STIMULUS RESPONSE DETECTION IN FMRI USING DIGITAL FILTERS, TEMPORAL CLUSTERING ANALYSIS AND A THREE-DIMENSIONAL SELECTION CRITERION

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ABSTRACT

A data-driven fMRI (functional magnetic resonance imaging) analysis method is proposed to detect responses when no clear a priori information is available to predict response onset or duration in a single-event or non-repetitive multi-event experiment. It is developed from pre-existing temporal clustering analysis methods with the applications of digital filters and temporal averaging. A novel three-dimensional selection criterion is employed to make use of the contribution from the signal of neighbouring voxels both in the same and adjoining slices on transverse section. The method has been applied to the whole-brain fMRI data from three different kinds of sensory experiments and the results demonstrate that the method is able to identify the time bins, during which the stimuli were applied and the voxels contributed to these identifications were in the brain regions, which were typically found activated in these kinds of sensory experiments.

1. INTRODUCTION

fMRI (functional magnetic resonance imaging) is one of the most widely used techniques to study brain activity and cognition. The analysis of fMRI data allows us to understand how the brain responds to specific stimuli. Analysis methods can be broadly divided into two categories: model-driven and data-driven methods. For the model-driven methods the detection of brain activation is carried out by comparing the temporal series of images to a model, which is based on the expected temporal variation of the signal intensity [8]. In contrast, data-driven techniques do not employ such a model [8]. Instead, methods such as independent component analysis (ICA) [13] and wavelet transform [3] are used to extract the main signal components from noise-containing fMRI time series.

Recently, a series of temporal clustering analysis (TCA) methods have been proposed as an alternative tool of data-driven techniques. These include original TCA [11], modified TCA [16], and iterative TCA [7]. All these methods are based on a dimension reduction of the four-dimensional (4D) fMRI data ($Y \times X \times T \times S$, where Y and X are the number of voxels in y and x axes respectively of each image plane, T is the number of volumes and S is the number of slices acquired during an experiment). One slice of data is processed at one time and the three-dimensional (3D) ($Y \times X \times S$) data in a slice are reduced to form a two-dimensional (2D) representation, in which the total number of voxels that reach a maximum at each time point is computed. In TCA with a 2D neighbourhood test [9], the spatial information available within a slice is also used to take advantage of the observation that physiologically plausible brain activations seldom occur in single isolated voxels. The method suggested in [10] uses the number of voxels detected in all available slices instead of just the voxels within a single slice to detect the response to stimuli.

This paper is an extension of the TCA approach in [10] incorporating a 3D selection criterion. The aforementioned 2D neighbourhood is extended into three dimensions by taking into account the adjoining slices on the transverse section. A threshold, γ, for how many neighbouring voxels a maximum voxel should have in order to contribute in the response detection was defined using the frequency counts throughout the whole brain. The voxels contributed to the final stimuli response detection are the ones with more than or equal to γ neighbouring voxels that also reach their maxima in the same time bin.

The proposed method has been applied to eight sets of fMRI data from three different kinds of sensory experiments. Without any information on the time course of stimuli, the results demonstrate that our method is able to detect the time bins, which fall into the period when the stimuli were applied and the voxels contributed are in the areas which were typically found in these kinds of sensory experiments, e.g., [1, 4, 8], when the MRI time series contain clear responses to the stimuli.

2. METHOD

The method can be broken down into six steps: (1) initial data processing (2) filtering processes (3) temporal averaging (4) locating the maximum response (5) a three-dimensional selection criterion and (6) stimulus response detection. The details of each step can be found in the following subsections.

2.1 Initial data processing

Firstly, the whole volume of 4D fMRI data set ($Y \times X \times T \times S$, where s denotes the s-th slice on transverse section, $s = 0, \cdots, S-1$, S is the number of acquired slices, $Y \times X$ are the number of voxels in y and x axes respectively of each image plane and T is the nur

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the experiment) is motion corrected using a locally written software [2] and a brain mask is obtained by employing the FSL brain extraction tool [15]. The method takes one slice of data at one time [6], in matrix form: $\underline{\boldsymbol{D}}_{ori,s}$ of size $Y \times X \times T$. The M_s valid voxels obtained from the mask of slice s corresponding to the brain tissue are distributed at co-ordinates $[\underline{\boldsymbol{m}}_{(s,y)};\underline{\boldsymbol{m}}_{(s,x)}]$, where $\underline{\boldsymbol{m}}_{(s,y)} = [m_{(s,y_1)}, m_{(s,y_2)}, \cdots, m_{(s,y_{M_s})}]$, $\underline{\boldsymbol{m}}_{(s,x)} = [m_{(s,x_1)}, m_{(s,x_2)}, \cdots, m_{(s,x_{M_s})}]$, and $(m_{(s,y_i)}, m_{(s,x_i)})$ are the y and x co-ordinates respectively of the i-th voxel of the brain mask in the slice s. Thus, the time series of voxels representing brain tissue in slice s are $\underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_\mu)}, m_{(s,x_\mu)}, \tau)$, where $\mu = 1, \cdots, M_s$ and $\tau = 1, \cdots, T$. This 3D information is reduced to two dimensions in the TCA methods as $\underline{\boldsymbol{D}}_{2D,s}$, a $M_s \times T$ matrix in Appendix (1) [7, 11, 16] and the percentage of signal change (psc) of intensity for each time series is calculated using $\underline{\boldsymbol{D}}_{psc,s} = (\underline{\boldsymbol{D}}_{2D,s} - \underline{\boldsymbol{D}}_{exp,s})./\underline{\boldsymbol{D}}_{exp,s} \times 100\%$, where ./ indicates the element-by-element division for two matrices,

$$\underline{\boldsymbol{D}}_{exp,s} = \begin{bmatrix} E\{\underline{\boldsymbol{D}}_{2D,s}(1,:)\} & \cdots & E\{\underline{\boldsymbol{D}}_{2D,s}(1,:)\} \\ \vdots & \ddots & \vdots \\ E\{\underline{\boldsymbol{D}}_{2D,s}(M_s,:)\} & \cdots & E\{\underline{\boldsymbol{D}}_{2D,s}(M_s,:)\} \end{bmatrix},$$

a $M_s \times T$ matrix and $E\{\cdot\}$ denotes expectation [8].

2.2 Moving-Average and Bandpass Filtering Processes

At this stage, a moving average filter is applied to each time series, i.e., each row of $\underline{\boldsymbol{D}}_{psc,s}$. A bandpass filter is also applied, in order to eliminate low and high frequency artefact due to, such as, heartbeat, breathing and scanner-related drift. Details of the bandpass filter designed for this work can be found in Section 4. The matrix containing filtered time series is denoted as $\underline{\boldsymbol{D}}_{filtered,s}$ of size $M_s \times T$.

2.3 Temporal Averaging

As in [9, 10], the data are now grouped into time bins, i.e., the average of every non-overlapping n time points in $\underline{\boldsymbol{D}}_{filtered,s}$, so that the voxel responses to a same block of stimuli at different time points are more likely to be detected throughout the brain. The matrix that proceeds to the next stage is $\underline{\boldsymbol{D}}_{processed,s}$, a $M_s \times (T/n)$ matrix.

2.4 Locating the Maximum Response

For each voxel time series, the time bin of the observed maximum is found. The matrix $\underline{\boldsymbol{R}}_{max,s}$ as in Appendix (2) of size $M_s \times (T/n)$ reflects the maximum signal for each voxel in $\underline{\boldsymbol{D}}_{processed,s}$. A binary matrix, $\underline{\boldsymbol{D}}_{checking,s,\tau}$,of size $Y \times X$ is generated for obtaining the spatial information of voxels which reach their maxima in time bin τ:

$$\underline{\boldsymbol{D}}_{checking,s,\tau}(m_{(s,y_\mu)}, m_{(s,x_\mu)}) = \begin{cases} 1, & \text{if } \underline{\boldsymbol{R}}_{max,s}(\tau,\mu) = 1 \\ 0, & \text{otherwise} \end{cases} \quad (3)$$

for $\tau = 1, \cdots, T/n$ and $\mu = 1, \cdots, M_s$.

In the conventional TCA methods [7, 11, 16], the matrix $\underline{\boldsymbol{R}}_{max,s}$ is summed column wise, so that the time window in which the maximum number of voxels reached their maxima may be identified for each point in the time series in a single slice.

In our method, before this summation takes place, for every time bin a 3D selection criterion is applied to all voxels, which are detected to have reached their maxima.

2.5 A Three-Dimensional Selection Criterion

Based on that voxels corresponding to a stimulus appear in clusters with various sizes and shapes, a 3D selection criterion is applied to identify voxels that are more physiologically plausible by taking into account the adjoining slices on transverse section. In $\underline{\boldsymbol{D}}_{checking,s,\tau}$, a $3 \times 3 \times 3$ neighbourhood is formed for each entry with 1. For example, if the first voxel reaches its maximum at time bin τ is at co-ordinate $(m_{(s,y_\alpha)}, m_{(s,x_\alpha)})$, its number of neighbouring voxels in a $3 \times 3 \times 3$ neighbourhood which also reach their maxima is $N_{s,\tau}[m_{(s,y_\alpha)}, m_{(s,x_\alpha)}]$ in (4). The window size $3 \times 3 \times 3$ is chosen, so that the activation in the small brain regions can also be detected.

$N_{s,\tau}[m_{(s,y_\alpha)}, m_{(s,x_\alpha)}] =$

$$\left[\sum_{s'=s-1}^{s+1} \sum_{y'=m_{(s',y\alpha)}-1}^{m_{(s',y\alpha)}+1} \sum_{x'=m_{(s',x\alpha)}-1}^{m_{(s',x\alpha)}+1} \underline{\boldsymbol{D}}_{checking,s',\tau}(y',x') \right] - 1 \quad (4)$$

The number of neighbouring voxels that the maximum voxel of each processed time series has is recorded for all available slices, for which a histogram is obtained. Only the voxels with the number of neighbouring voxels in the upper 20% of the histogram (rounds to the nearest integer towards infinity) are taken into account. This number of neighbouring voxels threshold is γ.

A new matrix, $\underline{\boldsymbol{R}}'_{max,s}$, is formed to count the number of voxels that have met the 3D selection criterion.

$\underline{\boldsymbol{R}}'_{max,s}(\mu,\tau) =$

$$\begin{cases} \underline{\boldsymbol{D}}_{processed,s}(\mu,\tau), & \text{if } N_{s,\tau}[m_{(s,y_\mu)}, m_{(s,x_\mu)}] \geq \gamma \\ 0, & \text{otherwise} \end{cases} \quad (5)$$

for $1 \leq \mu \leq M_s$ and $1 \leq \tau \leq T/n$.

The matrix $\underline{\boldsymbol{R}}'_{max,s}$ is then summed column wise to form $\underline{\boldsymbol{F}}_s$, in order to identify the time bin in which the maximum number of voxels reach their maxima simultaneously.

$$\underline{\boldsymbol{F}}_s = [F_1, F_2, \cdots, F_{T/n}] \text{ where } F_q = \sum_{p=1}^{M_s} \underline{\boldsymbol{R}}'_{max,s}(p,q) \quad (6)$$

2.6 Stimulus Detection

For all the available S slices, $\underline{\boldsymbol{F}} = \sum_{s=1}^{S-2} \underline{\boldsymbol{F}}_s$, a $1 \times (T/n)$ vector, returns the number of voxels that reach their maxima and meet our selection criteria at each time bin. Slices 0 and $S-1$ are not used, since their 3D neighbourhood can not be formed. For an experiment that contains κ stimuli, we record only the first 2^κ time bins (referred to as first maximum, second maximum, so on) with the largest numbers of maximum voxels and generate the corresponding activation maps by colouring the detected voxels using red. 2^κ was chosen, because we expect that the time bins corresponding to the stimuli would have more detected maximum voxels compared to other time bins and we also consider the possible detection of resting state network [5].

3. EXPERIMENTS

The proposed method was applied to eight sets of fMRI data from three different ki

Data	γ	1st Max	2nd Max	3rd Max	4th Max
VIS1	8	**V** 70-80 [1]	80-90	-	-
VIS2	10	80-90	**V** 70-80	-	-
VIS3	9	**V** 70-80	230-240	-	-
VIS4	8	220-230 [2]	260-270	-	-
VIS-AUD	10	280-290	0-10	**A** 220-230 [3]	**V** 70-80 [4]
VIS-MOT1	8	**V** 70-80	**M** 250-260	30-40	100-110
VIS-MOT2	8	**V** 70-80	130-140	140-150	210-220
VIS-MOT3	10	180-190	**M** 250-260 [5]	90-100	310-320

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 activation map for the results with a superscript may be found in Fig.1 to 5.

method validation. The voxel dimensions were 3.75mm $\times$ 3.75mm $\times$ 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 are 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 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.

4. PARAMETERS USED IN THE APPLICATION TO fMRI DATA

A 5-point moving-average filter was used for all experiments. The digital Butterworth bandpass filter used had the passband frequency range: [1/80-1/40] Hz and the stopband frequencies at 1/100 Hz and 1/20 Hz for all experiments. The filter was chosen for its flat passband response and the frequency range reflects the estimated response duration. The filters were implemented in Matlab [12, 14]. The parameter n for the temporal averaging was 5, which result in every time bin equal to 10 seconds. The $3 \times 3 \times 3$ neighbourhood threshold, γ, computed for the 3D selection criterion can be found in Table 1.

5. RESULTS AND DISCUSSION

5.1 Results from the Proposed Method

The stimulus response detection results are in Table 1 for all eight sets of data, including the time bins corresponding to the first and second maxima, i.e., two largest number in the four highest maxima for VIS-AUD and VIS-MOT1-3 and where the associated activation maps contain typical responses, e.g., auditory: [1], motor: [4] and visual: [4, 8], to these sensory stimuli it is marked with **A**, **V** and **M** for auditory, visual and motor stimulus respectively. Due to the page constraints, only one activation map with three slices is shown for some of the results and the figure number is given in superscript in Table 1.

For data containing only visual stimuli (VIS1-4), the method is able to detect the responses in primary and extrastriate visual cortices for three out of four sets. In VIS1-3, the time bins detected fall into the period when the visual stimuli were applied. Fig.1 is an example of the visual activation map and the average time series of the detected voxels (in red), original and processed (filtered and temporally averaged), are given to show that the detected voxels exhibits the typical blood oxygenation level dependent (BOLD) response [8] to stimuli. However, no strong response during when the visual stimuli were applied was found in the first and second maxima in VIS4. The first maximum found in VIS4 is in Fig.2, from which the characteristics of the pattern of the BOLD response were observed.

In VIS-AUD, the auditory and visual responses were detected in third and fourth maxima respectively. Fig.3 is the activation map for time bin: 220-230s (third maxima), where voxels in auditory cortex reached their maxima and their average time series, where a typical 1.5% increase in the fMRI BOLD signal due to stimuli, was found. Fig.4 shows the activation map for the fourth maximum, which was detected in time bin: 70-80s (fourth maxima) and in the primary and secondary visual areas.

Both visual and motor stimuli were detected in VIS-MOT1. Only the visual response was detected in VIS-MOT2 and only the motor response was found in VIS-MOT3, which is shown in Fig.5 with its average time series plot.

In order to investigate the reason of not able to detect the responses to the stimuli for some data, the time series were extracted from the typical activation areas corresponding to these stimuli, i.e., the time series were extracted from SMA (supplementary motor area) of VIS-MOT2 and from primary and extrastriate visual areas of VIS4 and VIS-MOT3. Here the time series extraction for VIS4 and VIS-MOT2 are given as examples. In Fig.6, the primary and extrastriate visual areas are indicated in blue for VIS4 and their average time series plot is given, which does not appear to have the same characteristics as the time series extracted from the visual response detected in VIS1 in Fig.1. In Fig.7, where the SMA area of VIS-MOT2 is indicated in blue and the time series were extracted from these voxels. The average time series did not contain a peak during the period during which the motor stimuli were on.

5.2 Comparison with the Modified Temporal Clustering Analysis Method

Our method was developed from the modified temporal clustering analysis method proposed in [16], which used a single slice of fMRI data at a time and every point in the time series was considered. In order to compare our work to the original method, the original method, i.e., no filtering and temporal averaging and neighbourhood test applied, was applied to all the slices in VIS-AUD. The time points, at which the sum of signal percentage of change is the greatest in the time series, can be found in Table 2. T

Slice	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Time[a]	86	196	198	196	198	196	280	282
Slice	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Time	196	196	196	196	196	196	128	196
Slice	**17**	**18**	**19**	**20**	**21**	**22**	**23**	
Time	280	196	130	130	196	180	198	

Table 2: The time when the maximum number of voxels reached their maxima obtained using the original MTCA method [16] on individual slices in VIS-AUD. [a]: time that the maximum was detected (seconds)

maxima are shown for 5 slices (slice 9-13) that had appeared in Figs. 3 (slice 9-11) and 4 (slice 11-13) and they can be found in Fig. 8. As shown in Table 2, the time with the maximum number of voxels that reach their maxima did not fall into the period when either visual or auditory stimuli were applied.

6. CONCLUSION

A data-driven method is proposed for detecting responses to stimuli in fMRI data, which uses pre-existing temporal clustering analysis methods with digital filters and a three-dimensional selection criterion. The validation of our method using eight sets of data from three different kinds of sensory experiments demonstrate that our method is able to identify the correct temporal and spatial locations of brain activity, when the response to the experiments produce the largest BOLD changes in the time series without any *a priori* information on the experimental paradigm.

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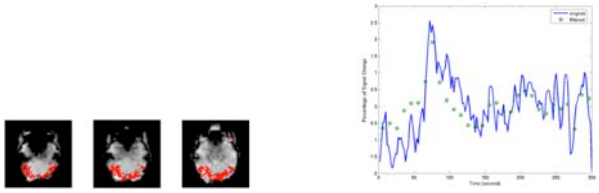


Figure 1: Visual Experiment VIS1: the activation found in the primary and extrastriate visual areas for the time bin detected (70-80s) and the average original and processed time series in percentage of change of the detected voxels in these slices.

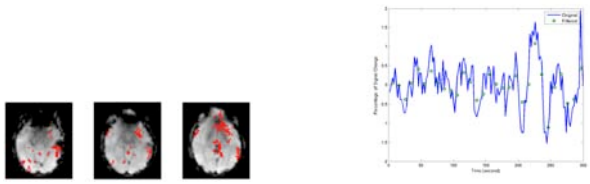
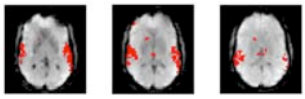


Figure 2: Visual Experiment VIS4: the activation found in the time bin detected (220-230s) and the average original and processed time series in percentage of change of the detected voxels in these slices.

APPENDIX

$$\underline{\boldsymbol{D}}_{2D,s} = \begin{bmatrix} \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_1)}, m_{(s,x_1)}, 1) & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_1)}, m_{(s,x_1)}, 2) & \cdots & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_1)}, m_{(s,x_1)}, T) \\ \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_2)}, m_{(s,x_2)}, 1) & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_2)}, m_{(s,x_2)}, 2) & \cdots & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_2)}, m_{(s,x_2)}, T) \\ \vdots & \vdots & \ddots & \vdots \\ \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_{M_s})}, m_{(s,x_{M_s})}, 1) & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_{M_s})}, m_{(s,x_{M_s})}, 2) & \cdots & \underline{\boldsymbol{D}}_{ori,s}(m_{(s,y_{M_s})}, m_{(s,x_{M_s})}, T) \end{bmatrix} \quad (1)$$

$$\underline{\boldsymbol{R}}_{max,s}(\mu,\tau) = \begin{cases} \underline{\boldsymbol{D}}_{processed,s}(\mu,\tau), & \text{if } \underline{\boldsymbol{D}}_{processed,s}(\mu,\tau) \text{ is } \max\{\underline{\boldsymbol{D}}_{processed,s}(\mu,:)\} \\ 0, & \text{otherwise} \end{cases} \quad \text{for } 1 \le \mu \le M_s \text{ and } 1 \le \tau \le T/n \quad (2)$$



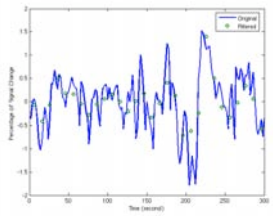
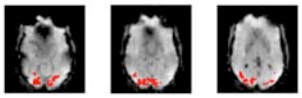


Figure 3: Visual and Auditory Experiment: VIS-AUD: the activation found in the auditory cortex for the time bin detected (220-230s) and the average original and processed time series in percentage of change of the detected voxels in these slices.



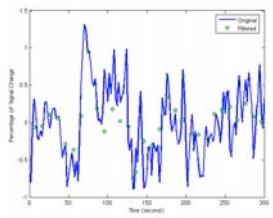
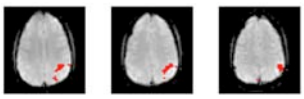


Figure 4: Visual and Auditory Experiment VIS-AUD: the activation found in the primary and extrastriate visual areas for the time bin detected (70-80s) and the average original and processed time series in percentage of change of the detected voxels in these three slices.



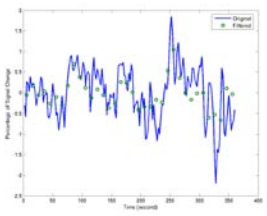
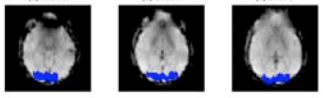


Figure 5: Visual and Motor Experiment VIS-MOT3: the activation found in the SMA (supplementary motor area) for the time bin detected (250-260s) and the average original and processed time series in percentage of change of the detected voxels in these slices.



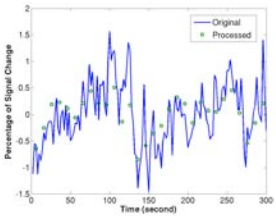
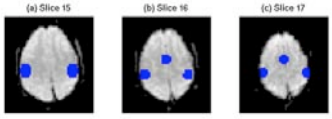


Figure 6: Visual Experiment VIS4: selected voxels (in blue) for typical visual response in Slice 6-8 and the average original and processed time series in percentage of change for the selected voxels in these slices.



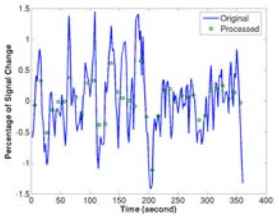


Figure 7: Visual-Motor Experiment VIS-MOT2: selected voxels (in blue) for typical motor response in Slice 15-17 and the average original and processed time series in percentage of change for the selected voxels in three slices.

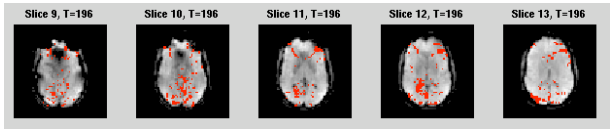


Figure 8: The voxels detected in Slice 9 to 13 in VIS-AUD using the conventional MTCA method.