. The algorithm can be described by the following general procedure: (1) All elements in matrix $\underline{\boldsymbol{D}}_{binary}$ are scanned, preliminary labels are assigned to nonzero elements, and label equivalences are recorded in a union-find table (2) The equivalence classes are resolved using the union-find algorithm (3) The elements are relabelled based on the resolved equivalence classes [12][15].

2.3. Detection of Components of Activated Voxels

The components found in Sec.2.2 contain voxels which are related spatially and temporally as well as isolated ones. fMRI derived contrast from the blood oxygenation level dependent (BOLD) phenomenon. Because this phenomenon originates from macroscopic veins in the vicinity of neurons, voxels labelled as 'activated' are seldom isolate. A selection process is proposed for the components which contain the features of activated voxels: (1) The sum of percent signal change of all the contributed voxels at the time of detection in one component is calculated (2) A histogram is formed using the normalised values obtained in (1) for all the components. (3) The Otsu algorithm [14] which is largely used in the area of image segmentation is applied to normalised sum of percent signal changes of all components. This step is applied, in order to divide the components into two groups by maximising the variance between them, because the group of connected components that contain responses to the stimuli are expected to have larger sum of percent signal change of all detected voxels compared to the rest of the components. The components with only one voxel are discarded. (4) Due to the nature of the four dimensional connected components labelling process, some components might share the same temporal information but spatially unrelated. We would like to obtain at first the temporal information of the neuronal response, i.e., what happened in the whole brain at certain time (either a single time point or period formed by an identified connected component), therefore the temporal information is condensed by combining the components which have overlapped time points. These components are merged to form a single final component. (5) An activation map is generated for each component found in (4) as well as for components which do not have overlapping time points with other components by colouring the detected voxels red. The temporal information is also provided, i.e., when the detected maximum starts and how long it has sustained by sorting the times when the detected voxels reached their maxima.

3. DATA USED FOR METHOD VALIDATION

Although the proposed method can be applied to any single-event experimental design, a validation experiment of visual stimulation was used since the brain regions activated in this kind of experiment have long been characterised [2, 7]. The data were acquired on a 1.5 Tesla GE scanner at Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London.

A period of 8-Hz flickering checkerboard visual stimuli was presented to a healthy subject between 60 and 120 seconds (s) after the start of the experiment, which lasted 300s. 150 volumes of 20 axial slices were acquired with a repetition time (TR) = 2s. Each slice contains 64 $\times$ 64 voxels and the voxel dimensions were 3.75mm $\times$ 3.75mm $\times$ 5.5mm. The four sets of data for methodology validation are labelled: VIS1, VIS2, VIS3 and VIS4.

4. RESULTS

In Sec. 4.1, the results of using the MTCA with a $3 \times 3 \times 3$ neighbourhood selection criterion with different temporal averaging window widths are given, in order to demonstrate the effects from the choice of this parameter. In Sec. 4.2, the results from the proposed method are given.

4.1. Results from the MTCA with a $3 \times 3 \times 3$ neighbourhood selection criterion with different temporal averaging window widths

The MTCA method with a $3 \times 3 \times 3$ neighbourhood selection criterion [10] was applied to VIS2 with different window lengths for temporal averaging (4, 6, 10 and 12 seconds). The time bins with two largest numbers of detected voxels were recorded for each window length and the contributing voxels in the primary and secondary visual cortices were denoted with '**V**' in Table 1. Temporal averaging windows of 6, 10 and 12 seconds enabled correct detection of the stimulus response. Not surprisingly, wider windows prevented detection as the window width approached the value of the duration of the stimulus length and narrower windows diminished the power of detecting the temporal maximum resulted by the stimulus as the activated voxels might not have reached their maxima during the same short period. When working on the fMRI data from the experiments for which the information of the expected response could not be obtained, it would be difficult to make the most appropriate

choice on the window width for temporal averaging unless useful prior information is available.

4.2. Results from the proposed method

The proposed method has been applied to VIS1-VIS4. The number of components found in each data set varies: 5 components were found in VIS1, 6 in VIS2, 4 in VIS3 and 7 in VIS4. The time periods of response for these components can be found in Table 2 and wherever these voxels lie in the areas of primary and extrastriate visual areas they are marked with '**V**' and the activation maps can be found in the figures with their numbers shown as superscripts in Table 2. For reason of space, only slices with detected voxels are shown.

VIS1 is taken as an example to show the output of the intermediate steps. There were 13995 voxels inside the brain mask and 3205 of them had a peak response greater than or equal to 1.5 percent signal change. The total number of connected components found was 1303. The histogram of sum of percent signal change is shown in Fig. 2. 890 components containing an isolated voxel were discarded. Five components were found on the right hand side of the threshold in the histogram and the periods of the connected voxels can be found in Table 2. Component 2 was particularly of interest: the voxels were found to reach their maxima between 72 and 96 seconds after the start of the experiment, which was exactly during the period when the visual stimulation was applied and the voxels were distributed in the primary and extrastriate visual areas. The time series of these voxels were extracted and their average was plotted in Fig. 3, which exhibited the characteristics of BOLD time series: a positive response, 2-3 percent signal change at 1.5 Tesla peaking 5-8 seconds after the stimulus commenced [7].

The output of the proposed method differs from the original method [5] and the modified method [18] in that a number of connected components are given and these components provide both spatial and temporal information on the neuronal response not only during the time when the stimulation was applied, but also the areas which have recently been identified as part of a 'default network' of brain activity [3]. The method also removed artefacts that were probably of type-one error in origin.

The response to the visual stimulation was also found in VIS2-4. In VIS2, the response was found during 76-98 seconds in Component 1 and the activation map is in Fig. 4. In VIS3, the response to the visual stimulation appeared in Component 1, which was detected by the spatially and temporally connected voxels during the period 72 to 86 seconds and the contributing voxels were in the primary and extrastriate visul areas as shown in Fig. 5. In [9, 10], the methods were not able to detect the response to the visual stimulation in VIS4. By applying the proposed method, some responses to visual stimulation were detected in Components 5 and 7 in Fig. 6 and 7 respectively.

5. CONCLUSION

A novel, completely data-driven approach to detect responses in fMRI data obtained from single-event experiments is proposed. The method utilises the data from the whole brain and is free from the arbitrary defined temporal averaging window size and valid voxel threshold in previous methods. The method has been validated using four sets of fMRI data from a visual experiment and was able to detect the spatial and temporal information on responses to the visual stimulation as well as the responses which may have arisen from areas associated with default, resting state neuronal networks.

6. REFERENCES

[1] E.T. Bullmore, M.J. Brammer, S. Rabe-Hesketh, V. Curtis, R.G. Morris, S.C.R. Williams, T. Sharma and P.K. McGuire, "Methods for diagnosis and treatment of stimulus-correlated motion in generic brain activation studies using fMRI", *Human Brain Mapping*, vol. 7, pp. 38-48, 1999.

[2] V.D. Calhoun, T. Adali and J.J. Pekar, "A method for comparing group fMRI data using independent component analysis: application to visual, motor and visuomotor tasks", *Magnetic Resonance Imaging*, vol. 22, pp. 1181-1191, 2004.

[3] M. De Luca, C.F. Beckmann, N. De Stefano, P.M. Matthews and S.M. Smith, "fMRI resting state networks define distinct modes of long-distance interactions in the human brain", *NeuroImage*, vol. 29, no. 4, pp. 1359-1367, Feb 2006.

[4] EEG/MRI Matlab Toolbox, http://eeg.sourceforge.net.

[5] J.-H. Gao, and S.-H. Yee, "Iterative temporal clustering analysis for the detection of multiple response peaks in fMRI", *Magnetic Resonance Imaging*, vol. 21, pp. 51-53, 2003.

[6] D. Garcia, "Automatic image segmentation", (http://www.mathworks.com/matlabcentral/fileexchange/... loadFile.do?objectId=16205&objectType=FILE), MATLAB Central File Exchange, retrieved 20th September 2007.

[7] P. Jezzard, P.M. Matthews and S.M. Smith (editors), *Functional MRI an introduction to methods*, Oxford University Press, 2001.

[8] S. Lee, F. Zelaya, L. Reed, M.J. Brammer and S.A. Amiel, "A model-free method for fMRI analysis using temporal clustering and neighbourhood constraint", *12th Annual Meeting of the Organization for Human Brain Mapping*, 2006.

[9] S. Lee, F. Zelaya, S.A. Amiel and M.J. Brammer, "Stimulus response detection in fMRI using temporal clustering analysis, digital filters and a two-dimensional neighbourhood test", *Proc. of International Computer Symposium 2006, Medical and Bio Informatics Workshop*, vol. 3, pp. 1302-1307.

[10] S. Lee, F. Zelaya, S.A. Amiel and M.J. Brammer, "Stimulus response detection in fMRI using digital filters, temporal clustering analysis and a three-dimensional selection criterion", *Proc. of the EUSIPCO (European Signal Processing Conference) 2007*, pp. 433-437.

[11] Y. Liu, J.-H. Gao, H.-L. Liu and P.T. Fox, "The temporal response of the brain after eating revealed by functional MRI", *Nature*, vol. 405, pp. 1058-1062, 2000.

[12] Matlab, The Mathworks, Inc.

[13] M. McKeown and T. Sejnowski, "Independent component analysis of fMRI data: examining the assumptions", *Human Brain Mapping*, vol. 6, pp. 368-372, 1998.

[14] N.A. Otsu, "Threshold selection algorithm from gray level histogram", *IEEE Trans. System, Man, Cybernetics*, vol. 9, no. 1, pp. 62-66, Sep. 1979.

[15] R. Sedgewick, *Algorithms in C*, pp. 11-20, 3rd Edition, Addison-Wesley, 1998.

[16] S.M. Smith, "Fast robust automated brain extraction", *Human Brain Mapping*, vol. 17, no. 3, pp. 143-155, 2002.

[17] J.W. Woods, *Multidimensional Signal, Image, and Video Processing and Coding*, Academic Press, 2006.

[18] S.-H. Yee and J.-H. Gao, "Improved detection of time windows of brain responses in fMRI using modified temporal clustering analysis", *Magnetic Resonance Imaging*, vol. 20, pp. 17-26, 2002.

Temporal Window Length (seconds)	**4**	**6**	**10**	**12**	**20**
Time bin with the largest number of detected voxels	88-92	84-90	80-90	84-96	80-100
Time bin with the second largest number of detected voxels	84-88	72-78 **V**	70-80 **V**	72-84 **V**	280-300

Table 1. The neuronal activation detected using the MTCA with a $3\times3\times3$ neighbourhood constraint [10] for VIS2, where the numbers are the detected time bins and **V** indicates the contributed voxels are in the primary & extrastriate visual areas.

fMRI data	**VIS1**	**VIS2**	**VIS3**	**VIS4**
Component 1	260-270	76-98 $\mathbf{V}^4$	72-86 $\mathbf{V}^5$	300
Component 2	290-300	148-156	232-242	224-240
Component 3	72-96 $\mathbf{V}^2$	224-236	180-186	262-270
Component 4	148-162	22-30	188-196	68-74
Component 5	206-214	288-296	N/A	120-130 $\mathbf{V}^6$
Component 6	N/A	36-42	N/A	176-188
Component 7	N/A	N/A	N/A	100-112 $\mathbf{V}^7$

Table 2. The neuronal activation detected using the proposed method on four sets of fMRI data from a visual experiment. The numbers are the temporal information in seconds for each component, i.e., how long the detected voxels sustained and when the contributed voxels are in the primary and extrastriate visual areas it is denoted with **'V'**. 'N/A': for the data with fewer found components.

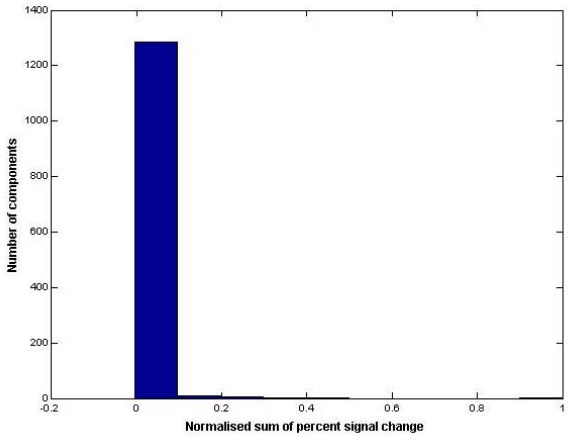

Fig. 1. VIS1: the histogram of the frequency against normalised sum of percent signal change for all connected components.

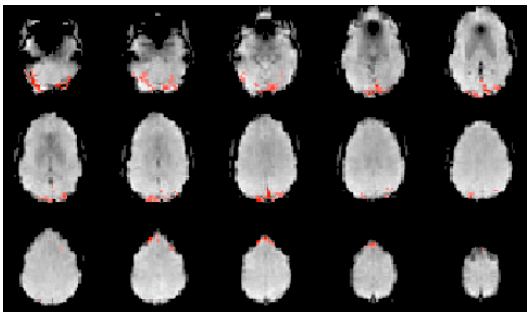

Fig. 2. VIS1: the activation map for Component 3. Detected period: 72-96 seconds after the start of the experiment and the voxels contributed are in the primary and extrastriate visual areas.

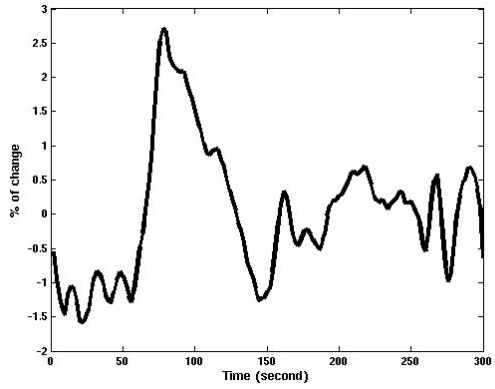

Fig. 3. VIS1: the time series extracted from the detected voxels in Component 3 in Fig. 2.

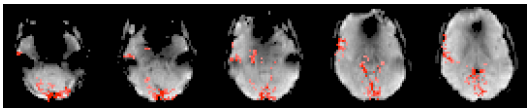

Fig. 4. VIS2: the activation map for Component 1. Detected period: 76-98 seconds after the start of the experiment and the voxels contributed are in the primary & extrastriate visual areas and auditory cortex.

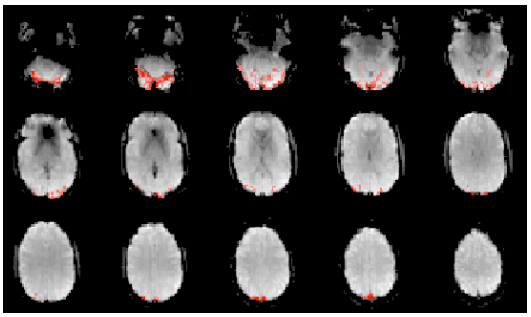

Fig. 5. VIS3: the activation map for Component 1. Detected period: 72-86 seconds after the start of the experiment and the voxels contributed are in the primary and extrastriate visual areas.

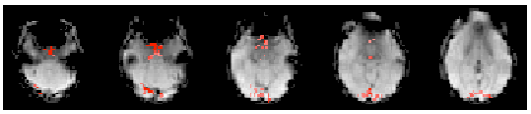

Fig. 6. VIS4: the activation map for Component 5. Detected period: 120-130 seconds after the start of the experiment and the voxels contributed are in the primary and extrastriate visual areas.

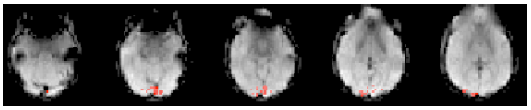

Fig. 7. VIS4: the activation map for Component 7. Detected period: 100-112 seconds after the start of the experiment and the voxels contributed are in the primary visual areas.