Estimation of Connectivity in the Human Brain Using Functional MRI data: Statistical Approach

Andrew Cheng
apcheng@ucsd.edu

Daphne Fabella
dfabella@ucsd.edu

Terho Koivisto
tkoivisto@ucsd.edu

Daniel Zhang
yiz029@ucsd.edu

Gabriel Riegner *
gariegner@ucsd.edu

Armin Schwartzman *
armins@health.ucsd.edu

Abstract

Using correlation analysis to detect connected networks in the brain is no new feat in neuroscience. Our project carefully considers which statistical methods to employ in estimating the connectivity in a resting-state brain through fMRI data. First, using facts of standard errors and correlations gives confidence of what errors we are expecting to see in simulation versus actual fMRI data collected in resting state scans. Then, extracting valuable data from pairwise correlated matrices of time series data. Then, utilizing benefits of factorization methods such as PCA and ICA to analyze the graphs and find the most interesting components.

Code: https://github.com/tikkuni/DSC180A-Capstone-ProjectA09

*Capstone mentor

1 Introduction

Functional magnetic resonance imaging (fMRI) still proves to be a key tool to deciphering the mysterious architecture of the brain after its first uses in the early nineties. Due to the high spatial resolution (in millimeters) and relative ease of getting a scan, data for fMRI scans has become highly available and useful. These scans still lack temporal resolution due to how fMRI blood-oxygen-level-dependent (BOLD) signals work, where it is the blood flow that is being measured rather than the signals in the brain. This will make our temporal resolution in seconds rather than some other scanning methods (e.g. MEG, EEG, NIRS) that are in milliseconds. Understanding and simulating fMRI data is crucial for advancing our knowledge of neural function.

Our project will mainly focus on data from the Human Connectome Project (HCP), which has a collection of $1,200$ fMRI scanned adult brains. The data is in the form of voxels, which are pixels that exist in a three-dimensional space of a brain mapping to an intensity of a BOLD signal at a specific point in time. With the amount of different brains, it would be impossible to map one to one comparisons between specific voxel locations in the brain. So, we rely on atlases to map regions of the brain to be able to compare brains, as well as conduct group analyses on the fMRI data. An atlas is built by statistically creating regions in the brain that have a probability of being composed of neurons with similar function. By using an atlas we are also able to conduct statistical analysis because it would be impossible to estimate each voxel of the brain due to there being too many parameters to estimate the data.

By the end of the project, we aim to have explained the functional connectivity by using correlation and pairwise correlations of time series data. This will replicate key findings of a 2005 paper on the correlated and anticorrelated functional networks of the brain (Fox et al. 2005). Our project undertakes the replication of the Default Mode Network (DMN) by calculating the pairwise correlation of brain regions to explain the importance of resting-state imaging of the brain to understand the functional connectivity of the brain. The DMN is highly interesting in that it's possible to detect neurological decay, caused by diseases such as Alzheimer's by looking at the connectivity of the DMN (Grieder et al. 2018).

2 Methods

2.1 Correlation and Standard Errors

A common approach for estimating functional connectivity is finding the correlation values between two brain regions' activity over time. Each brain regions' activity serves as a single dataset. Each dataset is a time series vector of BOLD signal values expressed as the vector $x_j \in \mathbb{R}^n$ where x_j has the values for the jth region and n is the number of timepoints. To calculate pairwise correlation between these two sets of data, each BOLD signal datapoint is centered and standardized according to its respective region's time series.

Box 1 *Standardizing each datapoint before performing pairwise correlation*

Standardizing a Dataset

$$x_j = [x_{1j}, x_{2j}, ..., x_{nj}]^T$$

$$standardized(x_j) = \left[\frac{x_{1j} - \hat{\mu}_j}{\sigma(x_j)}, \frac{x_{2j} - \hat{\mu}_j}{\sigma(x_j)}, ... \frac{x_{nj} - \hat{\mu}_j}{\sigma(x_j)} \right]$$

with mean

$$\hat{\mu}_j = \frac{1}{n} \sum_{i=1}^{n} (x_i)$$

and standard deviation

$$\sigma(x_j) = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (x_i - \hat{\mu}_j)^2}$$

where
x_j *= time series data for region j*
n *= number of time points*

After standardizing the datasets, pairwise correlation is given by finding the sum of products between each datapoint, then dividing by the degrees of freedom.

The formula for Pairwise Correlation

$$Cor(x_1, x_2) = \hat{\rho}_{x_1 x_2} = \frac{\Sigma x_{i1} x_{i2}}{n-1}$$

Pairwise correlation $\hat{\rho}$ can be interpreted as the linear relationship between the BOLD signal activity of regions x_1 and x_2. The magnitude of $\hat{\rho}$ tells us the strength of their relationship, and the sign of $\hat{\rho}$ tells us the direction of the relationship, negative or positive. These sample correlation values help us capture the linear relationships between two brain regions and, thus, estimate functional connectivity.

When analyzing a dataset encompassing more than two brain regions, a correlation matrix can be employed to explore the linear relationships among all possible pairs. To interpret this correlation matrix, we can look at each of its entries. The i, jth entry of the correlation matrix gives the correlation value between the ith and jth variables. The correlation matrix can be found by first centering and standardizing the data, as seen in Box 1, then use the following formula:

Box 2 *Pairwise Correlation Matrix C*

$$C_{jxj} = \frac{X^T X}{n-1}$$

where
X_{jxn} = *centered and standardized time series matrix*
j = *number of regions*
n = *number of time points*

In calculating correlation values, however, sample size significantly impacts its variability from the expected population correlation value. The formula of standard error, under the assumption that the dataset is not correlated with itself, describes the relationship in detail.

Box 3 *Standard Error of Correlation*

$$SE(Cor(x_1, x_2)) = SE(\hat{\rho}) = \frac{1}{\sqrt{N}}$$

where
N = *number of samples*
$\hat{\rho}$ = *sample correlation*

The variability of correlation, when quantified as standard error, scales down as sample size increases. To further understand the contribution of sample size when estimating the true correlation between brain regions, we can perform simulations. Simulating expected results and comparing real findings is decisive for giving us a metric of how well we are modeling the connectivity in the brain, as well as helping us identify interesting relationships between given regions.

When we generate random samples from a multivariate normal distribution with a fixed mean and covariance matrix, we have access to true population values. Having access to these true population values allows us to calculate the estimated standard error of pairwise correlations calculated from two different sample sizes. In our simulation we generated samples from a multivariate normal distribution with a center and correlation matrix as

follows:

Box 4 *Simulated Multivariate Normal Distribution*

$$\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \sim N\left(\mu = 0, \Sigma = \begin{pmatrix} 1 & \rho = 0.5 \\ \rho = 0.5 & 1 \end{pmatrix}\right)$$

where

X_1, X_2 = *dataset of each variable*

μ = *center of distribution*
Σ = *correlation matrix*

With the simulated values, we observed how the samples with less pairwise values ($n = 100$) showed much more variability from the expected correlation compared to the samples with more pairwise values ($n = 10,000$).

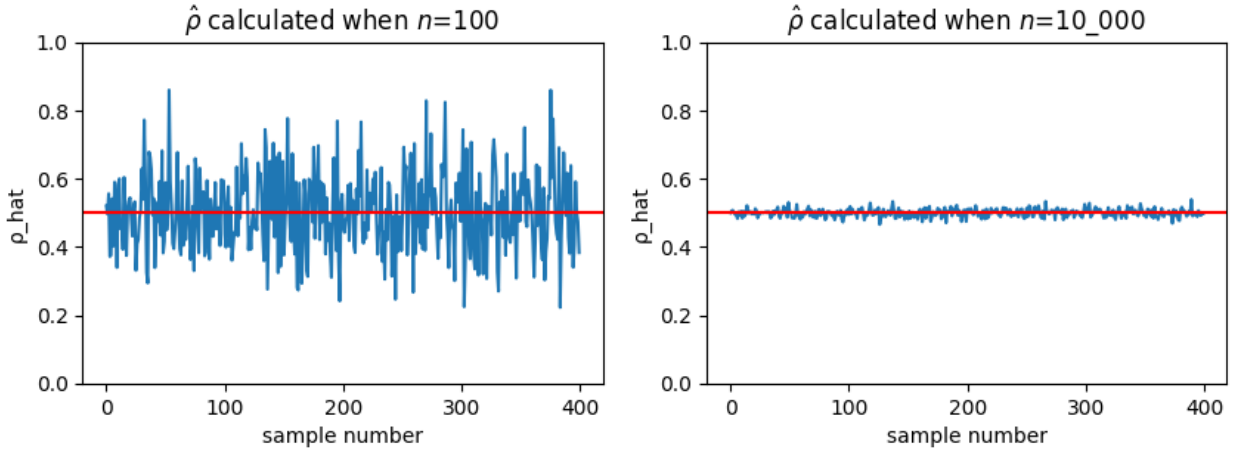


Figure 1: Comparing Variability of $\hat{\rho}$ Generated from Different Sample Sizes.

To be more precise, the standard error of correlation ($\hat{\rho}$) when $n = 100$ was approximated at 0.00560, while the standard error of correlation ($\hat{\rho}$) when $n = 100$ was approximated at 0.000560; when n scaled up by 100, the standard error scaled down by $\sqrt{100}$.

To test this inverse relationship, we simulated many random samples with incrementing sample sizes, then calculated the standard error of their respective correlation values.

Box 5 *Simulated Multivariate Normal Distribution*

$$\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \sim N\left(\mu = 0, \Sigma = \begin{pmatrix} 1 & \rho = 0.5 \\ \rho = 0.5 & 1 \end{pmatrix}\right)$$

where

X_1, X_2 = *dataset of each variable*

μ = *center of distribution*
Σ = *correlation matrix*

Box 6 *Standard Error of Sample Pairwise Correlations*

$$SE(\hat{\rho}) = \sqrt{\frac{\sum_{i=1}^{N} |\hat{\rho}_{x_1 x_2 i} - \rho|^2}{N}}$$

where

i = *ith sample*
N = *number of samples*
$\hat{\rho}_{x_1 x_2}$ = *sample pairwise correlation*
ρ = *true pairwise correlation*

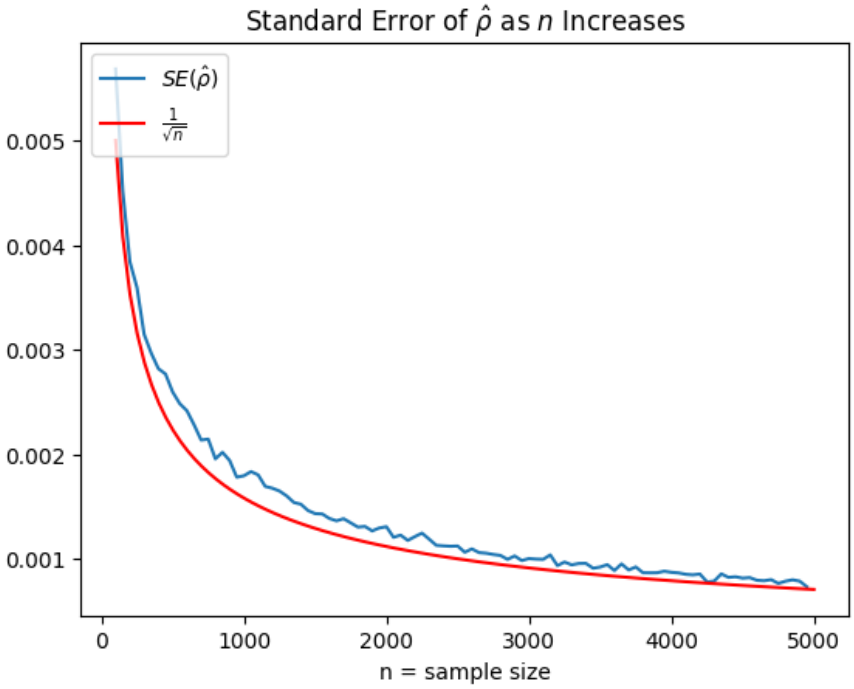


Figure 2: Standard Error of $\hat{\rho}$ as Sample Size Increases.

When plotted against the equation $y = \frac{1}{\sqrt{n}}$, we see how the estimated standard error of the simulated correlation values behave similarly. This confirms the relationship between sample size and the standard error of $\hat{\rho}$ illustrated in Figure 3 and described in Box 2. This formula for standard error can be used to identify interesting correlation values of activity between brain regions when estimating functional connectivity, and in understanding the relationship between and n, we can generate stronger estimates of the true functional connectivity between brain regions by using larger sample sizes.

2.2 PCA and ICA

One of the ways we can analyze fMRI data is by decomposing the data into different components. This is called multivariate decomposition, where the data we observe comes from a number of separate sources that have been mixed together. We can then use factorization methods to identify these components and locate the regions of the brain that have correlated activity. The next two methods are commonly used to pinpoint areas of interest in the brain.

The first factorization method is Principal Component Analysis (PCA). PCA finds the orthogonal eigenvectors of the covariance matrix, otherwise known as the principal components. For example, given a set of points in 2D space, the first principal component is the direction along which the data has the most variance. The second principal component is the direction that explains the next greatest amount of variance and is uncorrelated with the first principal component. PCA has the benefit of being easy to understand and to implement. It can also be used for data reduction, where we only perform analysis on the principal components instead of thousands of individual data points (voxels) of the fMRI scan. However, as PCA is only sensitive to Gaussian data, it is not useful for many of the signals in fMRI data that do not follow a Gaussian distribution.

On the other hand, Independent Components Analysis (ICA) is able to find the components only if the data is not orthogonal (independent variables of the dataset are correlated) nor Gaussian. This factorization method was created to solve blind source separation problems, where signals from multiple sources have been mixed together, and the goal is to identify the different sources. The model for ICA is defined as $X = As$, where X is the data we observe, s is the set of components we are trying to identify, and A is the mixing matrix that combines the components. By assuming that the individual components are statistically independent, the resulting combination is likely to be non-Gaussian and able to be decomposed with ICA.

Next we will compare how the two approaches have their benefits and downsides. First we will display how both approaches work with Gaussian data, then non-Gaussian data. Due to how ICA does not work well with data that follows a Gaussian distribution, minimizing the Gaussianity from this data means that only the noise will be left. What we find next points to being wary of using PCA and ICA by themselves.

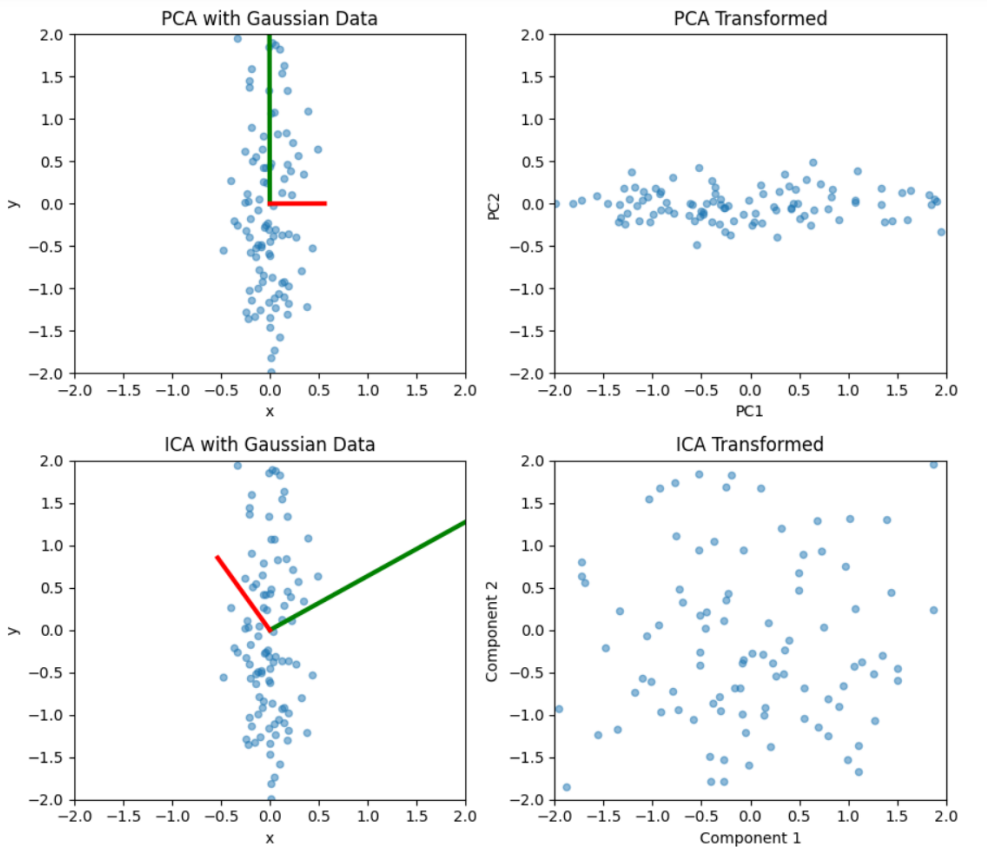


Figure 3: Comparison of PCA and ICA on Gaussian Data.

From Figure-3, we can see that PCA works well at finding the first and second principal components of Gaussian data, which are represented by the green and red lines respectively. The green line explains almost all of the variance and the red line explains the rest. When transformed with the principal components as the axes, the PCA result lies flat on the first principal component axis and is a useful visualization. On the other hand, ICA does not work well on Gaussian data. After minimizing the Gaussianity, the lines will be fitted to the noise that is left from generating the data.

In the context of brain connectivity research the PCA approach is useful for how easy it is to implement in higher than two dimensions. In fMRI data we have large images of the brain (in voxels) in a time series, using PCA is beneficial for finding components in high dimensional data. PCA will find regions that share variance, which in effect allows us to find clusters of similar function in the brain. The disadvantage of PCA is the assumption of Gaussian data, which we will show in the next figure.

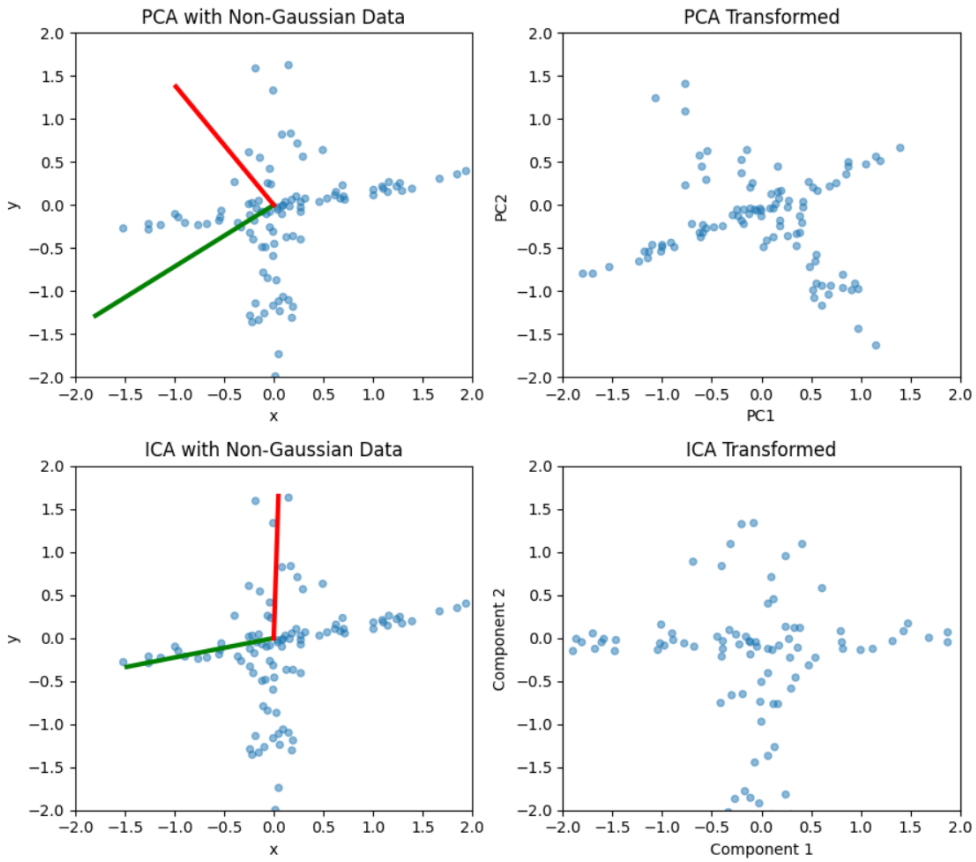


Figure 4: Comparison of PCA and ICA on Overlapped Non-Gaussian Data of Two Sources.

PCA does not work well for non-Gaussian data and the components that are found do not coincide with the mixture components that we want. When transformed, the result is still rotated and is not useful as a visualization of the explained variance. However, ICA works very well with non-Gaussian data and is able to find the first two components. The transformed result aligns well with the component axes, and is useful in visualizing the variance explained by the two components.

Due to how brain signals work we are more likely to see non-Gaussian signals when recording fMRI data. But, ICA is not guaranteed to give the same results every time due to variability between brains. It is also important to note that analyzing non-Gaussian data means that ICA is especially sensitive to outliers, which we need to keep in mind when doing our analysis.

In the context of finding connected components or networks we need to apply the knowledge of ICA and PCA to carefully construct an atlas that will correctly implement correlations in networks. Successfully applying this will uncover the intricate networks of the brain.

3 Application to resting-state fMRI Time Series Data

3.1 Pairwise Correlation in Time Series

In order to generate pairwise correlation in time series, we need to create a matrix between the time series data points, using the formula for creating a correlation matrix (Box 2).

This equation works as long as the time series data is centered with its mean at zero and standardized with the standard deviation at one. By using a standardized matrix we can ensure that the resulting non-diagonal elements fall between -1 and 1. Otherwise, the matrix generated would be a covariance matrix as mentioned above in Methodology Section II. PCA and ICA.

Using the Nilearn package, we generated a **correlation matrix** from the standardized resting state time series dataset.

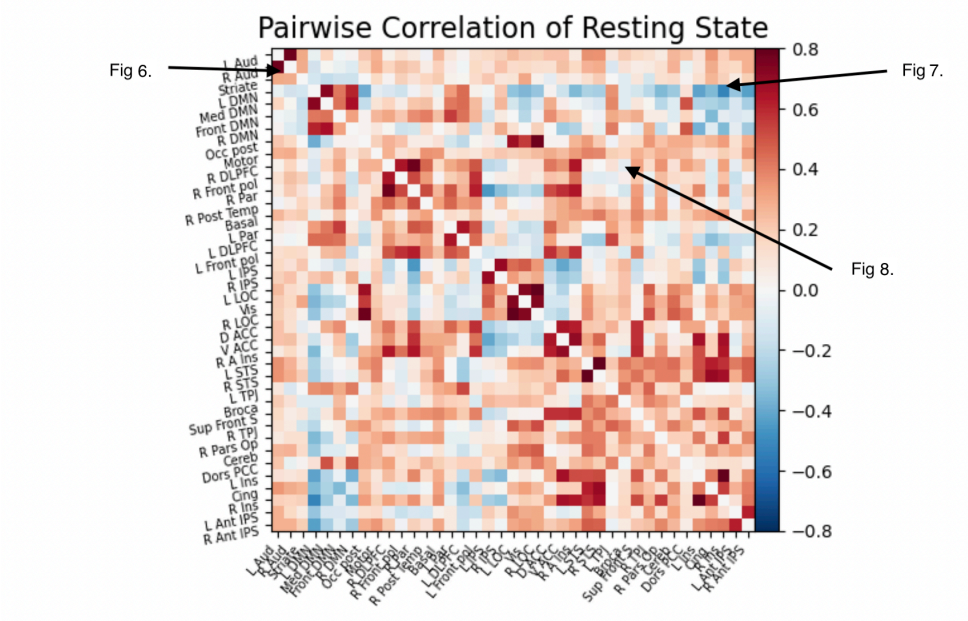


Figure 5: Visualizes the correlation matrix with positive correlated values in red, negatively correlated blue, and uncorrelated white. The resulting matrix is symmetric, and displays the correlations between each and every region.

Figure 6 is an example of positive correlation between two regions. As can be observed, the left and right auditory regions have the same activation peaks in the times series graph. This makes sense as auditory regions should both be related to each other.

In addition to positively correlated regions, there are also negatively correlated ones. In this example, the right insular region and left default mode network peak and dip at the same time. We can infer that these regions can take over each other's functions, as when one powers on, it tells the other to turn off. Interestingly as seen in Figure 7, there are more positively correlated regions compared to negative ones in a resting state.

Lastly, we have uncorrelated regions. We can infer that these regions are not dependent on each other and most likely have unrelated functions. For example in Figure 8, we are comparing the motor region that has to deal with movement and the broca region that is in

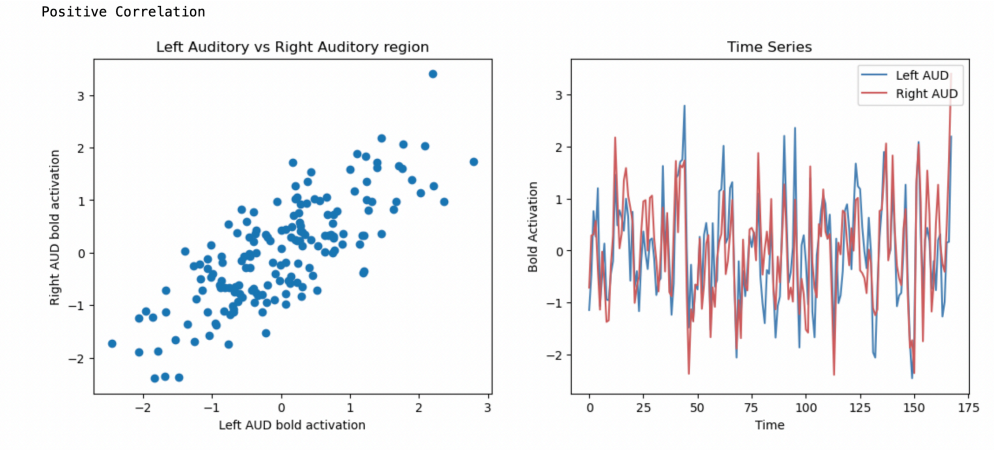


Figure 6: Plot of positively correlated regions.

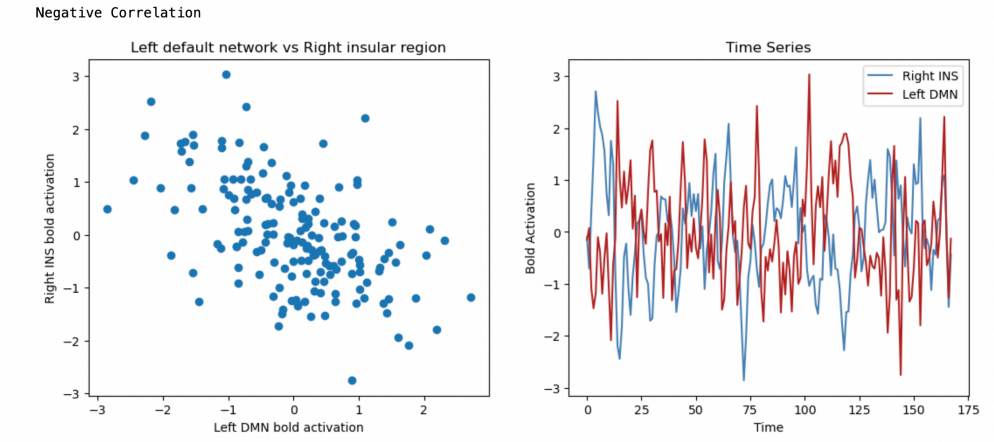


Figure 7: Plot of negatively correlated regions.

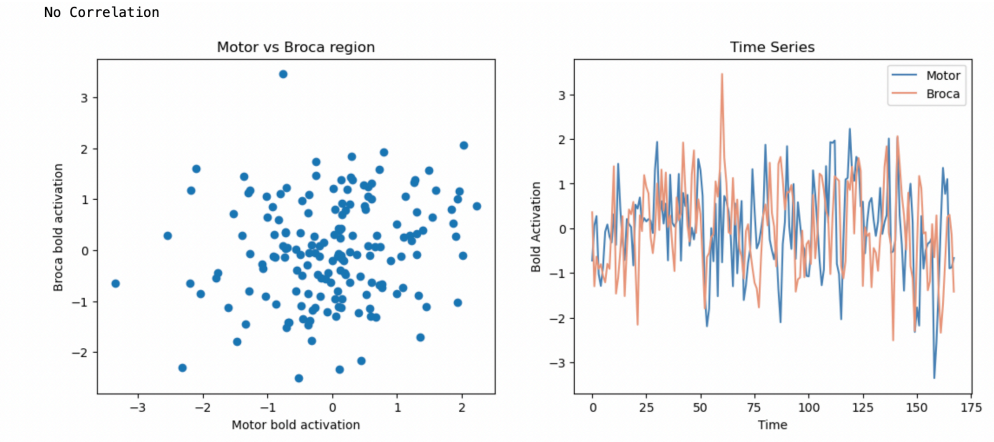


Figure 8: Plot of uncorrelated regions.

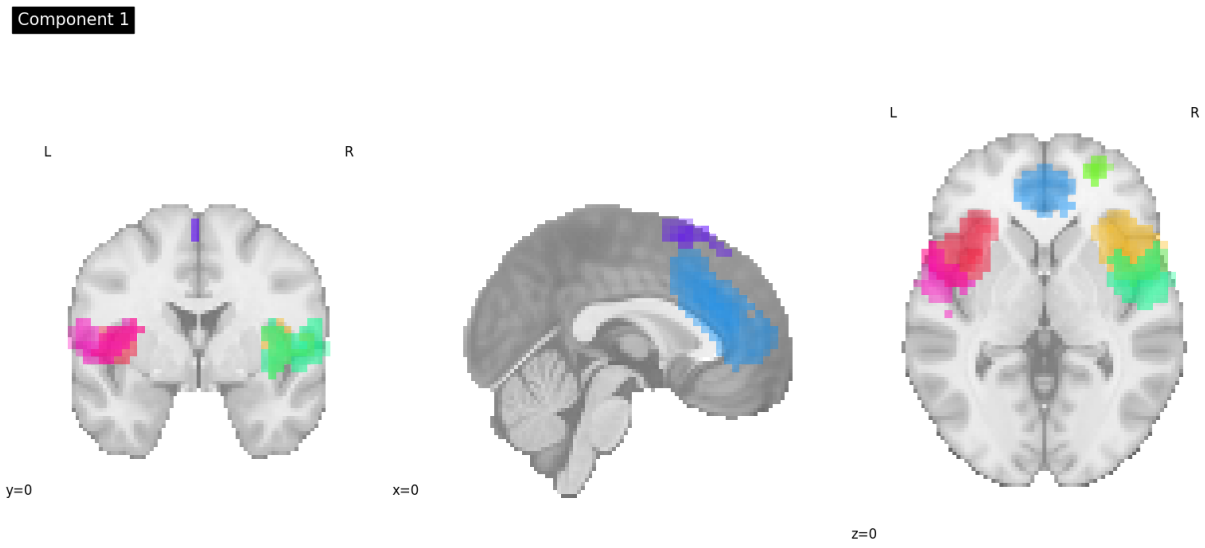
charge of speech. In a resting state, the motor region and the speech related broca regions do not influence each other at all.

The correlation matrix is an excellent method to generate pairwise correlations in a time series dataset. It is computationally simple as it only requires a single matrix multiplication operation. However, as stated in section 2.1 Correlation and Standard Error, the amount of time series data n is proportional to the variance of the correlation matrix. Therefore, we need a large amount of data to generate accurate results and to draw stronger conclusions on the connectivity of the human brain.

3.2 PCA & ICA

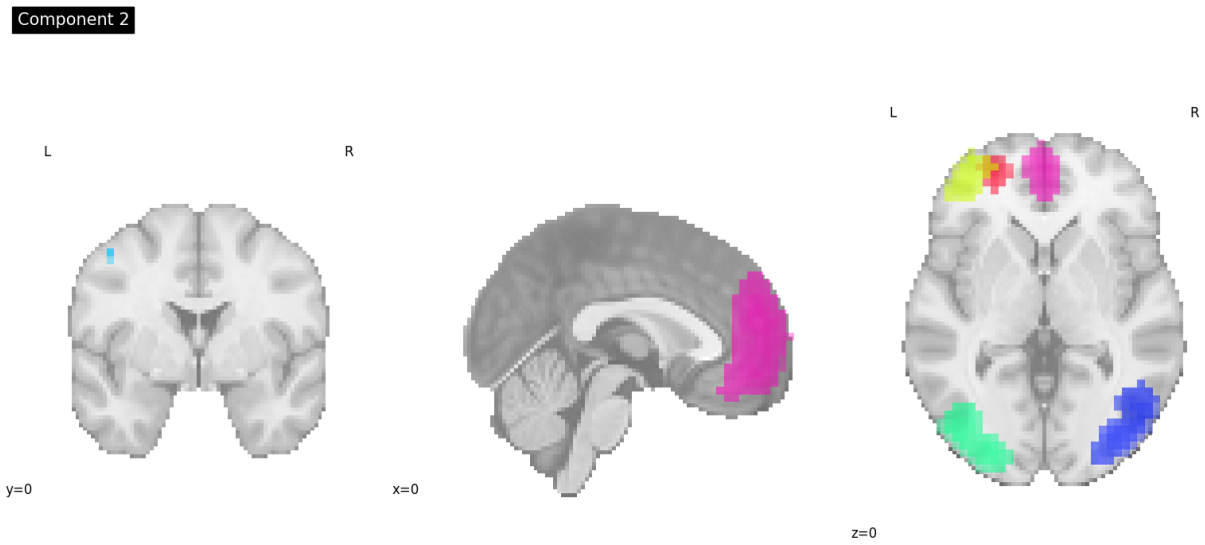
Using the same method as in Pairwise Correlation in Time Series (Box 2), we generated a correlation matrix from the time series dataset in the Nilearn package. We then found the principal components by calculating the eigenvalues and eigenvectors of the correlation matrix.

The principal components are composed of multiple brain regions each with different degrees of influence. By filtering out regions that have an insignificant impact, we can isolate the few regions of the brain that are most relevant to a specific principal component. For this dataset, we decided on a threshold of 0.21 to minimize the amount of overlap in the regions.



PC1 Regions	L Ins, L STS, R A Ins, R Ins, R STS, Sup Front S, V ACC

Figure 9: Regions of the first principal component at (0,0,0).



PC2 Regions	D ACC, Front DMN, L DLPFC, L Front pol, L LOC, L Par, R LOC, R Par, Vis

Figure 10: Regions of the second principal component at (0,0,0).

The separate regions of the brain corresponding to the first principal component are highlighted with different colors. All of these regions are correlated with each other.

We also performed Independent Component Analysis on the time series dataset. Using sklearn.decomposition's FastICA algorithm, we fit and transform the data before normalizing. We decided on a threshold of 1.2 for the mask and mapped the result back to a 3D representation. Let's take a look at the ICA components.

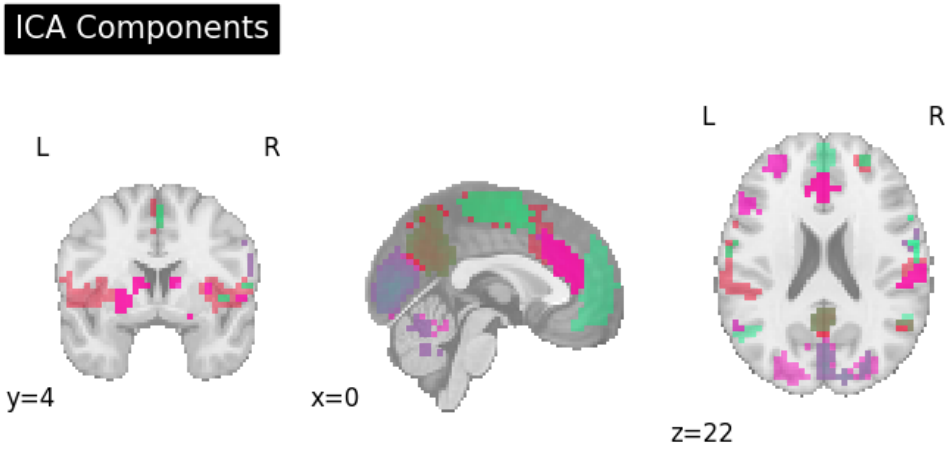
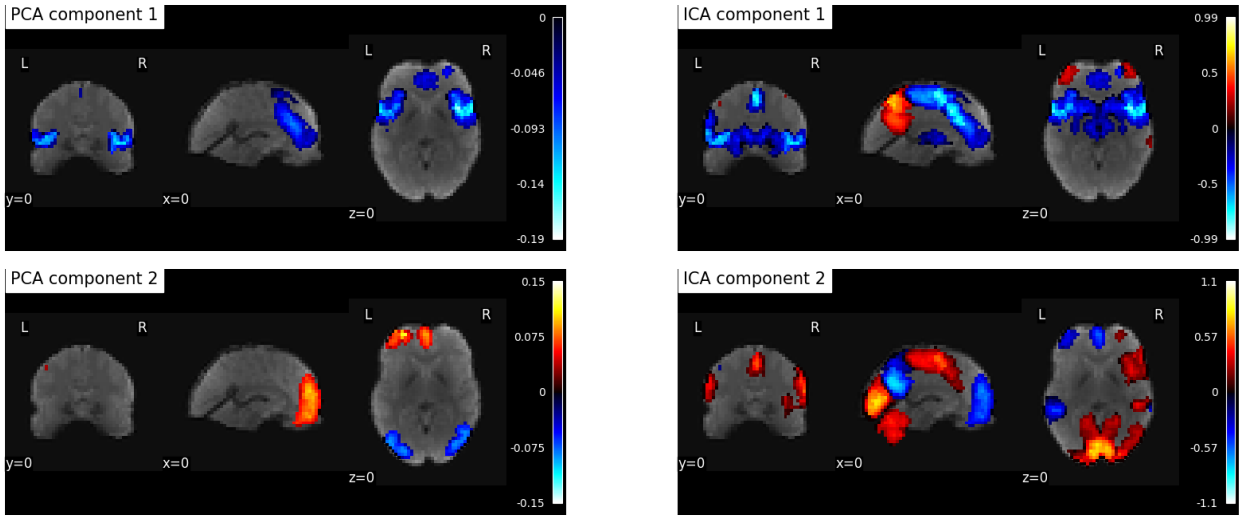


Figure 11: Locations of different ICA Components at (0,0,0).

From the visualizations above, we can see that ICA components consist of a greater number of locations compared to the principal components found with PCA. The overlapping colors in Figure 11 shows that some brain regions contribute to more than one ICA component.

We can visualize the differences between PCA and ICA directly.



	Component 1 Regions	Component 2 Regions
PCA	L Ins, L STS, R A Ins, R Ins, R STS, Sup Front S, V ACC	D ACC, Front DMN, L DLPFC, L Front pol, L LOC, L Par, R LOC, R Par, Vis
ICA	Cing, Dors PCC, L Ins, L STS, Motor, R A Ins, R IPS, R Ins, R STS	Cereb, Front DMN, L Ant IPS, L Aud, L DLPFC, L DMN, L Front pol, L Par, L TPJ, Med DMN, R Ant IPS, R Aud, R DMN, R Pars Op, R Post Temp, R TPJ

Figure 12: Regions of PCA and ICA Components 1 and 2 at (0,0,0) with BOLD signal.

From Figure 12, we can see that the second ICA component found all four regions of the Default Mode Network, indicating that ICA is able to find existing networks in the brain.

However, there are other regions that are not a part of the DMN included in the second ICA component, which may be a limitation of this methodology. In addition, ICA produces a different result every time it is run, which makes it difficult to compare results between subjects.

4 Conclusion

In conclusion, functional magnetic resonance imaging (fMRI) provides high spatial resolution data that can be collected in large volumes and processed to understand the structure of our brain. Studying its blood-oxygen-level-dependent (BOLD) signals provides information about localized activity in the brain that can help identify networks that are important in clinical application.

Our project utilizes data from the Human Connectome Project (HCP), which contains fMRI scans from 1,200 adult brains. We are particularly interested in the activity of different brain regions over time. To standardize the location of these brain regions, we employ an atlas which mitigates the complications that arise with the natural variability of brain structures across many individuals. Employing techniques such as pairwise correlations, PCA and ICA on the time series data helps replicate key findings about neural networks that estimate functional connectivity, especially when studying the resting state. Studying functional activity using resting state fMRI data helps identify the Default Mode Network (DMN), a brain network often used to understand mental illness and to detect neurological decay.

In the methodology section, we outlined our approach to estimating functional connectivity, including correlation and standard error calculations, as well as the application of Principal Component Analysis (PCA) and Independent Component Analysis (ICA). In applying these methods onto randomly generated data, we saw how sample size affected the standard error of correlation and how a distribution's shape affected the decomposition of PCA and ICA. These findings reinforced how larger sample sizes help create more robust estimates of functional connectivity. They also emphasized how, when performing multivariate decomposition and factorization, it is important to understand whether the data is Gaussian.

In the application section, we applied our approaches onto a single subject's resting fMRI data using an atlas estimated via Multi-subject Dictionary Learning. From the correlation calculations, we visualized the pairwise correlation matrix that captures the linear relationships between brain regions, uncovering positive, negative, and uncorrelated connections. PCA and ICA provided insights into the different regions of the brain that account for the most variability in the time series BOLD signal data during resting state.

There still exists a limitation on using statistical-based methods on analyzing and detecting networks in the brain. One main reason, ICA assumes statistical independence of signals in the brain, which most of the time isn't true. Future work is needed in finding non-linear relationships in the signals that comprise the networks. We plan to explore deep learning methods to uncover these relationships and compare it to results in this project.

The combination of correlation analysis, PCA, and ICA still aid in understanding the networks within the human brain and their functions, contributing to further discovery in neuroscience research.

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Acknowledgements

We extend our deepest appreciation to our mentor, Armin Schwartzman, whose guidance and unwavering support have been instrumental throughout statistical and neuroscience project. He has been an invaluable source of wisdom, providing not only scholarly expertise but also profound insights that have enriched our research and personal development.

We also want to express our gratitude to our PhD advisor, Gabriel Riegner, for his insightful feedback and scholarly guidance. Riegner has played a pivotal role in shaping the direction of our research and has been an unwavering advocate for our academic and professional growth.

We are fortunate to have had the opportunity to work under the mentorship of Schwartzman and Riegner. Their collective expertise, encouragement, and support have been indispensable, and we are truly grateful for the profound impact they have had on our academic journey as well as our capstone project.

Data were provided [in part] by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.