An Analysis of fcMRI data in Schizophrenia

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Abstract

We report analyses intended to explore the functional magnetic resonance imaging (fMRI) data collected in studies conducted by Repovs et al., on the manner in which brain network connectivity is related to schizophrenia [**?**, **?**]. A host of exploratory analyses, combining both classical linear modeling methods and machine learning, were undertaken in order to gain further insights into the fMRI data examined.

1 Introduction

The human central nervous system is a complex dynamic network, consisting of numerous functional regions that coordinate everything from simple behaviors to complicated thoughts. In an effort to better understand the manner in which functional changes contribute to the symptoms of schizophrenia, Repovs et al. conducted neuroimaging studies, including both functional connectivity magnetic resonance imaging (fcMRI) and diffusion tensor imaging (DTI), on many subjects, with their goal being to characterize the activity of several brain regions chosen a priori, and to develop an understanding of how the functional activities of these regions may differ across health states [**?**, **?**].

2 Data

The analyses reported in this paper are based on data generated in a series of neuroimaging experiments conducted by Barch, Repovs, & Csernansky. The aim of these experiments was to ascertain the activity of several brain networks thought to be associated with depressed cognitive function in individuals with schizophrenia by collecting functional connectivity magnetic resonance imaging (fcMRI) data on healthy individuals, individuals with schizophrenia, and the (healthy) siblings of participants in either of the two former groups [**?**]. For the purposes of the analyses reported in this paper, the imaging data were acquired from the OpenfMRI project (`https://openfmri.org/`), where they are listed with accession number ds000115. The data is available for groups of subjects, with each subject-specific data directory containing anatomical MR imaging data, functional MR imaging (using the BOLD contrast) data, and diffusion tensor imaging (DTI) data. In this preliminary report, the analyses are restricted to the BOLD functional MR imaging data, for eight subjects among the pool of 102 subjects for which data are available, with most analyses (ranging from linear modeling to machine learning with K-Means) taking the form of exploratory examinations into the structure of this imaging data.

3 Methods

Literature notes that different regions of the brain exhibit different levels and patterns of activities during performance of cognitive tasks [**?**]. Some regions are associated with marked increase in activities and some with decrease in activities. They are often given a priori in papers. One of the goals of our analysis is to identify activation regions during the performance of n-back tasks using unsupervised learning methods (e.g., K-Means), comparing the regions isolated in this manner with those assumed in the literature. Specifically, we want to find regions that are associated with dynamic, task-related and functional aspects of brain activities, instead of just anatomical subdivisions. Two preliminary types of analysis are performed and introduced below, along with diagnostic checks of the validity of the results.

4 Results

4.1 Data fetching and pre-processing

For all BOLD datasets, we removed the first five images to allow measurements to achieve steady state. In addition, we prepared scripts to detect the root mean square (RMS) difference outliers using the inter-quartile range (IQR) to define outliers. This is because they could imply a sudden widespread shift in signals caused by hardware issues. We have run all the analysis with the outliers removed so far, but will run a portion of the analysis with the outliers in the future and discuss the impact of excluding outliers.

Some preprocessing tasks are analysis-specific. As will be discussed in a later section, we scaled BOLD measurements per time step to use them as one of the feature sets for k-means clustering.

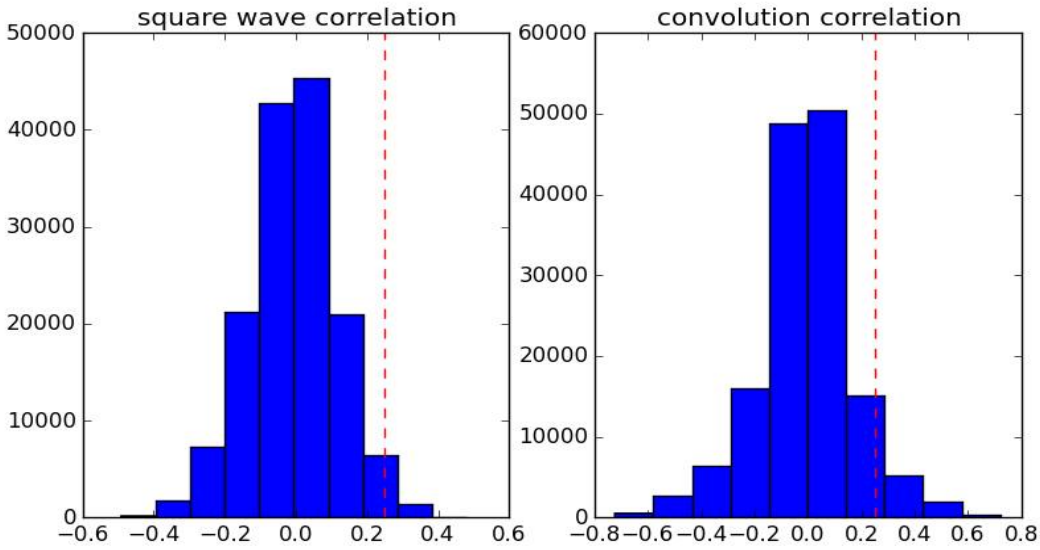
4.2 Correlations with baseline functions

This set of methods aim to produce an image identifying the regions which show significant signal change in response to the task by calculating correlation coefficients (r) between the bold signal along the time course and a reference waveform, for each voxel. A high value of the correlation coefficient means that fluctuation of the signal in the locale of the brain is task-dependent, hence activated by the task.

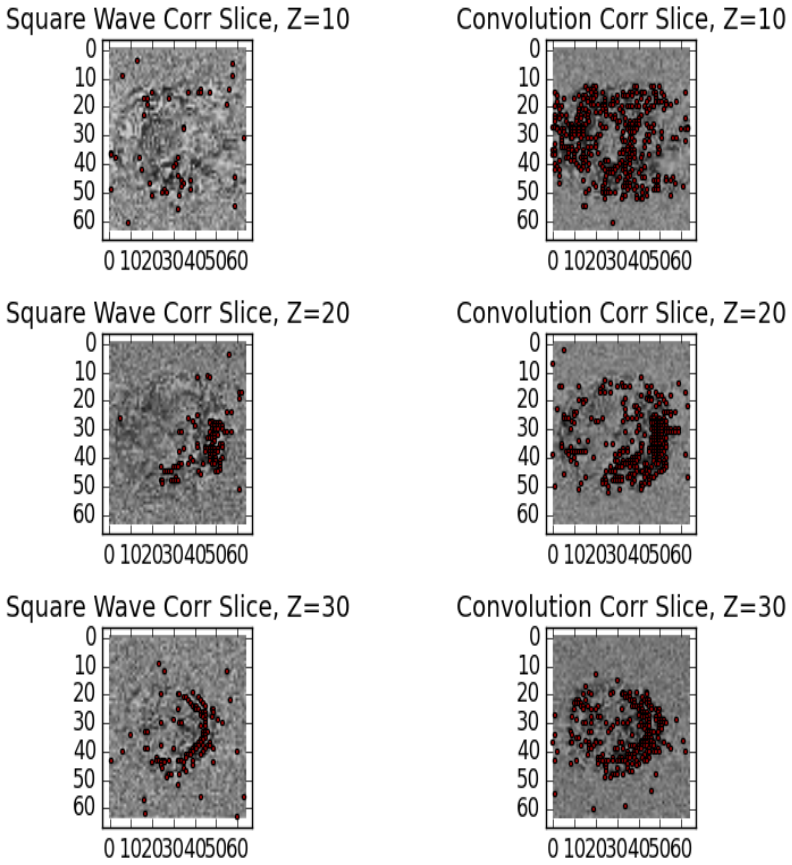
For a bold signal X, and a reference waveform Y, the correlation coefficient is calculated as

$$r = \frac{\Sigma(X - \bar{X})(Y - \bar{Y})}{\sqrt{\Sigma(X - \bar{X})^2 \Sigma(Y - \bar{Y})^2}} \tag{1}$$

The two methods we are testing here are differentiated by two types of reference waveforms: (1) square wave using on-off neural prediction from condition file (SW method), and (2) a convolved function on neural predictions and a gamma haemodynamic response function (HRF) (CF method).



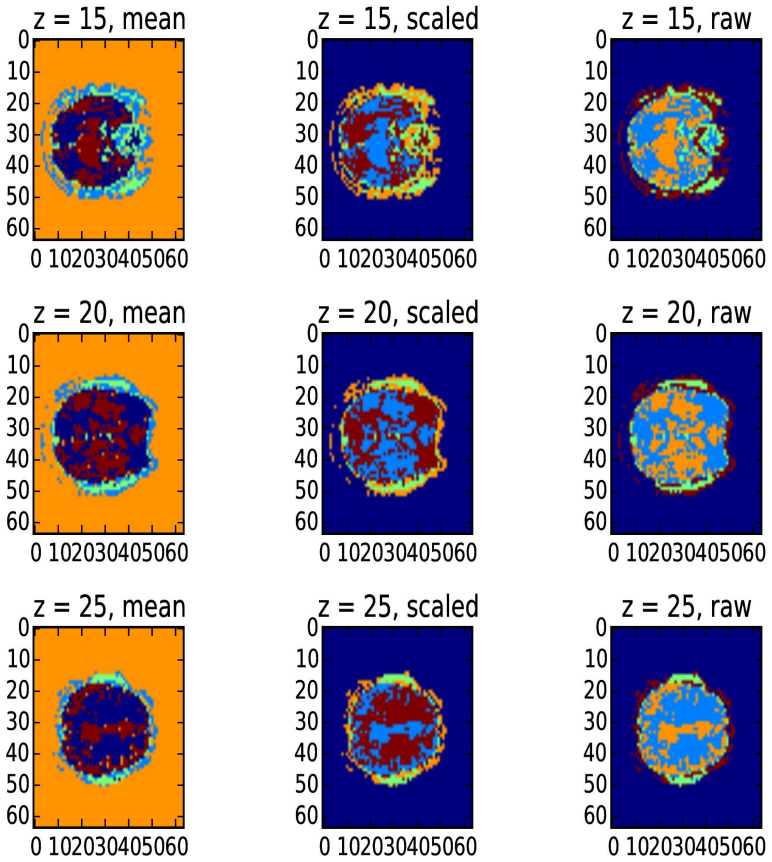
Here, we want to compare the two types of analysis and decide on the better way to find the activation regions. After calculating the correlations using both square wave time course (SW method) and the convolved reference time course (CR method) , we plot the histogram of r-values and get an idea about the range and the distribution of the correlation. Gathering that information, we decided on the threshold 0.20 to say whether a voxel is active or not active. We plot the voxels which correlates to the reference waveform with r ¿ 0.20 in red, so that we can visually examine the activeness of the voxels in the brain. By comparing the active regions under square wave time course (left) and convolved time course (right), we can clearly see that it is hard for SW method to detect the activeness while the CR method gives more reasonable and detailed results.Therefore, we will use the convolved reference waveform for detecting the task-dependent voxels in our future analysis.



4.3 Clustering with k-means

K-means clustering is an unsupervised technique which aims to partition n observations into k clusters based on a feature set of n features. Each observation is classified into the cluster with the nearest mean. In our case, n is the number of voxels. k is chosen to be 5 although ideally, we should run K-means with multiple k values [**?**]. Clustering results across the three runs of the same subject are merged together using a voting algorithm [**?**]. We used three sets of features as described below to obtain three sets of clustering results: (1) mean of BOLD signals over time course for every voxel, (2) all signals in the time course for every voxel, (3) all signals in the time course for every voxel, centered and normalized over all signals in the corresponding time step.

We do not involve the conditional file in the clustering. This is because the underlying time courses are the same across methods as we compare across the same subjects. Since Feature Set (1) only uses mean as a single feature, it determines the clusters only based on intensity of the BOLD signals and can be used a naive set of non-functional clusters (i.e. the other two or future methods should deviate from this to reveal functional clusters). A comparison of results across the three input feature sets is shown.



Overall, basic and anatomical rather than functional clusters are revealed. For example, the cerebral cortex is clustered together as well as the distinct Thalamus-related region in the center of the brain. Although there are visible differences across subjects and runs, the differences across methods are almost negligible. A scaled feature set has eliminated the intensity but does not deviate from the naive clustering. The reason could be that there is too much noise in the data. As an example, a drift term might be alone in determining the clustering results.

4.4 Validation

As we adopted a simple linear regression to fit our MRI data cross the predicted neural time course, we need to check linear model assumptions before we conclude validity of the model. One of the most important assumptions of linear model is the normality of residuals.

Among the methods proposed to check normality, normal Q-Q plot is the most commonly used. The Gaussian Q-Q plot compares residuals on the vertical axis with a standard normal population on the horizontal axis. The linearity of the points indicates normality. This method is straightforward and intuitive. However, it has obvious weaknesses: (1) It can not evaluate multiple vectors of residuals at same time; (2) there is no clear threshold to assert normality. Therefore, it is not suitable for our normality test because we need to check the normality on a per-voxel basis.

We used the Sharpiro-Wilk Test in which H_0 is $r_1, \ldots, r_n$ is normally distributed. If the p-value we get from test statistic is less than the chosen α level, then the null hypothesis is rejected and there is evidence that the data tested are not from a normally distributed population.

Notice that we cannot naively compare all of these p-values individually with α, our type I error. Otherwise, our integrated type I error of test is $alpha^N$, vanishing as $N \to \infty$, which is too strict to check multiple normality. Take the 11th subject as the example, if just compare p-values per voxel and $\alpha = 0.05$, more than half of the test ($\frac{94397}{147456} = 0.64$) will be rejected.

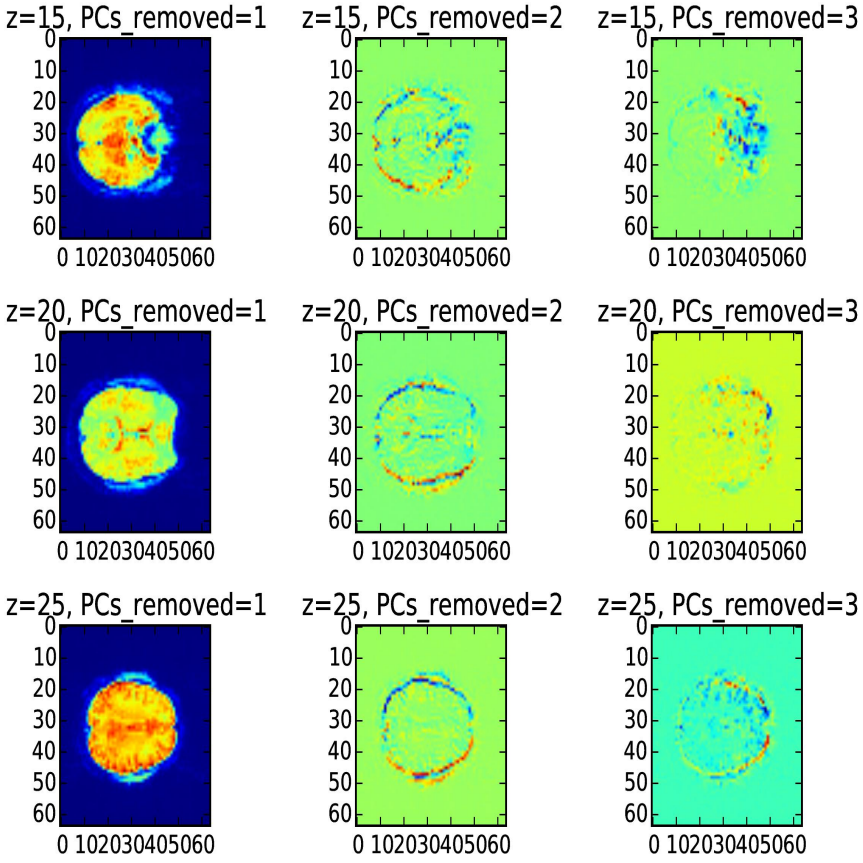
We have adopted several methods to handle this multiple comparison problem. 1) Bonferroni procedure, in which reject the null if $p < \alpha/n$, where n is the sample size. 2) Hochbergs setup, in which order the p-values $p_1, \ldots, p_n$ is associate with corresponding hypothesis $H(1), \ldots, H(n)$.Reject all

hypotheses $H(k)$having $p(k) \leq \alpha/(n+1-k)$, where $k = 1, 2, \ldots, n$. 3) Benjamini-Hochberg procedure, in which Order the p-values $P(1), P(2), \ldots, P(n)$ and their associated hypothesis $H(1), \ldots, H(n)$. Reject all hypotheses H(k) having $P(k) \leq (k/n) \times \alpha$ $(k = 1, \ldots, n)$.
To be consistent with previous example, these three methods are also implemented on the MRI data of 11th subject: (1) with Bonferroni correction and outliers removed, there are 32896 voxels out of 147456 are not normally distributed; (2) with Hochberg's procedure and outliers removed, there are 4843 voxels out of 147456 are not normally distributed; (3) with Benjamini-Hochberg's procedure and outliers removed, there are 0 voxels out of 147456 are not normally distributed.

5 Discussion

5.1 analysis that will be performed

Extending and finetuning K-Means: We will continue working towards our goal of revealing functional clustering of the brain. This can be done by:
Improving the input features by inspecting and removing first principal components of the datasets. This need to be done with care by visually inspecting the principal components and consulting literature on the types and characteristics of noise. One criterion of noise can be that the fluctuation has a period clearly greater than the on-off cycle of the task.
Improving input features by fitting the BOLD signals to a linear model and using the residuals as input to K-means clustering. Using the same example above, a drift term can be included in the design matrix so that it can be removed in the residuals. This is the opposite of linear modelling to fit the data since in this case, the aim is not to have a model to fit the data as best as possible but to make use of the residuals in subsequent classification algorithms.



Improving other analyses: applying the same methods of noise reduction in K-means in other analyses, such as correlations to refine the results and possibly make comparisons with K-means. This is because both types of analysis serve to discover activation regions.

Scaling analyses to make comparisons across different subject groups: at this stage, we focused on developing the scripts to analyze and make comparisons within single subjects. From now on, we will apply the analyses across subject groups in order to draw conclusions on differences in healthy and schizophrenia subjects. To achieve this, some averaging techniques are necessary for cross-group comparison. One example already mentioned is the merging algorithm for K-means clustering. Research other machine learning techniques to further explore activation regions.
Since one of our goals is to demonstrate activation regions revealed by the datasets and compare those provided in the literature, we need to transform coordinates to and back from Talairach space since most coordinates in literature are provided in that space.

5.2 discussion about the data

The dataset we use for our analysis is multi-layered and ambiguous in some sense. In our dataset, there are 3 tasks runs for each subject as well as 7 condition files explained the scan timeline for each run. At the first glance, it is hard to see which one is useful and should be analyzed, and it is only after deep investigation and wide research about the format of the data that we can start the accessing the real data we need.
In our analysis, the condition record we used has fraction seconds for scan duration (0.769951s), a very small proportion of TR. In the previous analysis, the duration we dealt with are always a multiple of TR (2.5s), in which reasonably chose TR as the unit. While in our case, if we still stick to use TR=2.5s as the scale, meaning we have to divide 0.769951 by 2.5 (around 0.30798) to fit the scale, the resulted convolution will be far deviated from the real scenario which will be reflected as huge errors in the future analysis. Therefore, we adopted the following strategy to tackle this problem: 1) rescale data, converting from 2.5s to 0.1s as the unit; 2) in each 2.5s interval, we chose the median value to represent convolved data in that time interval; 3) convolve the data in the standard approach. This gives the convolved function that we used in the analysis of correlation.
Further, the analysis done in the paper Brain Network Connectivity in Individuals with Schizophrenia and their Siblings is based on the Resting State dataset, and they investigate the connectivity of the regions in the brain for patients and healthy controls. We tried to reproduce their result using the data, however, we encounter the problem of separating the resting state data from the entire time set since it involves complicated techniques that way beyond our ability. Consequently, it is important for us to find another potential, executable topic given the current dataset and develop a coherent rigorous statistical analysis.
Above all, we are dealing with the real world imperfect data and we need to effectively exploit the data we currently have and be open minded to all the interesting issues arose from the data which may be investigated in the future.