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# A Data-driven fMRI Analysis Method Using Temporal Clustering Technique and an Adaptive Voxel Selection Criterion*

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*Abstract–* **A data-driven fMRI (functional magnetic resonance imaging) analysis method is proposed for studying brain responses to stimulation when the information for predicting their onset or duration is unavailable. The method is suitable for experiments involving a single event or non-repetitive multiple events. The method is built upon the pre-existing temporal clustering analysis techniques with additional features that make use of the signal changes of the neighbouring voxels to ensure that the selected voxels for response detection are those most likely to have been activated by the stimuli. For method validation, eight sets of fMRI data from three different kinds of sensory experiments are applied. The results demonstrated that our method is able to detect the time bins during which the stimuli were administered and the identified voxels corresponding to the brain areas, which are typically activated in this kind of experiments. Moreover, in these eight sets of data, the accuracy of stimulation response detection is 75% compared to 58.33% without the selection criterion.**

***Keywords: magnetic resonance imaging, image analysis, brain, digital filters, signal analysis***

## 1 Introduction

fMRI (functional magnetic resonance imaging) has been one of the most popular methods for studying brain activity. The brain activation can be detected by analysing the BOLD (blood oxygenation level dependent) time series, typically at each voxel in the brain. The analysis methods can be broadly divided into two categories: model-driven methods and data-driven methods [10]. In model-driven methods, a model, such as the convolution of a stimulus function with the haemodynamic response function, is generated and the best fit is found in the fMRI data for response detection. In data-driven methods, such a model is not used or in some cases unavailable and the brain activation is detected using only the information within the fMRI data.

In the category of data-driven methods, the techniques such as independent component analysis (ICA) [16] and wavelet transform [4] have been used to help extract main components of responses from fMRI time series. Recently, a number of temporal clustering analysis (TCA) techniques [9, 12, 13, 14, 19] have been suggested. These are designed to detect the brain response for the fMRI data involving a single event or non-repetitive multiple events. The methods are based on the dimensional reduction; the 4-D fMRI data ($x \times y \times$ time $\times$ slice) are reduced to two dimensions by processing one slice at a time and loosing the spatial information and computing the number of voxels reaching their maxima at each time point in [9, 14, 19] or time bin in [12, 13]. The time point or time bin with the maximum number of detected voxels is of interest. In [9, 14, 19], the methods were applied to a single slice of fMRI data. In [12], the spatial information of the detected voxels within a slice was also taken into consideration by introducing a $3 \times 3$ neighbourhood test, since the physiologically plausible brain activations seldom occur in single isolated voxels. The method was extended to all available slices in [13], i.e., the temporal information of the detected responses was determined by all the slices. Both [12, 13] applied a selection criterion using the voxels in the $3 \times 3$ neighbourhood around each voxel that was detected to be the maximum. In [12], the voxels that reach their maxima at the same time bin were identified spatially and only the voxels that had more than 50% of their neighbouring voxels in their $3 \times 3$ neighbourhood that also reached their maxima contributed to the stimuli response detection. In [13], the number of neighbouring voxels that also reach their maxima is found for every detected maximum voxel at each

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time bin and a threshold was determined from the upper 20% in a histogram of numbers of neighbouring voxels.

In this paper, we propose a new voxel selection criterion, which examines the mean squared error in percentage of signal change between the detected voxel and all the possible combinations of its neighbouring voxels in the $3 \times 3$ neighbourhood. The proposed method is applied to eight sets of fMRI data of three different kinds of sensory experiments.

## 2 Method

The method can be broken down into three stages. Stage 1: Pre-processing of the fMRI data including head motion correction [3] and obtaining a brain mask [18]. Filtering processes are then applied to eliminate low- and high-frequency noise and the 4D fMRI data is reduced to a 2D data set using TCA techniques [9, 14, 19]. The data is processed slice by slice and only the time series of the voxels inside the brain mask are placed row by row in a 2D matrix. Stage 2: The voxels that are activated are selected using our proposed criterion. Stage 3: The brain response is detected using the information obtained in Stage 2 throughout the whole brain. The details can be found in the following sub-sections.

### 2.1 Stage 1: Pre-processing and Filtering

In the pre-processing step, the fMRI data are first corrected for head motion using in-house software [3] and a brain mask is obtained using FSL Brain Extraction Tool [18]. The 4D fMRI data set ($Y \times X \times S \times T$, where $Y$ and $X$ are the number of voxels in the $y$ and $x$ axes respectively, and $S$ is the number of slices and $T$ is the number of volumes acquired during the experiment) is processed slice by slice, i.e., the data dimension is reduced to 3 [8]. For each slice, the TCA data representation techniques [9, 14, 19] are applied, i.e., the 3D data are reduced to 2D by placing the time series of the voxels inside the brain mask row by row in a 2D matrix, therefore in a 2D matrix, $\underline{\boldsymbol{D}}_{ori,s}$, $s = 0, \cdots, S-1$, there are rows of time series corresponding to the voxels within the brain mask. The matrix $\underline{\boldsymbol{D}}_{ori,s}$ of size $N_s \times T$, where $N_s$ is the number of voxels inside the brain mask for slice $s$, allows us to observe the changes in the time series of every voxel inside the brain mask.

The unit of each time series in $\underline{\boldsymbol{D}}_{ori,s}, s = 0, \cdots, S-1$ is converted from signal intensity to percentage of signal change to form matrix $\underline{\boldsymbol{D}}_{psc,s}$ of size $N_s \times T$, $s = 0, \cdots, S-1$ so that the comparison from voxel to voxel can be made.

In order to eliminate the temporal spikes, a moving-average filter is applied to the time series in $\underline{\boldsymbol{D}}_{psc,s}$, followed by a bandpass filtering process to eliminate the high-frequency noise and low-frequency noise caused by slowly varying unwanted signals, such as heartbeat, breathing or scanner-related drifts [10]. The matrix with time series after filtering processes is regarded as $\underline{\boldsymbol{D}}_{filtered,s}$ of size $N_s \times T$.

The response detection is reinforced by temporal averaging [12, 13], which is carried out by taking the mean of the percentage changes in signal in a block of $n$ time points for each time series in $\underline{\boldsymbol{D}}_{filtered,s}$, since the activation in voxels throughout the brain to a block of stimuli may not happen at the same time point. The unit of the time series is now time bin rather than time point and the data matrix now becomes $\underline{\boldsymbol{D}}_{processed,s}$ of size $N_s \times (T/n)$.

### 2.2 Stage 2: Voxel selection

The goal of this stage is to select the voxels, which are more likely to be plausibly activated by the stimuli. The candidate voxels are obtained by applying the detection of the maximum signals in TCA methods [9, 14, 19], i.e., to determine the time point at which most voxels reach their maxima. In [12, 13], the spatial information of these voxels is used again to eliminate the isolated voxels.

In this work, voxels in the $3 \times 3$ neighbourhood of the voxel of interest, i.e., the detected maximum voxel, are examined using the mean squared error (MSE) between their percentages of change and the percentage of change of the voxel of interest. 'Adaptive neighbouring voxels' are named since all the possible combinations of these 8 neighbouring voxels are explored.

Mathematically, if a voxel which reaches its maximum at time bin $\tau$ is at co-ordinate $(m_{(s,y_\alpha)}, m_{(s,x_\alpha)})$, its $3 \times 3$ neighbourhood is formed using voxels in the range $[m_{(s,y_\alpha)} - 1 : m_{(s,y_\alpha)} + 1, m_{(s,x_\alpha)} - 1 : m_{(s,x_\alpha)} + 1]$ and their corresponding percentages of signal change are $P[m_{(s,y_\alpha)} - 1 : m_{(s,y_\alpha)} + 1, m_{(s,x_\alpha)} - 1 : m_{(s,x_\alpha)} + 1]$. At this point, we discard any voxel with more than four neighbouring voxels with zero values as it is more likely to be the voxel at the borders of the brain mask. For any voxel with more than four non-zero neighbouring voxels, the percentage of signal change of the neighbouring voxels at this time bin are placed in a vector, $\underline{\boldsymbol{V}}$. All the possible voxel combinations are found, i.e., ${}_LC_k$, where $L$ is the length of $\underline{\boldsymbol{V}}$ and $k = 1, \cdots, L$. The MSE between each possible combination and the voxel of interest is computed. The chosen MSE should be as small as possible whereas the number of neighbouring voxels included should be as great as possible. We search for the minimum MSE and obtain the neighbouring voxel combination that contains the maximum number of voxels and within 10% of the minimum MSE. The number of detected voxels is recorded for every slice at every time bin in matrix $\underline{\boldsymbol{F}}$ of size $S \times (T/n)$.

### 2.3 Stage 3: Stimuli Response Detection

The output of Stage 2, $\underline{\boldsymbol{F}}$, is used for stimuli response detection. The matrix is summed column wise, in order to find the time bins with the maximum numbers of detected voxels. The time bins with the top four numbers of detected voxels are recorded and their activation maps are generated by showing the corresponding coloured red. If the responses to the stimuli are the largest signals in the time series in all slices, the number of selected time bins should be the same as the number of stimuli in the experiments. However, it was observed in our data that the responses to the stimuli might not always be the greatest when all the slices are taken into account. The resting state network, e.g., [7] could also cause a large number of voxels reaching their maxima in the same time bin. In order to allow some flexibility, four time bins with the top numbers of detected voxels are given here.

## 3 fMRI Data and Parameters

The proposed method was applied to eight sets of fMRI data from three different kinds of experiments as part of the method validation. The voxel dimensions were 3.75mm × 3.75mm × 5.5mm for all experiments.

***Visual Experiment***

A block of 8-Hz flickering checkerboard visual stimuli was presented to a healthy subject between 60-120s (seconds) during an experiment lasting 300s. 150 volumes of 20 transverse slices were acquired with a repetition time (TR) = 2s. Four sets of data for methodology validation were labelled: VIS1, VIS2, VIS3 and VIS4.

***Visual and Auditory Experiment***

In addition to the aforementioned visual stimuli, a block of auditory stimuli occurred between 210-274s. The experiment, again, lasted 300s and 150 volumes of 25 transverse slices with TR=2s were acquired. One set of data was obtained: VIS-AUD.

***Visual and Motor Experiment***

The visual stimuli were the same as in VIS1-4 and VIS-AUD. Motor stimuli consisting of squeezing a rubber ball in the right hand at a rate of once every two seconds were administered between 240-300s in a 360s long experiment on a healthy subject with TR=2s. 150 volumes of 20 transverse slices were acquired. Three sets of data used are labelled VIS-MOT1, VIS-MOT2 and VIS-MOT3.

Parameters used in the proposed method: a 5-point moving average filter, a bandpass filter with passband between 1/80 and 1/40 Hz and the parameter $n$ for temporal averaging was 5, which resulted in one time bin equal to 10 seconds.

## 4 Results and Discussion

The stimuli detection results obtained with the proposed method can be found in Table 1, where the time bins corresponding to the four maximum numbers of detected voxels within a time bin are given. When the detected time bin falls into the period during which the stimuli were applied and the voxels contributed to this detection are in the brain areas which are typically found activated during these kinds of sensory experiments, a record is made in the table: 'A' for auditory cortex for auditory stimuli (e.g., [1, 2, 11]), 'M' for the SMA and motor areas for motor stimuli [6], and 'V' for the primary and extrastriate visual areas for visual stimuli [5, 6, 10]. The activation maps of five selected slices are shown for the cases when the stimulation responses were detected and the figure number is given in superscript in Table 1.

For the four sets of data with a block of visual stimuli only, our method is able to detect the brain response to the visual stimuli in three. The time bins detected that fall into the period during which the visual stimuli were applied is 70-80s for VIS1-3 and Fig.1-3 show that the voxels contributed to the temporal detection of the response are distributed in the primary and extrastriate visual areas.

The responses to both visual and auditory stimuli were detected in VIS-AUD. The third maximum was detected at time bin 220-230s, right after a block of auditory stimuli was applied and the voxels that contributed were in the areas of auditory cortex (Fig.4). The fourth maximum was detected at time bin 70-80s, during the period when a block of visual stimuli was applied and the voxels identified were in the primary and extrastriate visual areas as shown in Fig.5.

In three sets of VIS-MOT data, the responses to both visual and motor stimuli were detected in VIS-MOT1 during the period when the stimuli were applied and the voxels contributed are shown in red in Fig.6 and 7 respectively. The responses to the visual stimuli were found in the first maximum in VIS-MOT2 as in Fig.8 and the responses to the motor stimuli were found in the third

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| Data | First Max | Second Max | Third Max | Fourth Max |
|---|---|---|---|---|
| VIS1 | [1]70-80 **V** | 200-210 | 80-90 | 60-70 |
| VIS2 | 80-90 | 280-290 | 30-40 | [2]70-80 **V** |
| VIS3 | 230-240 | [3]70-80 **V** | 130-140 | 170-180 |
| VIS4 | 220-230 | 260-270 | 230-240 | 290-300 |
| VIS-AUD | 0-10 | 280-290 | [4]220-230 **A** | [5]70-80 **V** |
| VIS-MOT1 | [6]70-80 **V** | [7]250-260 **M** | 100-110 | 30-40 |
| VIS-MOT2 | [8]70-80 **V** | 130-140 | 140-150 | 210-220 |
| VIS-MOT3 | 180-190 | 170-180 | [9] 250-260 **M** | 90-100 |

Table 1: The time bin (in seconds) and spatial information detected for eight sets of fMRI data using the proposed method. **A**, **M**, and **V** indicate that the voxels contributed to the detected time bins are in the areas typically found in auditory, motor and visual sensory experiments respectively. The subscript is the figure number for the corresponding activation map.

| Data | First Max | Second Max | Third Max | Fourth Max |
|---|---|---|---|---|
| VIS1 | 70-80 **V** | 200-210 | 60-70 | 80-90 |
| VIS2 | 80-90 | 280-290 | 30-40 | 70-80 **V** |
| VIS3 | 230-240 | 70-80 **V** | 130-140 | 170-180 |
| VIS4 | 220-230 | 260-270 | 230-240 | 290-300 |
| VIS-AUD | 280-290 | 0-10 | 220-230 **A** | 230-240 |
| VIS-MOT1 | 70-80 | 250-260 **M** | 100-110 | 30-40 |
| VIS-MOT2 | 70-80 **V** | 220-230 | 130-140 | 40-50 |
| VIS-MOT3 | 180-190 | 250-260 **M** | 90-100 | 170-180 |

Table 2: The time bin (in seconds) and spatial information detected for eight sets of fMRI data without the proposed selection criterion. **A**, **M**, and **V** indicate that the voxels contributed to the detected time bins are in the areas typically found in auditory, motor and visual sensory experiments respectively.

maximum in VIS-MOT3 right after the stimuli were administered and the activated voxels are shown in Fig. 9.

In order to see the difference in response detection between with and without the adaptive selection criterion, the same procedure but without the adaptive selection criterion is applied to the same sets of data, i.e., at each time bin, all the voxels that reach their maxima in all slices are counted for the brain response detection. The time bins detected and their spatial information are given in Table 2. In comparison to the results from the proposed method, 7 out of 12 stimuli in all experiments (58.33%) were detected in the method without the adaptive selection criterion and 9 out of 12 stimuli (75%) were detected in the method with the adaptive selection criterion.

## 5 Conclusion

A data–driven fMRI analysis method is proposed using the pre-existing temporal clustering analysis technique with a novel adaptive neighbouring voxel selection criterion to detect brain responses. For validation purpose, the method has been applied to eight sets of fMRI data from three different sensory experiments. Where the fMRI time series contained the responses to the stimuli, our method is able to detect the time bins which fall into the periods during which the stimuli were on and the voxels found were distributed in the primary and extrastriate visual areas for the visual stimuli, auditory cortex for the auditory stimuli and SMA (supplementary-motor area) for the motor stimuli. The results were also obtained by using the same procedure but without the adaptive selection criterion: with the adaptive selection criterion 75% of the stimuli responses in these 8 sets of data were detected and without the adaptive selection criterion 58.33% of the stimuli responses were detected, regardless the existence of the stimuli responses in the fMRI time series.

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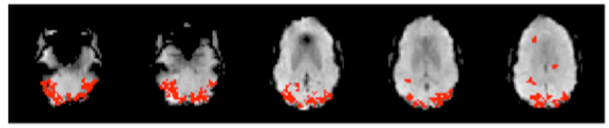

Figure 1: VIS1: the first maximum occurs in time bin 70-80s and the voxels detected are in the primary and extrastriate visual areas.

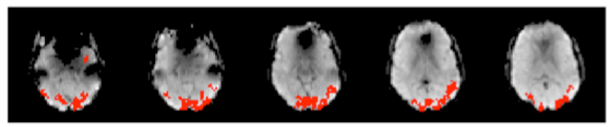

Figure 2: VIS2: the fourth maximum occurs in time bin 70-80s and the voxels detected are in the primary and extrastriate visual areas.

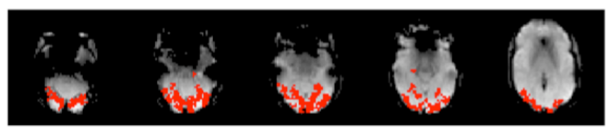

Figure 3: VIS3: the second maximum occurs in time bin 70-80s and the voxels detected are in the primary and extrastriate visual areas.

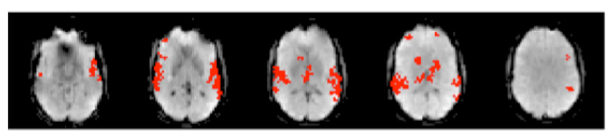

Figure 4: VIS-AUD: the third maximum occurs in time bin 220-230s and the voxels detected are in the auditory cortex.

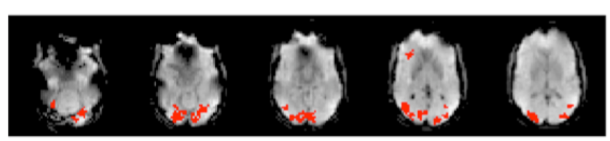

Figure 5: VIS-AUD: the fourth maximum occurs in time bin 70-80s and the voxels detected are in the primary and extrastriate visual areas.

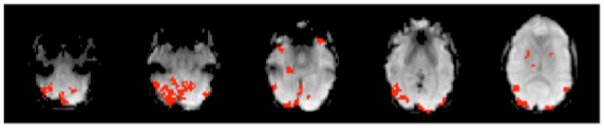

Figure 6: VIS-MOT1: the first maximum occurs in time bin 70-80s and the voxels detected are in the primary and extrastriate visual areas.

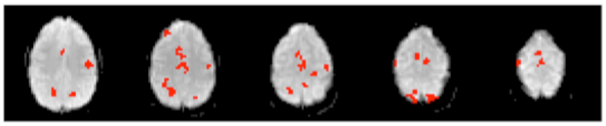

Figure 7: VIS-MOT1: the second maximum occurs in 250-260s and the voxels detected are in the motor areas.

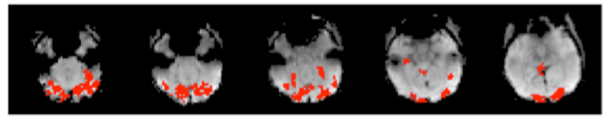

Figure 8: VIS-MOT2: the first maximum occurs in 70-80s and the voxels detected are in the primary and extrastriate visual areas.

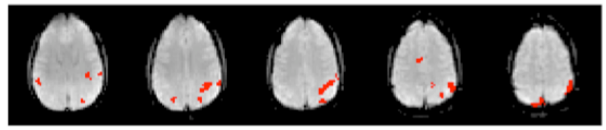

Figure 9: VIS-MOT3: the third maximum occurs in 250-260s and the voxels detected are in the motor areas.

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