Reproducing fMRI Data Analysis on Brain Connectivity

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Abstract

In this research paper, we analyze the fMRI data from the study done by Repov and Barch exploring the relationship between schizophrenia and brain connectivity [2, 3]. Instead of reproducing ANOVA analysis of within and between brain network connectivity, we focus on analyzing fMRI scans of one subject using generalized linear model. Before data analysis, we smoothed the data spatially and corrected noise in the fMRI data. On the preprocessed data, we perform student t test to identify the voxels responding to designed stimulus. Having localized the activated voxels, we closely examine the behavior of these voxels and validated our assumptions.

1 Introduction

The paper of which our research is based is titled "Working memory related brain network connectivity in individuals with schizophrenia and their siblings" [2, 3]. Schizophrenia is a chronic, severe, and disabling brain disorder. Previous studies have shown that changes in the function of a single brain region, or even a brain system, cannot explain the functional impairments seen in this illness [1, 2]. However, Repovs and Barch attempts to show that individuals with schizophrenia have reduced connectivity within and between neural networks, which could be a forward step to understanding schizophrenia.

Repov and Barch systematically examine changes in functional connectivity across rest and different task states in order to make an inference on characteristics of schizophrenia. They asses connectivity using blood oxygen level dependent (BOLD) time series acquired using fMRI. They find four types of participates, individuals with schizophrenia, the siblings of individuals with schizophrenia, healthy controls and the siblings of healthy controls. They designed three working memory loads of an N-back task and designated four regions of interest (ROIs). The four brain networks are: (1) Dorsal fronto-parietal network (FP), (2) Cingulo-opercular network (CO), (3) Cerebellar network (CER) and (4) "Default mode" network (DMN). The objective of the study is to examine the altered functional connectivity within and between these four brain networks when the participant perform a designated N-back task. With ANOVA analysis, it is found that individuals with schizophrenia and their siblings show consistent reductions in connectivity between both the FP and CO networks with the CER network.

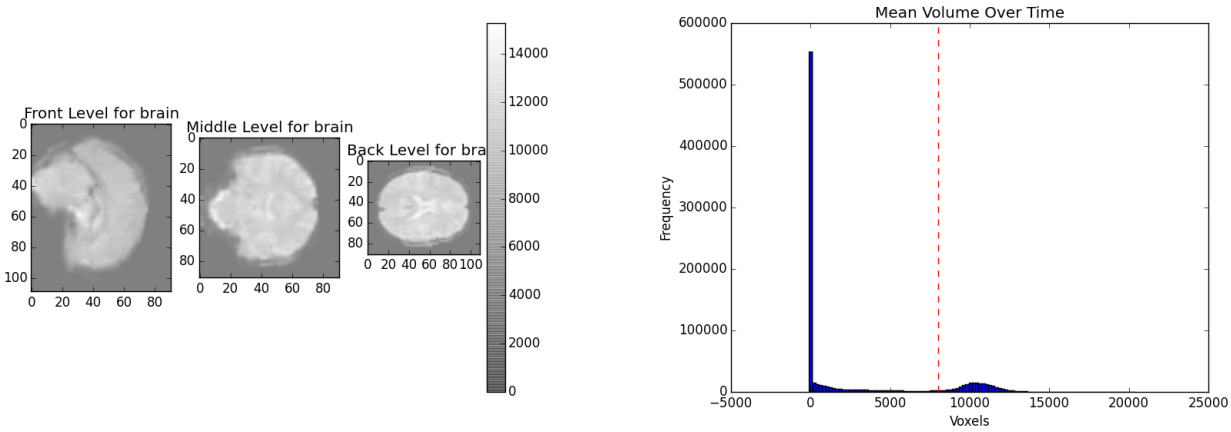
We narrow our focus and analysis on a single schizophrenic subject. The fMRI data in the study shows the changes in blood flow in the brain, and analyzing this data can help us understand how schizophrenic brains respond during task performance. We detail in the following the steps we take to analyze the data. We attempted both spatial and temporal smoothing on the voxels in order to reduce noise. We also performed spectral analysis on fMRI data to correct noise in the data. After preprocessing the data, we fit multiple linear regression model using two different sets of experiment conditions. Having obtained coefficient estimates, we performed Student t-tests on each voxel to examine whether the particular voxel has show significant activity subject to appropriate thresholds. Performing t-tests relying on a set of assumptions that we need to validate. We performed the Shaprio-Wilk test to check the normality assumption.

2 Data

The data used in their published paper is available on the website OpenFMRI.org. The are many data files grouped by subjects, but we will be focusing on only one schizophrenic subject–subject 001, who is male, Caucasian and Schizophrenic. The data has four dimensions ($91 \times 109 \times 91 \times 137$), consisting of three dimensional voxels that are moving across time. We removed the first four outlying data along the time dimension, which leaves us 133 images. (Need to add how to come to understand the BOLD signal = signal + noise, and the necessity of remove noise)

2.1 Mean Voxels Mask

We plot sample images of the brain from three different perspectives, which show how our dataset looks like. Since the paper talks about the noise in the data, we average our data by time and plot a histogram to check noise variance. The dataset contains a lot of signal noise at the outskirt of the brain. The signal in the images extends across several voxels, because nearby brain locations usually have similar response to the task. However, the noise in the data is mostly independent from one voxel to the next. Therefore, we reduce the noise by smoothing in space using averaging across the independent noise in the voxels. Based on the histogram, we decide to set the threshold to 8000 which includes the majority of useless information. Then we extract the data points that are larger than 8000 such that all signal noise is removed. Moreover, we apply the gaussian filtering to smooth by 2 standard deviation in all three spatial dimensions.



(a) Sample Images of Brain

(b) Histogram of Mean of Data

Figure 1: Data Preprocessing

2.2 Bonferroni Correction

The Bonferroni correction is a multiple-comparison correction used when several dependent or independent statistical tests are being performed simultaneously. In order to avoid a lot of spurious positives, the alpha value needs to be lowered to account for the number of comparisons being performed.

Suppose that the model is true so that $t_1, \ldots, t_n$ have the $t(n-p-2)$ distribution. They are not necessarily independent, and we would expect about $n\alpha$ number of $t_1, \ldots, t_n$ to be larger in absolute value than than $\alpha/2$ critical value of the $t(n-p-2)$. Therefore, we would be tagging $n\alpha$ of the subjects as outliers even when there are no outliers in the data.

To counter this, one takes a value of α much smaller than 0.05 while testing whether the ith observation is an outlier or not. A particularly conservative value is $\alpha = 0.05/n$. In this case, one can show that the probability that at least one subject is tagged as an outlier when in fact there are non is almost 0.05.

3 Convolution and Design Matrix

We need a good design matrix, containing data on the explanatory variables, to be used in our linear models to explain as much variation in the observed fMRI data as possible. We studied the design of the experiment closely. fMRI scans were acquired while participants perform specified memory tasks. They are to respond for each letter shown whether it was the same as a pre-specified letter (0-back), the same as the immediately preceding letter (1-back), or the same as the letter shown two trials previously (2-back). For our subject, there were three BOLD runs, each consisting of two blocks of 0-back, 1-back, or 2-back working memory task.

We examined the seven study conditions closely. The conditions are unusual from what we are familiar with in that they are consisted of fractions of durations and negative amplitudes. The first condition consists of the start-cues, the second condition consists of the task targets (amplitudes are all one), the third condition consists of the task non-target (the positive amplitude indicates correct identification of the target and the negative amplitude indicates the non-response to the non-target), the fourth condition consists of end-cues, and the fifth condition consists of durations of the two task blocks. There is no information on what the sixth file mean, and the seventh condition consists of the erroneous responses.

Since we were only familiar with convolution for block design, we initially used only the condition one, four and five, which give us the start time, the duration, and end time of the two task blocks. Due to the delay of signal after the onset of neural activity, we make use of the hemodynamic response function (HRF). The idea is to model the signal response as the convolution of the stimulus function with the HRF. Convolving with stimulus timing allows us to get idealized response as an explanatory variable (a regressor included in design matrix). We bear in mind the limitations of this design matrix due to its omission of trials within each of two task blocks.

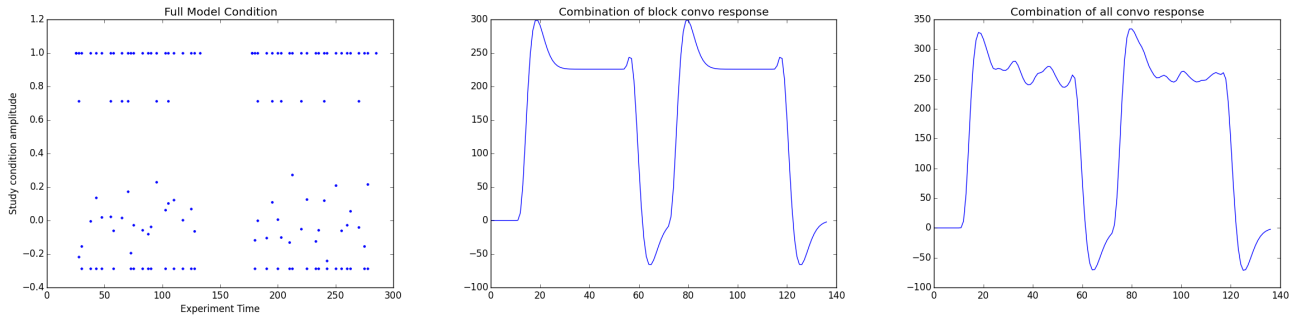


Figure 2: Combination of Block Design and Mixed Design

We are going to focus on the block design and mixed design in order to research on how the voxels work and what is the relationship between neural signal and blood pressure.

4 Linear modeling

The basic idea of linear models is to find the relationship between a response variable and one or more explanatory variables (regressors). For our purposes, we attempt to define a relationship between the BOLD signals and the working memory tasks. Mathematically, our model is as follows:

$$y = X\beta + \epsilon, X = \{1, x_1, x_2, \ldots, x_k\}.$$

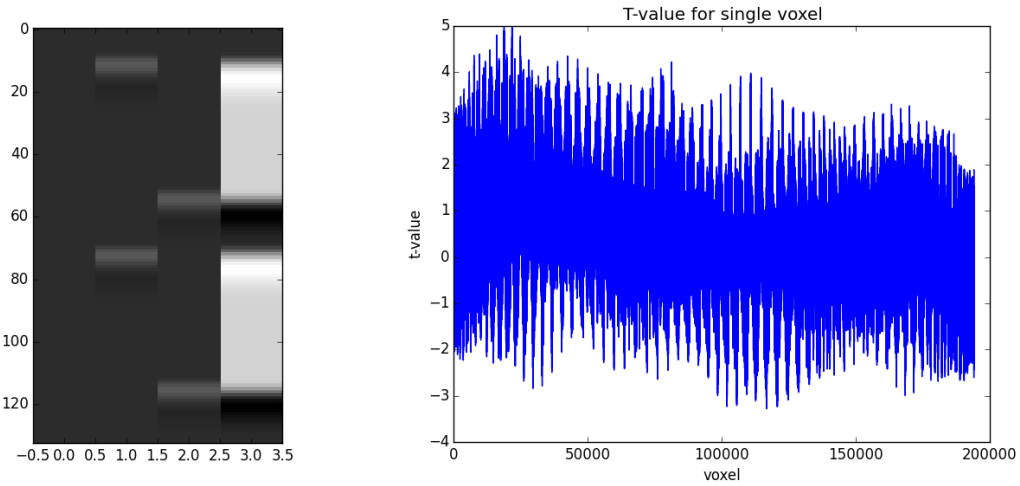
To perform hypothesis tests using this model, we assume linearity of the relationship, and $E[\epsilon|X] = 0, Var[\epsilon|X] = \Omega$. We solve for linear regression using generalized least square:

$$\hat{\beta} = (X^T\Omega^{-1}X)^{-1}X^T\Omega^{-1}Y.$$

After finding estimates for the βs, we perform Student t-test for each β_i, where $H_0 : \beta_i = 0, i = \{1, 2, \ldots, k\}$.

4.1 Block Design

We are interested in the simple block experiment in this research, so we are first to the fit block design to ordinary least square regression in order to define the basic relationship between neural signal and blood pressure. Here, we assume the error from data is followed independent and identically normal distribution and constant variance.



(a) Design Matrix for Block Design

(b) T-value of $\hat{\beta}_3$ in Block Design OLS

Figure 3: Block Design Model

Since the $\hat{\beta}_3$ in 2 demission is not easy to recognize which voxels are significantly active, we would like to reshape to 3 demission as the brain shape. Then, we plot the $\hat{\beta}_3$ and P-value of front, middle and back perspectives respectively.

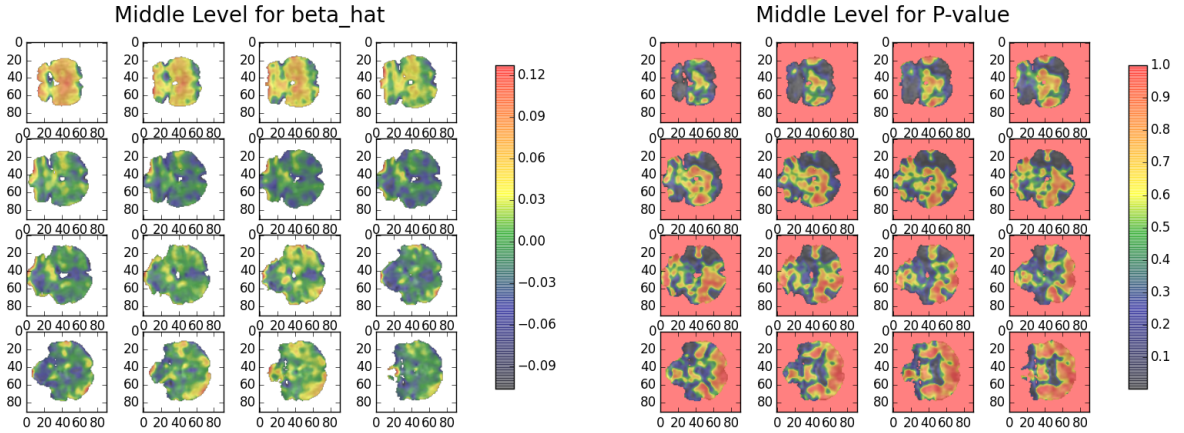


Figure 4: Middle Perspective of Brain in Block Design

In the $\hat{\beta}$ map, the warmer color is showing $\hat{\beta}$ is bigger, which means there is higher positive relationship between neural signal and blood pressure. However, if the color is more likely yellow, it means $\hat{\beta}$ is close to 0, so there is less or no relation at all. Therefore, We think the voxels are highly active during the experiment test located at the center of front and back brain. On the other hand, in the middle brain, majority of voxel are showing the negative relationship between neural signal and blood pressure.

In the p-value map, the dark region is showing higher confidence on the $\hat{\beta}$ value. the color of regions are more bright, we can judge that these voxels are not related to our experiment test. Therefore, We could not find many regions are highly significantly, however, if the voxels are on the edge of brain, most of them did not provide any information in the blood pressure, which makes sense to us.

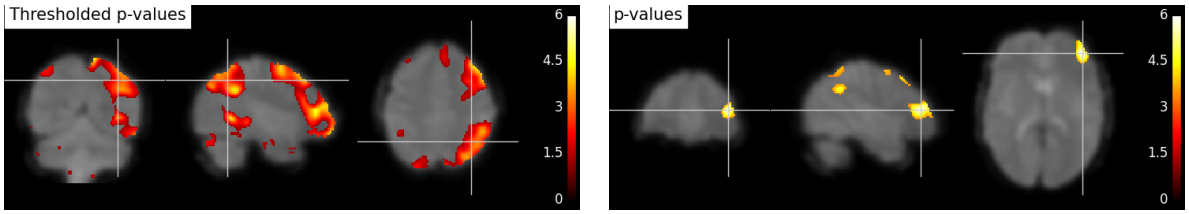


Figure 5: Highly Significant Voxels in the Block Design

In the left image, we set the threshold to 0.05, so find the red region contains highly significant active voxels. In the right image, as Bonferroni correction theory, we decide to set the threshold to 0.05/133, then we get a few very significant regions. However, most of them are located at the edge of brain, which does not make sense in the common knowledge. Therefore, we did not firmly believe this results, so in the next section, we are going to check heteroscedasticity test.

4.2 Heteroscedasticity Test

In the paper, it introduces that there is non-constant variance of blood measurement in the dataset, which means it breaks the assumption of ordinary least squares. If the variance of the Y is not constant, then the error variance will not be constant because it assumes there is linear relationship between true Y and X. The most common form of such heteroscedasticity in Y is that the variance of Y may increase as the mean of Y increases, for data with positive X and Y. We would like to apply heteroscedasticity test, called white test in order to statistical test on variance.

1. Set the null hypothesis: no heteroscedasticity; Ha: there is heteroscedasticity
2. Estimate by OLS, save squared residuals in e^2
3. Regress e^2 on all variables, their squares and all possible non-redundant cross-products
4. Form the auxiliar regression: nR^2 $X^2(p)$
5. Reject if nR^2 is too large

Intuition: The auxiliar model can be seen as trying to model the variance of the error term. If the R^2 of this auxiliar regression were high, then we could explain the behavior of the squared residuals, providing evidence that they are not constant.

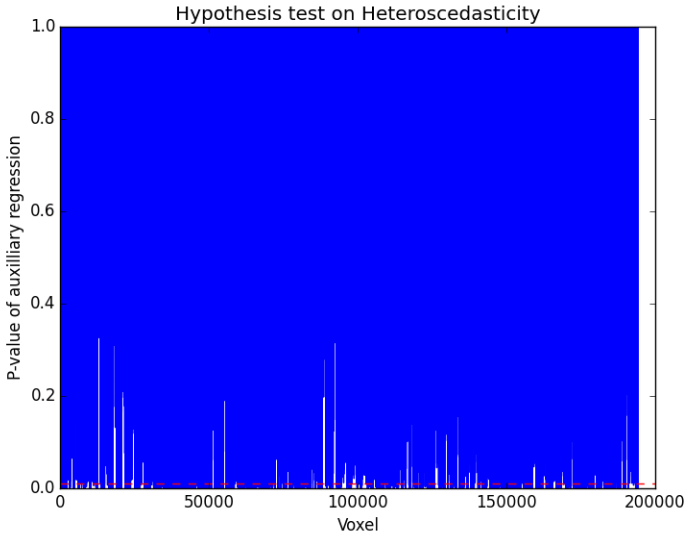


Figure 6: P value for Heteroscedasticity Test in Block Design

In the figure, we can see only few points under the red line, which voxels are been rejected the null hypothesis test.

The result I got is that there are total 194287 voxels, but only 3868 voxels have the significant P value which means reject our null hypothesis. Because only 2% voxels have the constant variance, we judge the most voxels keep non-constant variance in the dataset. Therefore, we could not apply ordinary least squares regression, however, a weighted least squares linear regression may be the preferred method of dealing with non-constant variance of error.

4.3 Mixed Design Model

Previously we used block design that has too long of duration, and therefore unable to explain much of the variation in the BOLD signals. We revised convolution of stimulus using a finer and higher resolution on time. With trials within task blocks convolved and included in the design matrix, we expect the result from linear regression have higher explanatory power. However, we need to be cautious because the task block conditions (conditions 1, 4, and 5) are likely to have colinearity problem with the trial conditions (conditions 2 and 3).

Figure xx shows the new design matrix has dimensions 133×7, where the first 6 columns are the convolved neural responses and the last column is the constant.

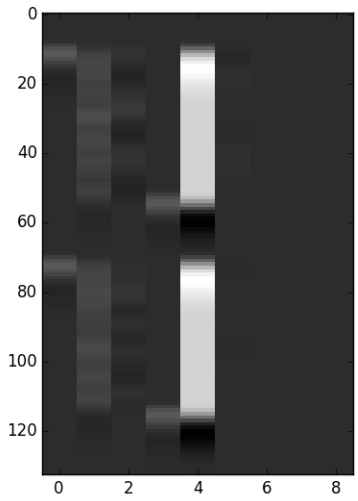


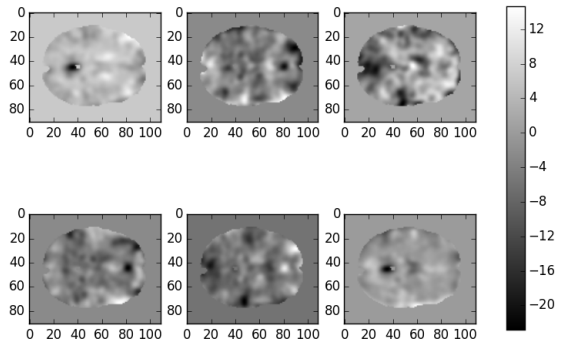
Figure 7: Design Matrix of Mixed Design

4.3.1 Full Model Linear Regression Results

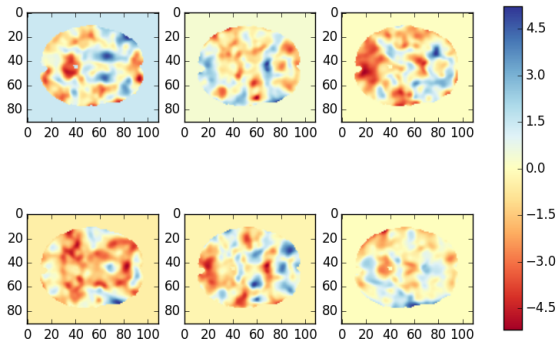
With the 133×7 full model design matrix, we obtained 6 beta estimates for each voxel using GLM. We perform t-test on each voxel, where the null hypothesis claims that $\beta_1+\beta_2+\beta_3+\beta_4+\beta_5+\beta_6 = 0$. Figure xx shows the statistical parametric maps. Each significant voxel is color-coded according to the size of its beta value, t value and p value. Since we are making multiple comparisons, we use the Bonferroni correction for setting threshold. Using 0.05/133 as the threshold, we found a number of voxels near the center of the brain to be significant. The mean MRSS across all voxels using all 6 study conditions is 2041.804.

4.3.2 Temporal Smoothing

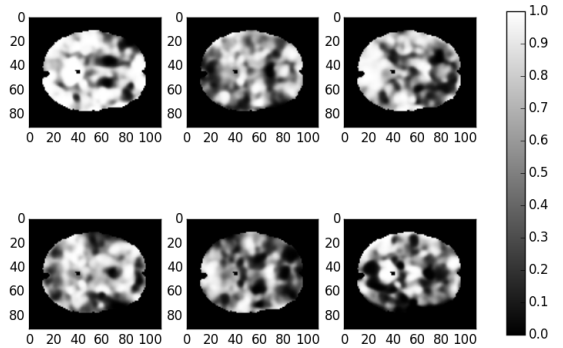
To reduce noise and improve signal in the fMRI data, we attempted smoothing of the fMRI data. We experimented with smoothing temporally using discrete cosine transformations. We added a set of discrete cosine transformation basis to the design matrix to filter out the low frequency noise present in the BOLD signal. This result in a larger design matrix of dimensions 133×14, which included the discrete cosine transformation basis.



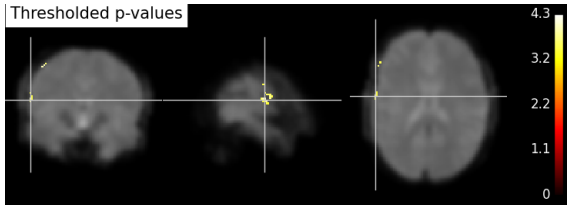
(a) β Map $(\beta_1, \ldots, \beta_6)$



(b) t Map



(c) p Map



(d) Significant p Map

Figure 8: Mixed Model Parametric Maps

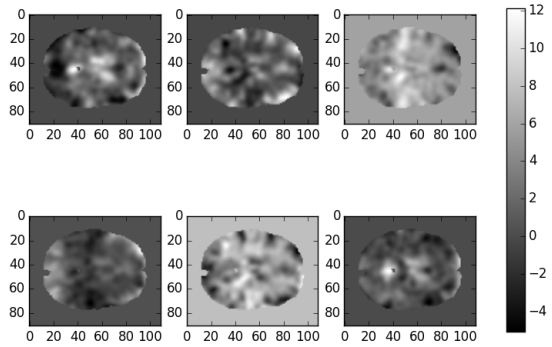
As the block model and the full model, we used GLM to obtain 6 betas of interest. We perform t-test on each voxel, where the null hypothesis claims that $\beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 = 0$. The mean MRSS across all voxels using all 6 study conditions is 2033.76. The mean MRSS is smaller than the full model, but we cannot conclude that this model is better yet. There are no voxels that are significant at the Bonferroni corrected threshold. We raised our conservative threshold to about 0.05/110, and there are two voxels that are significant.

5 Normality Test

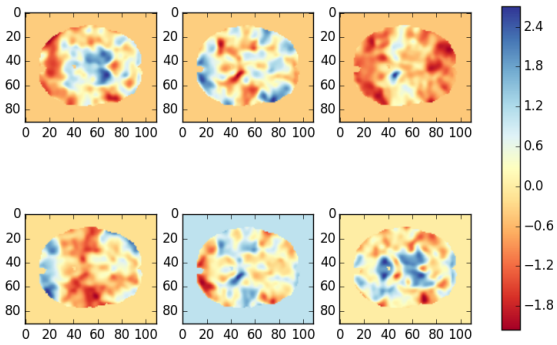
In our analysis part, we use linear model to fit real data. There are several assumptions on linear modeling, one of which is normality assumption on error term. Normality of the errors can be checked by checking normality of the residuals. The usual way is to draw a Q-Q plot and check whether it forms a straight line. However in this paper, since there are around 200,000 voxels, it would be hard to plot all of them and check for normality. Thus we use Shapiro-Wilk test in the paper to test for normality.

In Shapiro-Wilk test, a small p-value indicates non-linearity. We write a function to compute p-value of each voxel and plot those p-values in three brain perspectives. There are three linear models used in the paper. The 6 plots below are p-value plots: the three plots to the left are p-values for three different linear models using raw data. The other three plots are p-values for three different linear models using smoothed data.

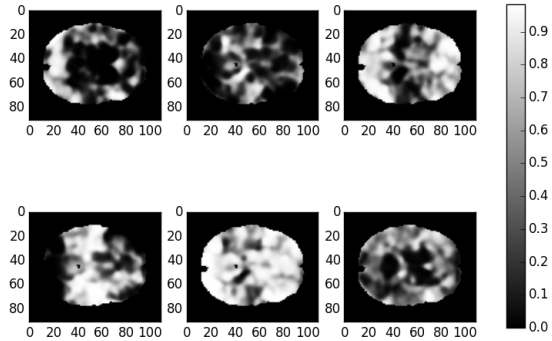
The bright areas in the above plots means errors in that area don't follow normal distribution. We can see that data before smoothed seems to follow normal distribution well, while data after smoothing



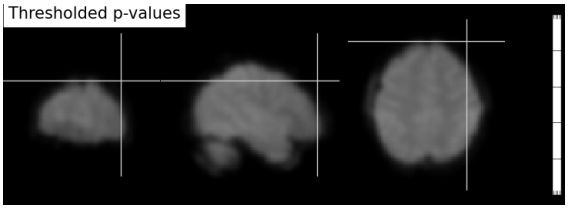
(a) β Map $(\beta_1, \ldots, \beta_6)$



(b) t Map



(c) p Map



(d) Significant p Map

Figure 9: DCT Model Parametric Maps

show some non-normality. This makes sense because there should be significant points for anatomy.

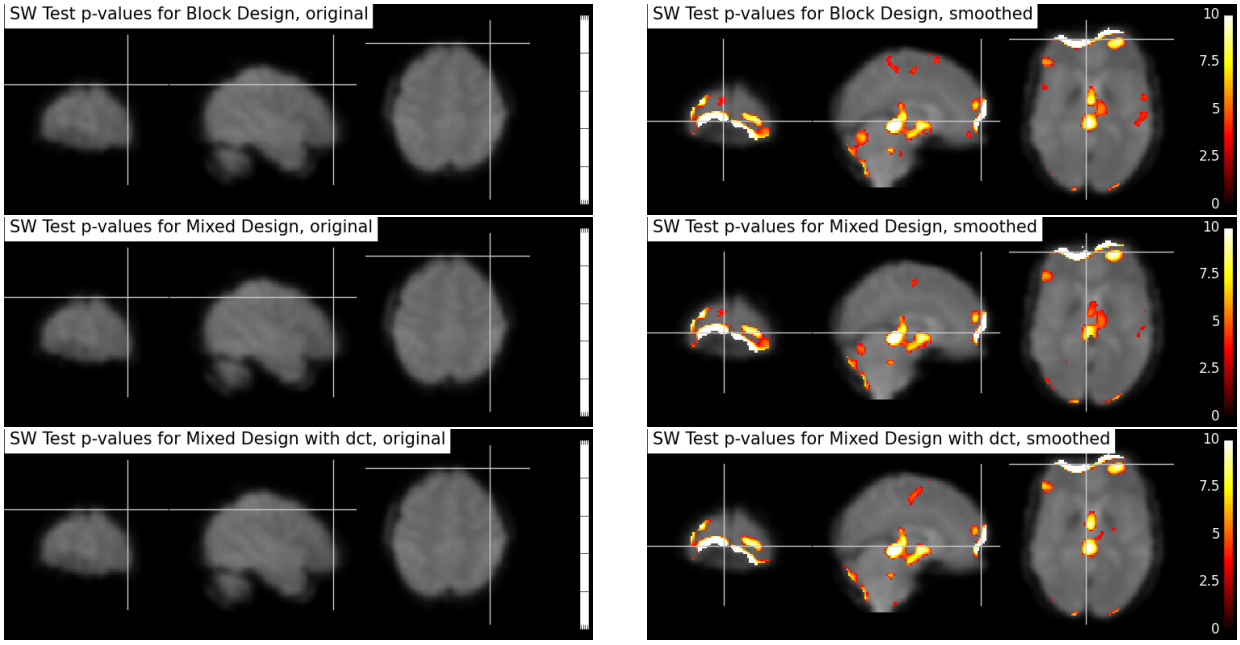


Figure 10: SW Test for Three Linear Models

Appendix

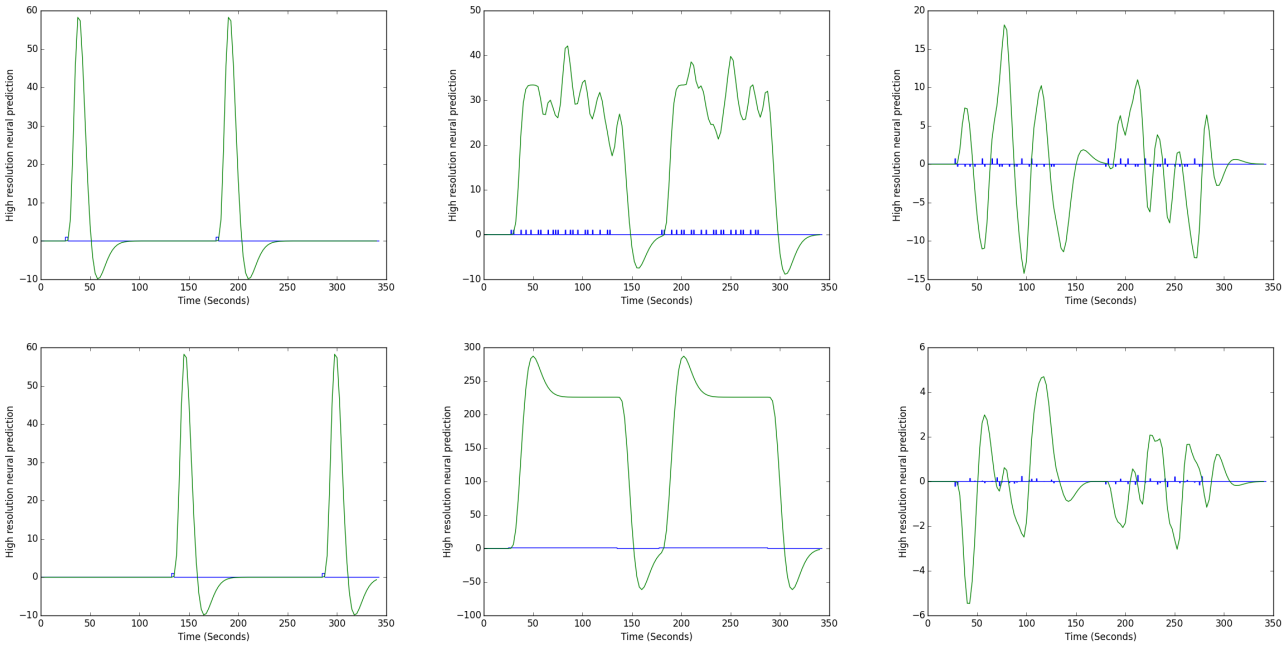


Figure 11: Convolution Response from 6 Conditions

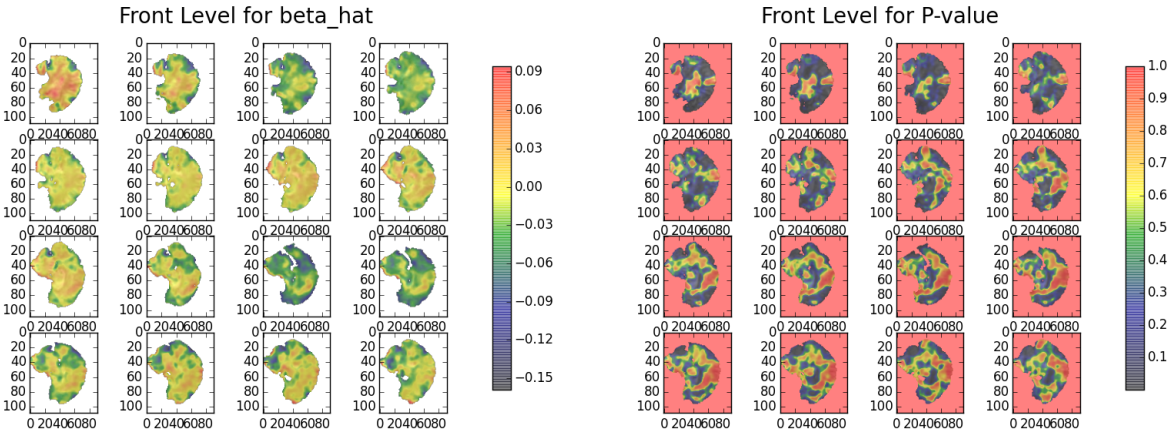


Figure 12: Front Perspective of Brain in Block Design

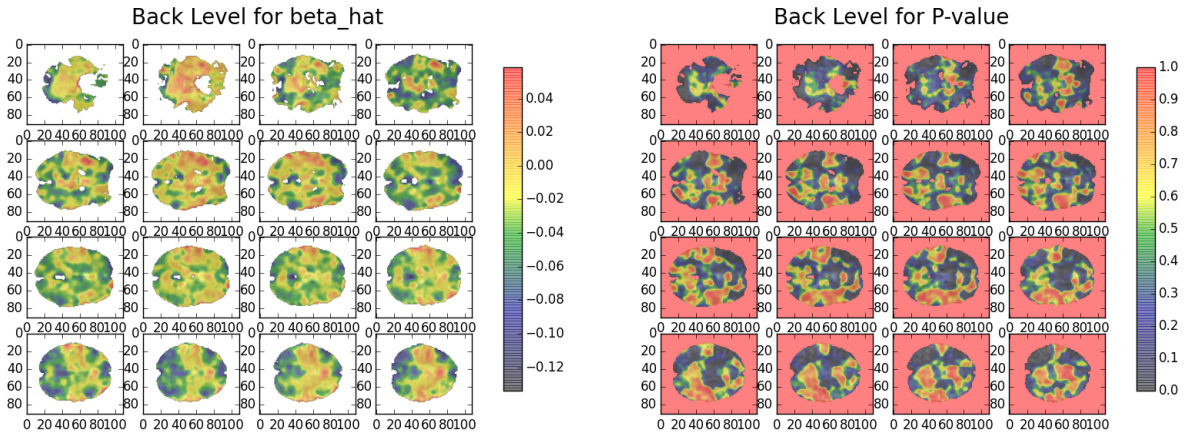


Figure 13: Back Perspective of Brain in Block Design

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[3] ——, *Working memory related brain network connectivity in individuals with schizophrenia and their siblings*, Frontiers in Human Neuroscience, 6 (May 2012), pp. 1–15.