DATA-DRIVEN FMRI GROUP CLASSIFICATION USING CONNECTED COMPONENTS AND GAUSSIAN PROCESS CLASSIFIERS

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is a popular tool for studying brain activity due to its non-invasiveness. Conventionally an expected response needs to be available for correlating with fMRI time series in model-driven analysis, which limits experimental paradigms to blocked and event-related designs. To study neuronal responses due to slow physiological changes, such as after a glucose challenge or a drug administration, for which the expected response is unavailable, we had proposed a data-driven method: connected component analysis. In this paper, a novel group classification method is proposed by using both connected components and Gaussian process classifiers. The results demonstrate that the method is able to differentiate insulin resistant volunteers from insulin sensitive volunteers by their neuronal response to glucose ingestion with an accuracy of 77%.

Index Terms— fMRI, data-driven, connected component, Gaussian process classifier, brain

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is one of the most popular techniques for studying brain responses due to its non-invasiveness, which permits longitudinal examination of healthy volunteers as well as patients and investigation of groups not possible using more invasive methods [24]. fMRI experiments can be broadly categorised as design-driven (blocked and event-related designs) or design-free [7]. In this paper, we concentrate on the kind of single-event experiments, which cause slow physiological changes, for example, a 40-minute scan after glucose ingestion [11, 13] and pharmacological studies [24].

fMRI data analysis methods can be broadly divided into two groups: model-driven and data-driven. When an expected response can either be obtained or estimated, a model-driven method, such as general linear modelling [4], can be applied to search for the brain regions, which demonstrate similar changes in their voxel time series to the expected response. However, when an expected response cannot be obtained or estimated accurately, data-driven analysis methods present a more appropriate alternative. The data-driven methods also have the advantage of data exploration, since no assumptions need to be made about the spatial or temporal characteristics of the neuronal responses.

To date, independent component analysis (ICA) is perhaps the most widely used data-driven analysis method [1, 2] and it provides an excellent data-exploratory tool. The entire data set is decomposed into components that are maximally independent statistically [3]. This method also has the advantage of isolating sources of noise automatically. However, the challenges remain: (1) the results are highly dependent on prior determination of the number of independent components (2) for the interpretation of the components identified; the users need to decide which components are responses to stimulation and which are noises [3]. Moreover, for experiments involving physiological changes (e.g., responses to glucose ingestion), anticipated inter-subject variability in neuronal responses make the interpretation of components extremely difficult.

A series of data-driven methods based on temporal maxima detected in voxel time series have been developed based on temporal clustering analysis (TCA) methods [5, 13, 14, 21, 25]. These methods process one slice at a time and seek the brain regions that have temporal maxima within a data-driven time window.

Built on temporal clustering analysis, we have developed a tool known as connected component analysis (CCA) [10, 12] for whole-brain data, which detected spatial- and temporal- connections in four dimensions (three-dimensional (3-D) brain images over time). The method was aimed for single-event experiments that cause slow physiological changes. CCA is based on two assumptions: (1) the single-event stimulation causes a temporal peak in the responding brain regions (2) the responding voxels occur in a spatially connected voxel-set (cluster). The method has the advantage that no prior information is required on expected results and the number of components does not need to be determined a priori; it depends on the spatial-temporal connections of temporal maxima in the data set. For a group of subjects, each of which may have different numbers of components identified, the group level analysis becomes challenging. A group analysis method has been proposed in [12] by extracting common information from various numbers of components obtained from each subject.

In addition to the identification of the spatio-temporal characteristics of the response, in this paper, we propose to use both connected components and Gaussian process classifiers to (1) classify two groups of subjects based on their connected components identified and (2) identify the discriminative regions between two groups.
2. CONNECTED COMPONENTS

After pre-processing steps (See Section 4 for details), the connected component analysis method was applied to the 4-D data, \( D \) of size \( X \times Y \times Z \times T \), where \( x = 1, \ldots, X \), \( y = 1, \ldots, Y \), \( z = 1, \ldots, Z \), \( t = 1, \ldots, T \). \( X \), \( Y \), \( Z \) and \( T \) are the number of voxels in \( x \)- and \( y \)-axes, and \( Z \) is the number of slices and \( T \) is the number of volumes acquired, for each subject. Step 1-3 were largely taken from [10, 12] with minor modifications.

2.1. Subject Level

**Step 1: Voxel temporal maximum/minimum detection**

For each subject, a 4-D of size \( X \times Y \times Z \times T \) was generated. Non-zero entires were then made for spatio-temporal connected components identified as described above. In the example in Step 1, the 4-D matrix output of subject 1 contain time series of length \( \{10-60\} \) at the voxels identified in \( C_{1,1} \) and \( C_{1,2} \).

2.2. Group Level

**Step 1: Components with common temporal information identification**

For all components identified in the subject level, the ones with common temporal information were identified. For example, subject 1 had 3 components identified, \( C_{1,1} \) at \( \{10-20\} \), \( C_{1,2} \) at \( \{40-60\} \) and \( C_{1,3} \) at \( \{200-340\} \) and subject 2 had 3 components identified \( C_{2,1} \) at \( \{10-60\} \), \( C_{2,2} \) at \( \{100-130\} \) and \( C_{2,3} \) at \( \{160-190\} \). \( C_{1,1} \), \( C_{1,2} \) and \( C_{2,1} \) were overlapping during \( \{10-60\} \); therefore they were selected for the next step.

2.3. CLASSIFICATION OF COMPONENTS

The 4-D outputs obtained from all subjects were then used as the feature for classification of different groups of subjects or different experimental conditions. The application of machine learning methods, such as support vector machine (SVM) classifier and Gaussian process, to fMRI data sets have shown good performances in predicting outcomes, e.g., [15, 16]. For classifying the 4-D matrices consisting of the connected component analysis output, a Gaussian process classifier was employed because of its multivariate regression property and provision of probabilistic classification [15, 22].

3. EXPERIMENT

A single-event experiment of glucose ingestion was carried out on a General Electrical Medical Systems SIGNA HDx 1.5 Tesla scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry for investigating the difference in neuronal response to glucose between insulin sensitive (IS) and insulin resistant (IR) subjects. Two groups of subjects were recruited, based on their homeostatic model assessment on insulin resistance (HOMA-IR) [6] and oral glucose tolerance test result. Group IS: 11 insulin sensitive subjects (9F/2M, mean age: 35 years with the range of 19-55 and HOMA-IR: 0.8 (0.6-1.2)); Group IR: 11 insulin resistant subjects (2F/9M, mean age: 37 with the range of 21-68, and HOMA-IR: 3.5 (0.5-5.0)).

Each subject had a 42.2 minute scan, which were acquired using gradient echo EPI with TR=10 seconds; TE=40ms and slice thickness=2mm, with a 0.2mm gap. Three volumes were acquired before subjects ingesting a glucose drink. 75g of glucose (Glucose BMS Monohydrate B.P., Bio-Medical Services, York, UK) for those with normal glucose tolerance or 50g of glucose for those with impaired glucose tolerance in 388ml of water, followed by a 250 volume acquisition. During scanning, subjects were listening to pleasant classical music and viewing indoor and outdoor scenery pictures during scans to ensure all individuals had a homogenous source of visual and auditory stimuli and to minimise the occurrence of sporadic changes in brain activity brought about by uncontrolled imagery, recollection of events or sleep.

4. PRE-PROCESSING STEPS

The first 5 volumes of data (3 volumes before ingestion and 2 volumes after ingestion) were discarded, in order to eliminate the
presence of non-steady state magnetisation. The rest of the data were then pre-processed using SPM5 [23] for slice-timing correction, realignment, normalisation to EPI template and spatial smoothing (FWHM=6 mm). A grey matter mask was generated using the default grey matter mask in SPM5 with probability \( \geq 0.2 \), from which CSF mask with probability \( \geq 0.1 \) was subtracted for completion. Only voxels inside the grey matter mask were analysed. For each subject the average time series for all voxels inside the grey matter mask were computed and used for correcting global trend using equ. (1). Each grey voxel time series was multiplied by the ratios, \( m(t) \), obtained in equ. (1).

\[
m(t) = \frac{V_{GM,mean}}{V_{GM}(t)}
\]

where \( V_{GM}(t) \) is the average time series of all voxels in the grey matter mask at time point \( t \) and \( V_{GM,mean} \) is the average of \( V_{GM} \) (1 : \( T \)).

The unit of the corrected time series was then transformed into per cent signal change from signal intensity for voxel-to-voxel comparisons using equ. (2). A 3-point moving-average filter was applied to remove high-frequency noise.

\[
V_{per}(t) = \frac{V_{ori}(t) - V_{ori}}{V_{ori}} \times 100\%
\]

where \( 1 \leq t \leq T \), \( V_{per} \) is the voxel time series in per cent signal change, \( V_{ori} \) is the voxel time series in original signal intensity and \( V_{ori} \) is the average of \( V_{ori} \).

5. RESULTS

5.1. Connected Components Identified

The connected components for both signal increase and decrease for both groups were computed. For signal increase, 9 out of 11 IS group subjects had components detected at the beginning of the scans, \( \{30-390\} \) seconds after the ingestion and 8 out 11 IR group subjects had components detected at the beginning of the scans, \( \{30-350\} \) seconds. For signal decrease, every subject in both groups had components identified at the early part of the scans; therefore these components were used for classification. Due to page constraints, only the temporal information of components, which contributed to the group common temporal information, is given in Table 1 for the IS group and Table 2 for the IR group. These results also demonstrate the strength of CCA on subject variability.

5.2. Classification Results

A 4-D matrix containing the section of the time series within the detected period of connected components as indicated in Table 1 and 2 at the corresponding voxels was generated for each subject. These matrices from two groups were then used for group classification using the PROBID toolbox [22], which resulted in sensitivity: 63.64%, specificity: 90.91% and accuracy: 77%. A test involving 1000 random permutations was applied to randomly assign group labels to the 22 data sets and the Gaussian process classifier was applied to each pair of permuted groups, which resulted in accuracy: 49.51%, mean sensitivity: 49.10%, mean sensitivity: 49.93% and no permutations achieved higher sensitivity and specificity than the results from actual groups (p=0.001). In other words, when the group labelling was not assigned according to the experiments, the classification accuracy was only by chance.

<table>
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<th>Subject</th>
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<tr>
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<td>30-100</td>
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</table>

Table 1. The temporal information (in seconds, after glucose ingestion) of components identified for signal decrease in insulin sensitive group that was used for classification

The most discriminative regions were shown in the weight map in Fig. 1. The voxels associated with the IS group were in red, whereas the voxels in yellow were associated with the IR group. The Talairach coordinates were obtained from these regions and the Talairach Client was employed for labelling brain regions [8, 9]. The pattern identified that associated with the IS group included a large cluster of voxels in putamen and anterior cingulate; other brain regions detected included bilateral dentate; bilateral cerebellar tonsil; right claustrum; bilateral culmen; bilateral declive; right fastigium; bilateral fusiform gyrus; right insula; right lateral globus pallidus; right medial frontal gyrus; right middle temporal gyrus; bilateral hippocampus and bilateral superior temporal gyrus. The pattern identified that associated with the IR group included a large cluster in left amygdala and other regions detected were bilateral anterior lobe; bilateral cerebellar lingual; left fusiform gyrus; bilateral inferior semilunar lobule; bilateral nodule; left parahippocampal gyrus; left pyramis; bilateral tuber, uncus and uvula.

6. CONCLUSION

A novel data-driven fMRI classification analysis method was proposed for studying neuronal response caused by slow physiological changes. Connected component analysis was employed to extract 4-D features, followed by a Gaussian process classifier for classification between groups of subjects. The results demonstrated that the method is able to classify insulin resistant subjects from insulin sensitive subjects using their response to glucose ingestion with 77% accuracy.

7. REFERENCES


Table 2. The temporal information (in seconds, after glucose ingestion) of components identified for signal decrease in insulin resistant group that was used for classification

<table>
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<th>C4</th>
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Fig. 1. Weight map. Red: associated with insulin sensitive group. Yellow: associated with insulin resistant group.


