Functional Brain Connectivity Patterns in Autism Spectrum Disorder: A Multivariate Statistical Study

Hanyu Wang

Abstract. Autism Spectrum Disorder (ASD) affects approximately 2.0% of Canadian children and youth [1] , presenting significant challenges due to its impact on behavior, cognition, and daily functioning. Understanding the disorder's neural basis is critical for improving diagnosis and intervention. This study investigates differences in brain connectivity between individuals with ASD and matched neurotypical controls using multivariate statistical techniques. Tools such as correlation matrices, permutation testing, effect size analysis (Cohen's d), and false discovery rate (FDR) correction are applied to identify robust connectivity patterns associated with ASD, aiming to inform the development of targeted therapeutic strategies.

Keywords: Autism Spectrum Disorder, Functional MRI, Multivariate Statistical Analysis, Permutation Test, Effect Size, False Discovery Rate Correction.

1 Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by impairments in social interaction and communication, along with restricted and repetitive behaviors. Individuals with ASD frequently experience comorbidities including anxiety, depression, epilepsy, and sleep disturbances, which further complicate the clinical picture. Neuroimaging studies have suggested that abnormal connectivity—particularly hyper-connectivity in certain brain networks—may be linked to the severity of social impairments in ASD [2]. To further explore these neural alterations, it is essential to conduct detailed comparative analyses between individuals with ASD and neurotypical populations. This research builds on that foundation by leveraging multivariate methods to examine connectivity differences, contributing to a more nuanced understanding of the neural architecture underlying ASD.

2 Data and Preprocessing

2.1 Data Description

This dataset includes brain activity and demographic data from 21 minors with autism and 26 neurotypical minors. The brain activity data, obtained from functional MRI (fMRI) scans, captures information from 110 brain regions across 196 time points. The demographic data includes age at the time of the scan, gender, and autism diagnosis. The tests show that there is no missing data in this dataset, therefore, no handling of missing data is needed. The following tables show the basic summary statistics of the dataset.

Table 1 Demographic Dataset Summary

Numerical Variables

Variables	Min.	1st Qu.	Mean	Median	3rd Qu.	Max
Age at Scan	7.00	10.88	12.80	13.25	14.42	17.83

Nominal Variables

Sex	Male: 33	Female: 14
Autism	Yes: 21	No: 26

2.2 Transformations

In this study, transformation methods were systematically employed to address the technical challenges inherent in the data, optimizing the validity of statistical analyses and the interpretability of the results.

To address the skewed distribution of fMRI signals, log-scaling and Fisher's Z transformation were applied to compress the dynamic range and stabilize the variance of high-signal intervals, thereby approximating a normal distribution and meeting the assumptions required for parametric testing.

Each brain region's time series was independently normalized to eliminate dimensional heterogeneity across regions by Z-score standardization, ensuring comparability in functional connectivity analysis. Additionally, for visualization and clustering purposes, min-max normalization was applied in some analyses to scale the data to the range [0,1].

2.3 Basic Analysis by Visualization

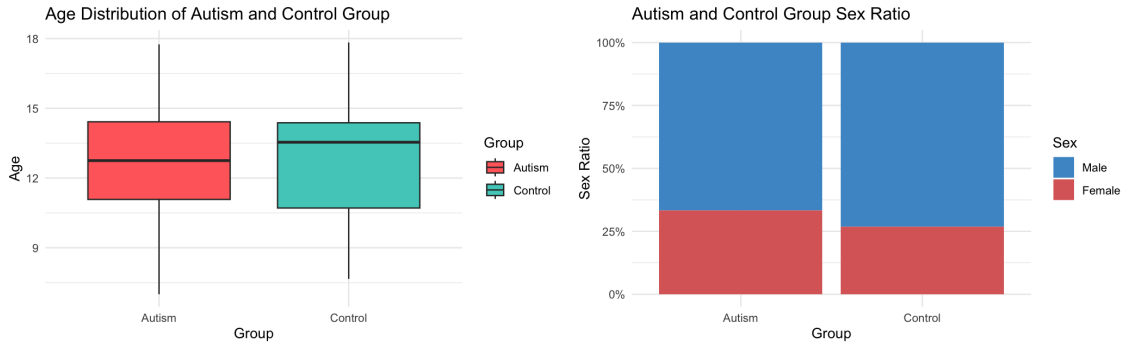
This study aims to compare individuals with and without autism based on three key aspects: demographic characteristics, brain regional activity, and inter-regional functional connectivity.

a. Demographic Characteristics

Table 2 Statistical Informations of the Demographic Data

Group	N	Age Mean	Age SD	Male	Female
Autism	21	12.86476	3.099825	14	7
Control	26	12.75615	2.836535	19	7

Fig 1 Demographic Characteristics of Study Participants.



Both the table and the left figure show that the age distributions of the two groups are comparable, with similar medians and interquantile ranges, indicating that there are no substantial age differences between the groups. The right figure illustrates the sex ratio in each group, revealing a higher proportion of males in both groups and no marked imbalance between them. Together,

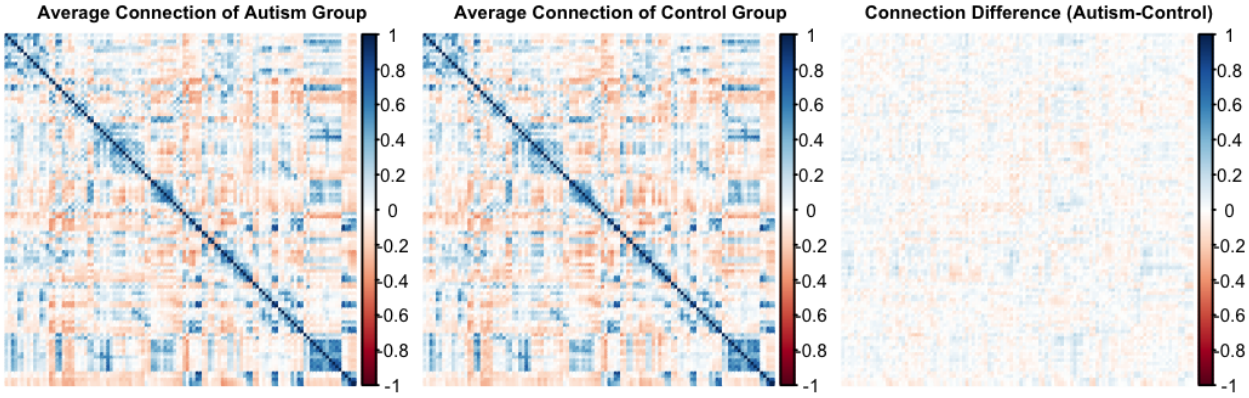
these informatics suggest that age and sex are well matched across the autism and control groups, reducing the likelihood that demographic differences influence Autism.

b. Brain Activities

Table 3 Statistical Informations of the fMRI Data (Mean after Standardization)

Group	Mean	SD	1st Qu.	Media	3rd Qu.
Autism	1.117985e-12	1	-0.6039656	0.05804884	0.6730291
Control	-3.080578e-1	1	-0.6075735	0.06067823	0.6763566

Fig 2 Functional Connectivity Matrices of Autism and Control Groups



Brain activity was similar between the two groups, however, Autistic group had slightly higher average activity intensity at all brain levels. This suggests that, there may be alteration in brain activities between autistic and neurotypical individuals in this dataset.

3 Methodology

3.1 Correlation Matrices

Functional connectivity matrices were computed for each subject based on pairwise Pearson correlation coefficients between brain regions, capturing the strength of synchronous activity. The resulting correlation coefficients were further transformed into Fisher's Z-scores to normalize the

distribution and enhance the validity of statistical testing. Autism is often associated with atypical patterns of inter-regional synchronization, particularly within networks such as the default mode network and salience network. Functional connectivity matrix analysis enables a comprehensive characterization of whole-brain network organization, facilitating the identification of Autism-related aberrant connections.

3.2 Permutation Test

A permutation test was conducted by randomly shuffling group labels (Autism vs. Control) to generate a null distribution, against which the observed group differences in functional connectivity strength were evaluated for statistical significance. Permutation testing does not rely on the assumption of normality and is particularly well-suited for small sample sizes, such as the 47 subjects in this study. It provides robust control of Type I error, ensuring the reliability of statistical inferences.

$$\text{Cohen's d} = \frac{\text{Group Mean Difference}}{\text{Pooled Standard Deviation}} \tag{1}$$

This metric quantifies the magnitude of the difference between groups.

In neuroimaging studies, statistical significance (p-value) can be influenced by sample size, and effect size offers a complementary measure of the practical or clinical significance of the observed differences. For instance, even if some connections do not reach statistical significance after FDR correction, a large effect size may suggest potentially important differences.

3.3 Multiple Comparisons Correction (FDR)

The p-values for 110 brain regions or thousands of functional connections were corrected for False Discovery Rate (FDR) to control the proportion of false positives.

Neuroimaging data typically have high dimensionality, leading to significant multiple comparisons challenges. FDR correction strikes a balance between detecting true differences and minimizing false positives, ensuring the reliability of the results.

4 Results

The final results indicate that the strengths of connectivities between brain regions, especially the increased connectivity of Left Middle Temporal Gyrus (posterior division) with other regions, differ between individuals with Autism and neurotypical controls. However, the data do not support significant associations with sex, age, or regional brain activities.

This result is consistent with expectations, as it aligns with the findings of Supekar et al., who reported increased hyper-connectivity in the brains of children with ASD.

a. Sex

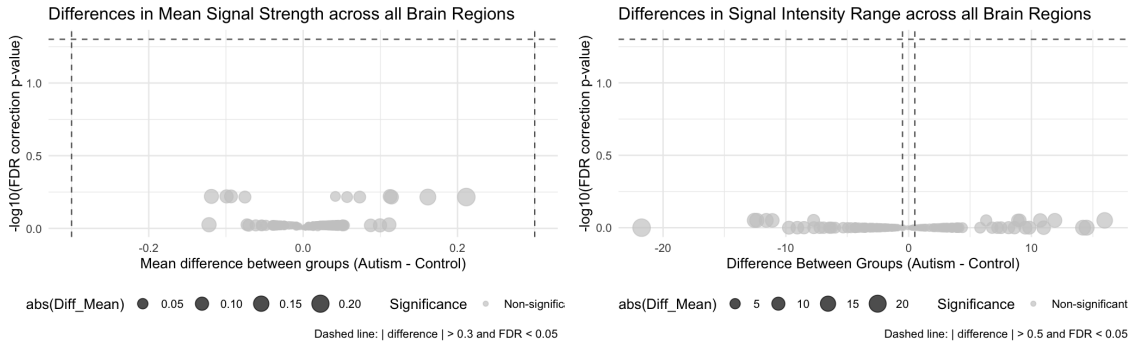
The independent samples t-test was conducted to compare the mean age between the two groups. The result revealed a t-statistic of 0.12401 and a p-value of 0.9019, indicating no significant difference in the mean ages between the two groups, as the p-value is much greater than the commonly used threshold of 0.05. The 95% confidence interval ranged from -1.6599 to 1.8771, further suggesting that the true mean difference between the groups could fall within this range. Consequently, we cannot conclude that there is a significant difference in the mean ages between the autism and control groups.

b. Age

The comparison of gender distribution between the autism and control groups was conducted using Pearson's Chi-squared test with Yates' continuity correction. The result showed a p-value of 0.8753, indicating no significant difference in gender distribution between the two groups.

c. Regional Brain Activities

Fig 3 Differences in Means and Ranges of Signal Intensities for Brain Regions



The figures display the differences between the Autism group and the control group in terms of average signal intensity (left) and the range of signal intensity (right) in different brain regions. The results indicate that there were no statistically significant differences between the groups in most brain regions ($|\text{FDR-corrected p-value}| < 0.05$), and no data points met the established thresholds for difference ($|\text{Difference}| > 0.3$ for left, $|\text{Difference}| > 0.5$ for right) and statistical significance. This suggests that, there are no systematic, significant differences in signal intensity or its range between individuals with and without Autism. The size of the data points represents the absolute value of the difference; however, the overall distribution is concentrated with minimal variation, further supporting this conclusion.

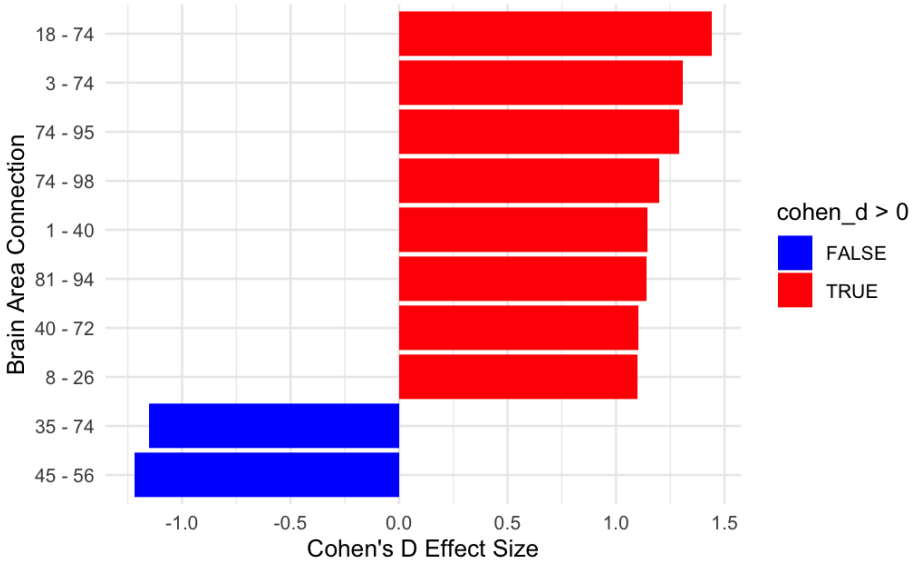
d. Connection between Brain Regions

The strengths of multiple connections between brain regions were observed to be different between the two groups (with p-values less than 0.05). Upon sorting by both uncorrected p-value and effect size, sorting by only the p-value, and sorting by only the effect size, the five most impactful connections were identified as Region18-Region74, Region3-Region74, Region74-Region95, Region45-Region46, and Region74-Region98.

Note: Region 3 is (12) - Left Putamen;
Region 18 is (401) - Right Middle Frontal Gyrus;
Region 45 is (3101) - Right Precuneous Cortex;
Region 46 is (3201) - Right Cuneal Cortex;
Region 74 is (1202) - Left Middle Temporal Gyrus, posterior division;
Region 95 is (3302) - Left Frontal Orbital Cortex;
Region 98 is (3602) - Left Lingual Gyrus.

The figure below presents the top ten brain region connections with the largest between-group differences, sorted by p-value. Results from the other two sorting methods can be found in Appendix Table 5 and Table 6.

Fig 4 Brain Connectivities with the Largest Effect Sizes (Sort by P-value)



Positive effect sizes (red) indicate stronger connectivity in the Autism group, while negative effect sizes (blue) indicate stronger connectivity in the control group. These findings suggest that these brain region connections, especially the increased connectivity of Left Middle Temporal Gyrus (posterior division) with other regions, exhibit pronounced differences between Autism and

non-autism groups, which may provide valuable insights into the neural mechanisms underlying Autism.

5 References

References

[1] Statistics Canada. "Release notice – Autism spectrum disorder: Highlights from the 2019 Canadian Health Survey on Children and Youth". In: *Health Promotion and Chronic Disease Prevention in Canada* 42.3 (2022), pp. 122–122. DOI: 10.24095/hpcdp.42.3.06.

[2] Kaustubh Supekar et al. "Brain hyperconnectivity in children with autism and its links to social deficits". In: *Cell Reports* 5.3 (2013), pp. 738–747. DOI: 10.1016/j.celrep.2013.10.001.

Appendix A: Tables

Table 4 Brain Regions with the Largest Differences in Activity Range

Region	Mean_Range_Autism	Mean_Range_Control	SD_Range_Autism
31	114.62973	136.37932	36.69701
64	70.41539	54.45424	36.83956
109	136.07900	121.59138	29.67146
107	149.77517	135.57758	47.70347
102	66.47353	79.03415	15.47514

Table 5 Brain Connectivity with Largest Effect Sizes (Sort by P-value and Effect Size)

from	to	diff_strength	cohen_d	p.value
18	74	0.2832137	1.442346	1.106859e-05
3	74	0.2455088	1.306682	3.249593e-05
74	95	0.2353787	1.291540	4.378912e-05
74	98	0.2085547	1.197955	1.306636e-04
45	56	-0.1893821	-1.220383	1.816108e-04
35	74	-0.1557640	-1.153375	2.341897e-04
81	94	0.1832819	1.138642	2.527048e-04
40	72	0.2127589	1.102241	4.461751e-04
12	39	0.1406246	1.085147	4.978572e-04
74	97	0.1975459	1.066026	5.721665e-04

Table 6 Brain Connectivity with Largest Effect Sizes (Sort by Effect Size)

from	to	cohen_d	p.value	p.adj
18	74	1.442346	1.106859e-05	0.06635618
3	74	1.306682	3.249593e-05	0.08750527
74	95	1.291540	4.378912e-05	0.08750527
45	56	-1.220383	1.816108e-04	0.21642365
74	98	1.197955	1.306636e-04	0.19583210
35	74	-1.153375	2.341897e-04	0.21642365
1	40	1.146633	5.879779e-04	0.25972660
81	94	1.138642	2.527048e-04	0.21642365
40	72	1.102241	4.461751e-04	0.25972660
8	26	1.097800	6.445453e-04	0.25972660

List of Figures

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Appendix B: Code

Install Packages

```
# install.packages(c("dplyr", "tidyr", "ggplot2", ""plotly","Hmisc", "corrplot","dplyr", "corrplot", "f

library(dplyr)
```

```
##
## Attaching package: 'dplyr'
## The following objects are masked from 'package:stats':
##
##     filter, lag
## The following objects are masked from 'package:base':
##
##     intersect, setdiff, setequal, union
```

```
library(tidyr)
library(ggplot2)
library(plotly)
```

```
##
## Attaching package: 'plotly'
## The following object is masked from 'package:ggplot2':
##
##     last_plot
## The following object is masked from 'package:stats':
##
##     filter
## The following object is masked from 'package:graphics':
##
##     layout
```

```
library(corrplot)
```

```
## corrplot 0.95 loaded
```

```
library(factoextra)
```

```
## Welcome! Want to learn more? See two factoextra-related books at https://goo.gl/ve3WBa
```

```
library(broom)
library(ggrepel)
library(purrr)
library(psych)
```

```
##
## Attaching package: 'psych'
```

```
## The following objects are masked from 'package:ggplot2':
##
##     %+%, alpha
```

1. Prepare Data

1.1 Load ABIDE Dataset

```
dt <- load("/Users/macbook/Desktop/ASD/asd_data.RData")
```

1.2 Check Data

```
print(dt)
```

```
## [1] "YALE_fmri"     "YALE_demo_var"
```

"dt": include 2 datasets, "YALE_fmri" & "YALE_demo_var"

```
summary(YALE_fmri)
```

```
##       Length Class      Mode
##  [1,] 110    data.table list
##  [2,] 110    data.table list
##  [3,] 110    data.table list
##  [4,] 110    data.table list
##  [5,] 110    data.table list
##  [6,] 110    data.table list
##  [7,] 110    data.table list
##  [8,] 110    data.table list
##  [9,] 110    data.table list
## [10,] 110    data.table list
## [11,] 110    data.table list
## [12,] 110    data.table list
## [13,] 110    data.table list
## [14,] 110    data.table list
## [15,] 110    data.table list
## [16,] 110    data.table list
## [17,] 110    data.table list
## [18,] 110    data.table list
## [19,] 110    data.table list
## [20,] 110    data.table list
## [21,] 110    data.table list
## [22,] 110    data.table list
## [23,] 110    data.table list
## [24,] 110    data.table list
## [25,] 110    data.table list
## [26,] 110    data.table list
## [27,] 110    data.table list
## [28,] 110    data.table list
## [29,] 110    data.table list
## [30,] 110    data.table list
## [31,] 110    data.table list
## [32,] 110    data.table list
## [33,] 110    data.table list
```

```
## [34,] 110    data.table list
## [35,] 110    data.table list
## [36,] 110    data.table list
## [37,] 110    data.table list
## [38,] 110    data.table list
## [39,] 110    data.table list
## [40,] 110    data.table list
## [41,] 110    data.table list
## [42,] 110    data.table list
## [43,] 110    data.table list
## [44,] 110    data.table list
## [45,] 110    data.table list
## [46,] 110    data.table list
## [47,] 110    data.table list
```

```
str(YALE_fmri[1])
```

```
## List of 1
##  $ :Classes 'data.table' and 'data.frame':   196 obs. of  110 variables:
##   ..$ #10  : num [1:196] -4.5 -9.63 -9.44 -3.06 3.74 ...
##   ..$ #11  : num [1:196] -4.4 -5.36 -1.24 5.6 8.77 ...
##   ..$ #12  : num [1:196] -2.264 -5.716 -4.535 -0.211 2.399 ...
##   ..$ #13  : num [1:196] 0.358 -5.676 -10.499 -8.833 -1.03 ...
##   ..$ #17  : num [1:196] 1.44 -0.366 -2.541 -3.112 -2.322 ...
##   ..$ #18  : num [1:196] 6.421 5.939 -0.181 -7.215 -9.444 ...
##   ..$ #26  : num [1:196] -0.181 7.706 16.039 16.447 5.578 ...
##   ..$ #49  : num [1:196] -4.873 -7.722 -6.487 -2.653 -0.721 ...
##   ..$ #50  : num [1:196] 0.834 1.348 0.934 -1.304 -4.378 ...
##   ..$ #51  : num [1:196] 0.38 -1.418 -1.956 -0.576 1.161 ...
##   ..$ #52  : num [1:196] -6.5 -8.4 -4.16 2.91 6.48 ...
##   ..$ #53  : num [1:196] 1.908 0.556 -2.898 -6.579 -8.034 ...
##   ..$ #54  : num [1:196] 3.94 5.69 3.7 -3.01 -10.59 ...
##   ..$ #58  : num [1:196] 2.14 10.45 12.12 1.21 -16.99 ...
##   ..$ #101 : num [1:196] 0.238 2.316 6.629 9.745 9.953 ...
##   ..$ #102 : num [1:196] 0.762 3.215 6.981 9.695 9.305 ...
##   ..$ #201 : num [1:196] -2.18 -6.8 -7.11 -1.74 5.48 ...
##   ..$ #202 : num [1:196] -0.846 -2.659 -2.585 -1.49 -1.12 ...
##   ..$ #301 : num [1:196] -3.18 1.73 9.57 12.65 8.75 ...
##   ..$ #302 : num [1:196] 1.1 1.3 -2.15 -6.38 -6.36 ...
##   ..$ #401 : num [1:196] -2.63 -1.31 0.483 2.093 3.882 ...
##   ..$ #402 : num [1:196] 0.487 4.239 7.314 9.068 8.762 ...
##   ..$ #501 : num [1:196] -3.01 -9.37 -7.39 5.78 18.75 ...
##   ..$ #502 : num [1:196] 1.578 1.4442 -0.0491 -0.8953 0.693 ...
##   ..$ #601 : num [1:196] -4.84 -6.62 -3.62 1.77 2.55 ...
##   ..$ #602 : num [1:196] 0.027 1.033 3.849 8.893 11.318 ...
##   ..$ #701 : num [1:196] -2.07 -6.82 -9.271 -6.71 -0.718 ...
##   ..$ #702 : num [1:196] -3.16 -7.25 -8.33 -4.74 1.63 ...
##   ..$ #801 : num [1:196] -1.995 -2.501 -1.198 0.599 0.684 ...
##   ..$ #802 : num [1:196] 2.597 2.469 1.499 0.232 -0.139 ...
##   ..$ #901 : num [1:196] 3.28 9.04 8.47 -3.63 -23.4 ...
##   ..$ #902 : num [1:196] -2.269 0.295 6.314 9.678 4.054 ...
##   ..$ #1001: num [1:196] -3.366 -1.028 1.488 0.748 -4.257 ...
##   ..$ #1002: num [1:196] -1.17 2.09 7.41 10.53 6.84 ...
##   ..$ #1101: num [1:196] -6.645 -6.715 -0.425 6.888 8.167 ...
##   ..$ #1102: num [1:196] -0.632 0.521 3.128 4.614 3.31 ...
```

```
##   ..$ #1201: num [1:196] -2.43 -0.925 3.135 5.844 4.145 ...
##   ..$ #1202: num [1:196] -1.44 1.6 5.26 7.38 8.08 ...
##   ..$ #1301: num [1:196] -0.399 3.497 9.361 12.673 9.42 ...
##   ..$ #1302: num [1:196] -0.0423 9.6493 18.4766 21.5258 17.0406 ...
##   ..$ #1401: num [1:196] -1.71 -4.86 -3.94 1.34 5.69 ...
##   ..$ #1402: num [1:196] -0.715 -1.587 -1.57 -1.066 -0.964 ...
##   ..$ #1501: num [1:196] 0.0956 -1.7428 -2.3854 -1.1106 0.5894 ...
##   ..$ #1502: num [1:196] 0.58 1.37 2.54 3.21 2.7 ...
##   ..$ #1601: num [1:196] 0.993 1.329 -1.238 -5.985 -9.175 ...
##   ..$ #1602: num [1:196] 0.917 7.128 11.066 7.97 -0.348 ...
##   ..$ #1701: num [1:196] -1.616 -5.946 -9.205 -7.699 -0.828 ...
##   ..$ #1702: num [1:196] -4.06 -8.09 -7.86 -3.21 2.59 ...
##   ..$ #1801: num [1:196] -2.99 -6.79 -9.56 -9.76 -6.83 ...
##   ..$ #1802: num [1:196] -3.438 -1.772 0.207 0.505 -0.666 ...
##   ..$ #1901: num [1:196] 1.5 1.11 -4.31 -9.23 -7.34 ...
##   ..$ #1902: num [1:196] 3.73 3.53 -2.13 -9.79 -12.42 ...
##   ..$ #2001: num [1:196] -0.81 -0.408 -2.49 -5.482 -4.944 ...
##   ..$ #2002: num [1:196] 1.88 4.86 5.62 2.11 -4.07 ...
##   ..$ #2101: num [1:196] 0.597 2.44 2.775 2.444 4.343 ...
##   ..$ #2102: num [1:196] -0.753 7.38 18.395 25.367 22.491 ...
##   ..$ #2201: num [1:196] 3.75 2.53 -5.1 -12.6 -12.7 ...
##   ..$ #2202: num [1:196] 7.58 10.43 3.49 -7.58 -13.1 ...
##   ..$ #2301: num [1:196] 5.47 3.6 -3.63 -9.73 -9.48 ...
##   ..$ #2302: num [1:196] 4.32 7.91 5.13 -2.7 -9.87 ...
##   ..$ #2401: num [1:196] 4.987 -0.338 -8.34 -12.584 -8.319 ...
##   ..$ #2402: num [1:196] 0.0692 -5.4758 -8.9185 -6.2886 1.4442 ...
##   ..$ #2501: num [1:196] 4.79 9.42 8.07 -1.64 -13.67 ...
##   ..$ #2502: num [1:196] 0.819 7.398 13.331 12.498 4.311 ...
##   ..$ #2601: num [1:196] -4.81 -14.74 -19.07 -15.16 -5.97 ...
##   ..$ #2602: num [1:196] -0.613 -3.596 -5.917 -6.312 -4.72 ...
##   ..$ #2701: num [1:196] 2.995 4.587 0.952 -5.488 -9.211 ...
##   ..$ #2702: num [1:196] 1.6 2.13 0.35 -2.65 -4.38 ...
##   ..$ #2801: num [1:196] -2.08 2.34 6.31 7.72 8.11 ...
##   ..$ #2802: num [1:196] -0.1665 0.0514 -0.369 -0.3922 0.8151 ...
##   ..$ #2901: num [1:196] -3.73 -2.86 1.49 4.99 4.67 ...
##   ..$ #2902: num [1:196] -4.01 -5.75 -2.55 3.26 6.49 ...
##   ..$ #3001: num [1:196] -2.506 -2.895 -0.843 2.591 5.83 ...
##   ..$ #3002: num [1:196] 0.938 0.617 -1.733 -4.018 -4.155 ...
##   ..$ #3101: num [1:196] 0.767 1.567 -1.055 -6.685 -12.061 ...
##   ..$ #3102: num [1:196] 1.4 2.15 -0.8 -5.69 -9.01 ...
##   ..$ #3201: num [1:196] 1.563 -1.794 -3.755 -0.644 4.477 ...
##   ..$ #3202: num [1:196] 3.73 4.066 0.824 -2.753 -4.089 ...
##   ..$ #3301: num [1:196] 1.17 0.596 -0.795 -1.013 1.101 ...
##   ..$ #3302: num [1:196] 6.72 7.27 1.62 -4.94 -5.97 ...
##   ..$ #3401: num [1:196] -0.884 -1.032 -0.623 0.774 2.76 ...
##   ..$ #3402: num [1:196] 2.209 2.53 0.434 -3.183 -5.846 ...
##   ..$ #3501: num [1:196] 2.2 2.21 -1.56 -8.37 -13.11 ...
##   ..$ #3502: num [1:196] 0.603 -0.878 -5.138 -9.2 -9.554 ...
##   ..$ #3601: num [1:196] 0.493 -0.492 -1.723 -4.104 -7.531 ...
##   ..$ #3602: num [1:196] 3.36 -1.13 -8.29 -11.39 -7.65 ...
##   ..$ #3701: num [1:196] -0.0805 -0.7828 -0.6161 0.7277 1.9565 ...
##   ..$ #3702: num [1:196] -1.82 -4.65 -6.23 -4.89 -1.81 ...
##   ..$ #3801: num [1:196] -0.812 -1.239 -1.785 -2.605 -3.321 ...
##   ..$ #3802: num [1:196] 1.3 0.89 -0.653 -2.347 -3.476 ...
```

```
##   ..$ #3901: num [1:196] 4.27 2.48 -4.02 -10.91 -13.85 ...
##   ..$ #3902: num [1:196] 2.4 0.98 -3.74 -7.84 -7.63 ...
##   ..$ #4001: num [1:196] 6.43 4.57 -3.83 -12.53 -15.41 ...
##   ..$ #4002: num [1:196] 4.14 2.96 -3.61 -10.56 -12.83 ...
##   ..$ #4101: num [1:196] -5.88 -12.09 -8.2 4.66 15.09 ...
##   ..$ #4102: num [1:196] -0.688 -6.489 -8.035 -1.804 6.485 ...
##   ..$ #4201: num [1:196] -0.839 -4.584 -5.06 -1.937 1.865 ...
##   ..$ #4202: num [1:196] -2.78 -5.567 -5.631 -3.155 -0.526 ...
##   ..$ #4301: num [1:196] -4.3639 -5.6637 -3.4183 -0.0868 0.4465 ...
##   .. [list output truncated]
##   ..- attr(*, ".internal.selfref")=<externalptr>
```

"YALE_fmri": list of 47 matrices, each 196x110

```
missing_fmri <- sapply(YALE_fmri, function(mat) sum(is.na(mat)))

cat("\n=== fMRI Data Missing Value Summary ===\n")
```

```
##
## === fMRI Data Missing Value Summary ===
```

```
cat("Total missing values:", sum(missing_fmri), "\n")
```

```
## Total missing values: 0
```

```
cat("Number of subjects with missing values:", sum(missing_fmri > 0), "\n")
```

```
## Number of subjects with missing values: 0
```

```
str(YALE_demo_var)
```

```
## 'data.frame':    47 obs. of  3 variables:
##  $ DX_GROUP   : Factor w/ 2 levels "1","2": 2 2 2 2 2 2 2 2 2 2 ...
##  $ AGE_AT_SCAN: num  15.92 12.75 9.75 8.67 14.42 ...
##  $ SEX        : Factor w/ 2 levels "1","2": 1 1 1 1 2 1 2 2 1 1 ...
```

"YALE_demo_var": data frame with 47 rows, 3 variables

```
missing_demo <- colSums(is.na(YALE_demo_var))

cat("Census Table Missing Value Summary:\n")
```

```
## Census Table Missing Value Summary:
```

```
print(missing_demo)
```

```
##    DX_GROUP AGE_AT_SCAN         SEX
##           0           0           0
```

There is no missing data

1.3 Time series preprocessing

```
YALE_fmri_processed <- lapply(1:length(YALE_fmri), function(i) {
  subject_mat <- YALE_fmri[[i]]
  subject_mat <- as.matrix(subject_mat)
  storage.mode(subject_mat) <- "double"

  global_mean <- mean(subject_mat)
```

```
  subject_mat <- subject_mat - global_mean

  min_val <- min(subject_mat)
  subject_mat_shifted <- subject_mat - min_val + 1e-3
  log_mat <- log(subject_mat_shifted)

  processed_mat <- apply(log_mat, 2, function(ts) {
    (ts - mean(ts)) / sd(ts)
  })

  if (i %in% sample(1:47, 3)) {
    sample_regions <- sample(1:110, 5)
    par(mfrow = c(2, 5), mar = c(3,3,2,1), oma = c(0,0,2,0))
    for (r in sample_regions) {
      hist(subject_mat[, r], breaks = 30, main = paste("Region", r, "-Original"),
           xlab = "", col = "skyblue")
      hist(processed_mat[, r], breaks = 30, main = paste("Region", r, "-After"),
           xlab = "", col = "salmon")
    }
    mtext(paste("Subject", i, "Pretreatment Quality Check "), outer = TRUE, cex = 1.2)
  }

  return(processed_mat)
})
```

2 Data Informations

```
head(YALE_demo_var)
```

```
##     DX_GROUP AGE_AT_SCAN SEX
## 442        2       15.92   1
## 443        2       12.75   1
## 444        2        9.75   1
## 445        2        8.67   1
## 446        2       14.42   2
## 447        2       10.67   1
```

```
summary(YALE_demo_var)
```

```
##  DX_GROUP  AGE_AT_SCAN    SEX
##  1:21     Min.   : 7.00   1:33
##  2:26     1st Qu.:10.88   2:14
##           Median :13.25
##           Mean   :12.80
##           3rd Qu.:14.42
##           Max.   :17.83
```

Note: DX_GROUP → Diagnosis (1 = Autism, 2 = Control). SEX → Gender (1 = Male, 2 = Female).

```
demo_summary <- YALE_demo_var %>%
  group_by(DX_GROUP = factor(DX_GROUP, labels = c("Autism", "Control"))) %>%
  summarise(
    N = n(),
    Age_Mean = mean(AGE_AT_SCAN, na.rm = TRUE),
```

```
    Age_SD = sd(AGE_AT_SCAN, na.rm = TRUE),
    Male = sum(SEX == 1),
    Female = sum(SEX == 2)
  )

print(demo_summary)
```

```
## # A tibble: 2 x 6
##   DX_GROUP     N Age_Mean Age_SD  Male Female
##   <fct>    <int>    <dbl>  <dbl> <int>  <int>
## 1 Autism      21     12.9   3.10    14      7
## 2 Control     26     12.8   2.84    19      7
```

```
subject_summaries <- lapply(YALE_fmri_processed, function(mat) {
  apply(mat, 2, function(ts) {
    c(
      Mean = mean(ts),
      SD = sd(ts),
      Q25 = quantile(ts, 0.25),
      Median = quantile(ts, 0.5),
      Q75 = quantile(ts, 0.75)
    )
  }) %>% t() %>% as.data.frame()
})

for (i in 1:length(subject_summaries)) {
  subject_summaries[[i]]$Subject_ID <- i
  subject_summaries[[i]]$Group <- YALE_demo_var$DX_GROUP[i]
}

summary_df <- do.call(rbind, subject_summaries)

summary_df$Group <- factor(summary_df$Group, levels = c(1,2), labels = c("Autism", "Control"))

group_summary <- summary_df %>%
  group_by(Group) %>%
  summarise(across(.cols = -Subject_ID, .fns = list(Mean = mean, SD = sd), .names = "{.col}_{.fn}"))

print(group_summary)
```

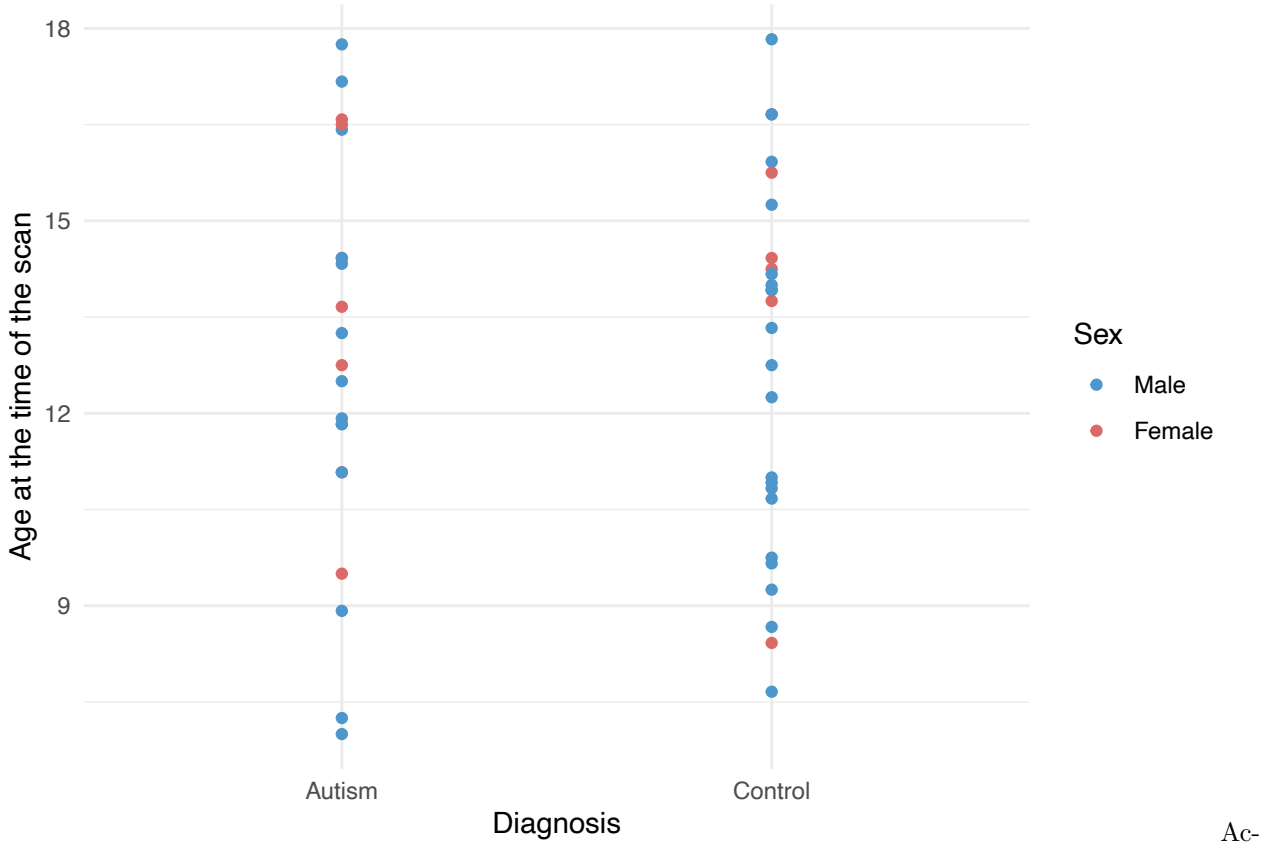
```
## # A tibble: 2 x 11
##   Group   Mean_Mean  Mean_SD SD_Mean    SD_SD `Q25.25%_Mean` `Q25.25%_SD`
##   <fct>       <dbl>    <dbl>   <dbl>    <dbl>          <dbl>        <dbl>
## 1 Autism   1.12e-12 5.37e-11       1 6.20e-17         -0.604       0.0988
## 2 Control -3.08e-17 3.69e-15       1 6.39e-17         -0.608       0.0978
## # i 4 more variables: `Median.50%_Mean` <dbl>, `Median.50%_SD` <dbl>,
## #   `Q75.75%_Mean` <dbl>, `Q75.75%_SD` <dbl>
```

3 Data Analysis

3.1 Analyze by demographic variables

```
ggplot(YALE_demo_var, aes(x = factor(DX_GROUP, labels = c("Autism", "Control")),
                          y = AGE_AT_SCAN,
```

```
                        color = factor(SEX))) +
  geom_point() +
  scale_color_manual(values = c("1" = "#4D97CD", "2" = "#DB6968"),
                     labels = c("Male", "Female")) +
  labs(x = "Diagnosis", y = "Age at the time of the scan", color = "Sex") +
  theme_minimal()
```



According to this graph, it can be preliminarily determined that Autism has no strong association with gender and age. Further verification follows:

```
shapiro_autism <- shapiro.test(YALE_demo_var$AGE_AT_SCAN[YALE_demo_var$DX_GROUP == "1"])
shapiro_control <- shapiro.test(YALE_demo_var$AGE_AT_SCAN[YALE_demo_var$DX_GROUP == "2"])

cat("Autism group normality p-values:", shapiro_autism$p.value, "\n")
```

```
## Autism group normality p-values: 0.5453883
```

```
cat("Control group normality p-values:", shapiro_control$p.value, "\n")
```

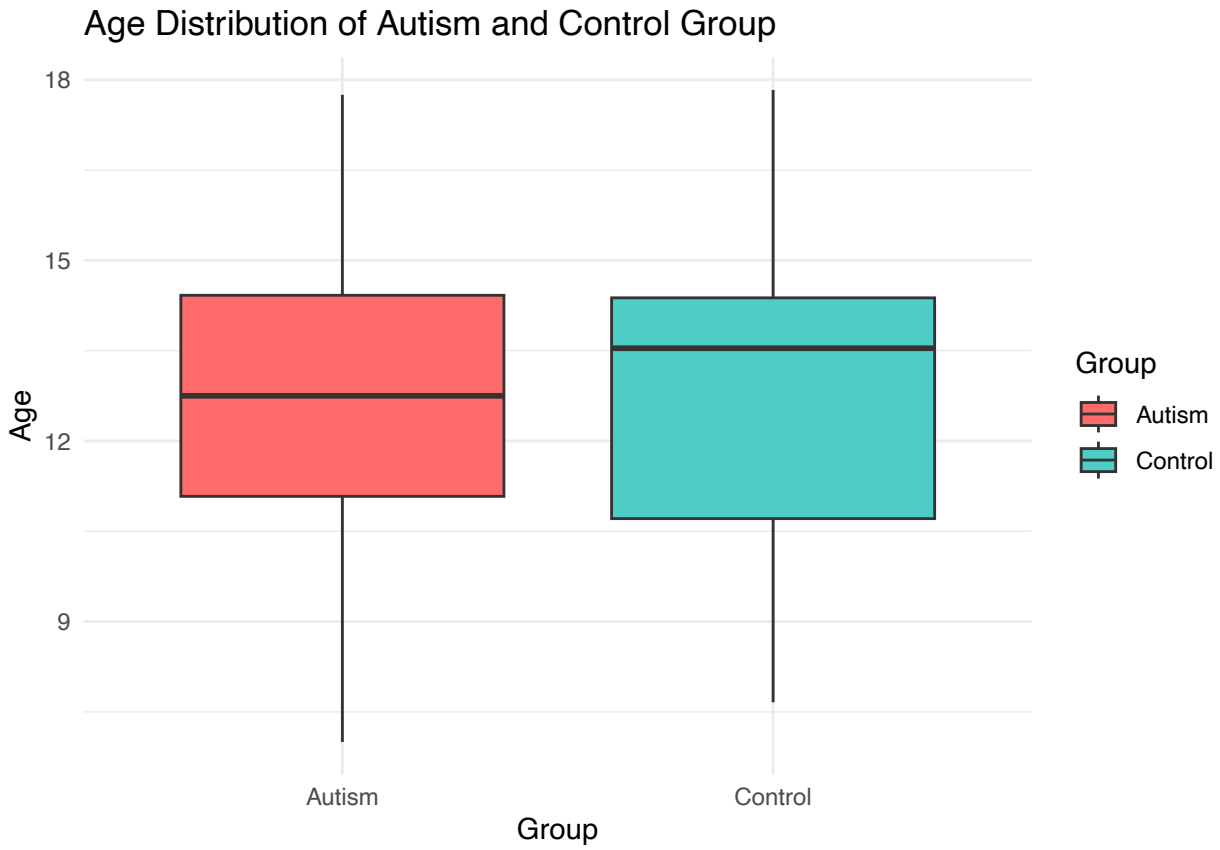
```
## Control group normality p-values: 0.4201061
```

```
# If both groups are normal, the T-test is used. Otherwise, the Mann-Whitney U test is used
if (shapiro_autism$p.value > 0.05 & shapiro_control$p.value > 0.05) {
  t_test <- t.test(AGE_AT_SCAN ~ DX_GROUP, data = YALE_demo_var)
  cat("T-test results:\n")
  print(t_test)
} else {
  wilcox_test <- wilcox.test(AGE_AT_SCAN ~ DX_GROUP, data = YALE_demo_var)
  cat("Mann-Whitney U test results:\n")
```

```
  print(wilcox_test)
}
```

```
## T-test results:
##
##  Welch Two Sample t-test
##
## data:  AGE_AT_SCAN by DX_GROUP
## t = 0.12401, df = 41.145, p-value = 0.9019
## alternative hypothesis: true difference in means between group 1 and group 2 is not equal to 0
## 95 percent confidence interval:
##  -1.659918  1.877134
## sample estimates:
## mean in group 1 mean in group 2
##        12.86476        12.75615
```

```
ggplot(YALE_demo_var,
       aes(
         x = factor(DX_GROUP, labels = c("Autism", "Control")),
         y = AGE_AT_SCAN,
         fill = factor(DX_GROUP)
       )) +
  geom_boxplot() +
  scale_fill_manual(
    values = c("#FF6B6B", "#4ECDC4"),
    labels = c("Autism", "Control"),
    name = "Group"
  ) +
  labs(
    x = "Group",
    y = "Age",
    title = "Age Distribution of Autism and Control Group"
  ) +
  theme_minimal()
```



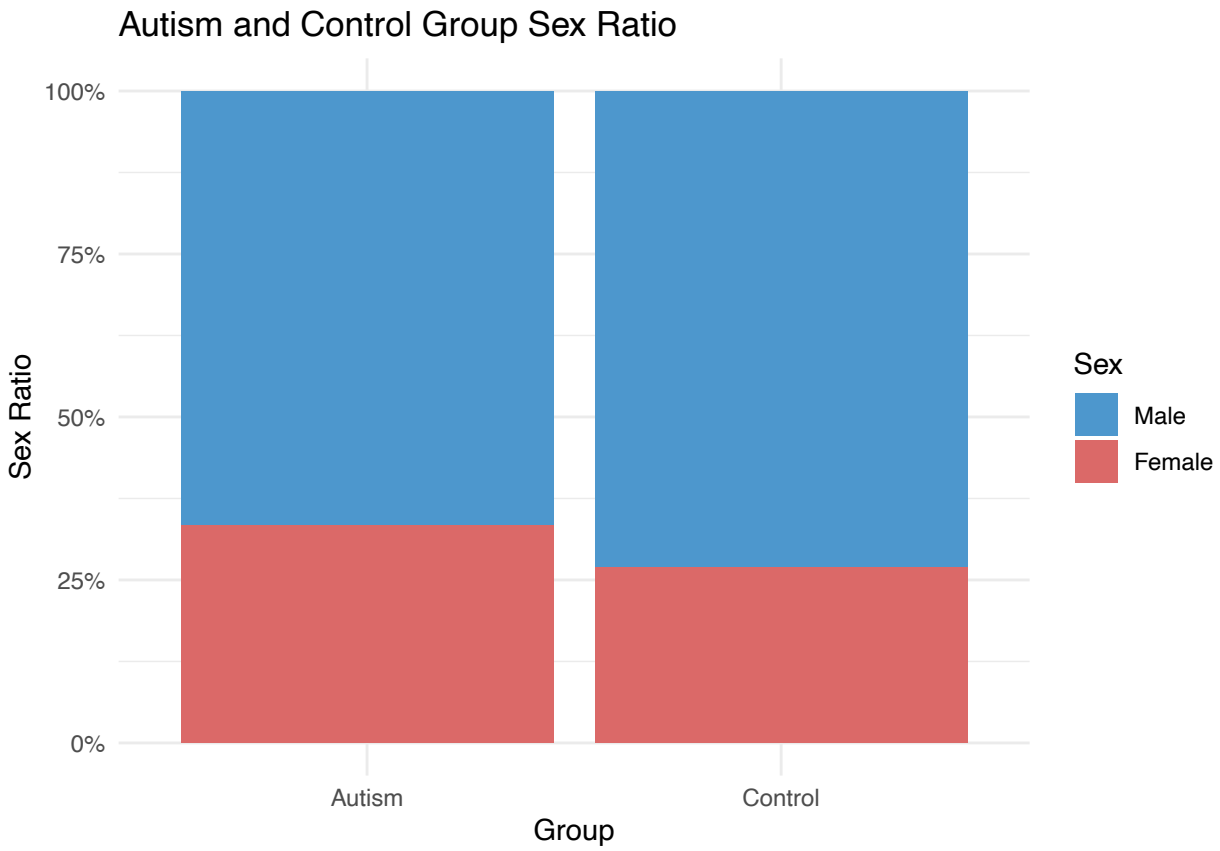
There was no significant difference in age.

```
sex_table <- table(YALE_demo_var$SEX, YALE_demo_var$DX_GROUP)

# Chi Square test (if expected frequency >= 5)
if (all(chisq.test(sex_table)$expected >= 5)) {
  chisq_test <- chisq.test(sex_table)
  cat("Chi-square test results:\n")
  print(chisq_test)
} else {
  fisher_test <- fisher.test(sex_table)
  cat("Fisher test results:\n")
  print(fisher_test)
}
```

```
## Chi-square test results:
##
##  Pearson's Chi-squared test with Yates' continuity correction
##
## data:  sex_table
## X-squared = 0.024641, df = 1, p-value = 0.8753
```

```
ggplot(YALE_demo_var, aes(x = factor(DX_GROUP, labels = c("Autism", "Control")),
       fill = factor(SEX))) +
  geom_bar(position = "fill") +
  scale_fill_manual(
    values = c("#4D97CD", "#DB6968"),
    labels = c("Male", "Female"),
    name = "Sex"
```

```
  ) +
  scale_y_continuous(labels = scales::percent) +
  labs(
    x = "Group",
    y = "Sex Ratio",
    title = "Autism and Control Group Sex Ratio"
  ) +
  theme_minimal()
```



There was no significant difference in sex distribution.

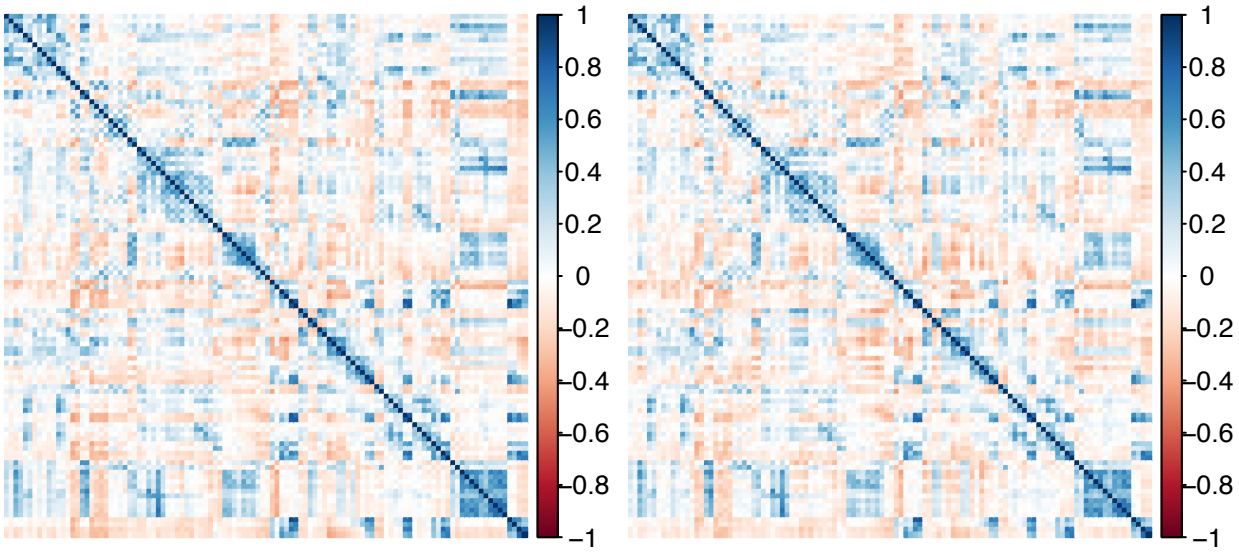
3.2 Consider Brain Activities

3.2.1 Overall Comparison

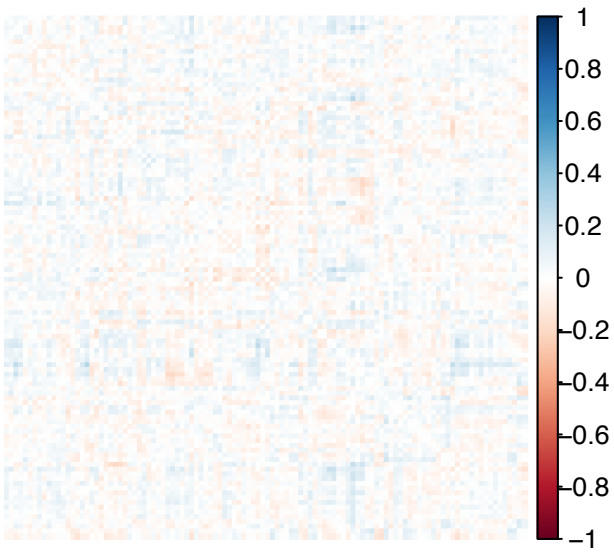
```
autism_mats <- YALE_fmri[YALE_demo_var$DX_GROUP == 1]
autism_cor_mean <- apply(simplify2array(lapply(autism_mats, cor)), 1:2, mean)

control_mats <- YALE_fmri[YALE_demo_var$DX_GROUP == 2]
control_cor_mean <- apply(simplify2array(lapply(control_mats, cor)), 1:2, mean)

par(
  mfrow = c(1, 2),
  mar = c(0, 0, 5, 0),
  oma = c(0, 0, 2, 0)
)
```

```r
add_title <- function(text, cex = 0.8, line = 3.5) {
  title(
    main = text,
    cex.main = cex,
    line = line
  )
}

corrplot(
  autism_cor_mean,
  method = "color",
  tl.pos = "n"
)
add_title("Average Connection of Autism Group")

corrplot(
  control_cor_mean,
  method = "color",
  tl.pos = "n"
)
add_title("Average Connection of Control Group")
```

Average Connection of Autism Group **Average Connection of Control Group**




```r
diff_matrix <- autism_cor_mean - control_cor_mean
corrplot(
  diff_matrix,
  method = "color",
  tl.pos = "n"
)
add_title("Connection Difference (Autism-Control)")
```



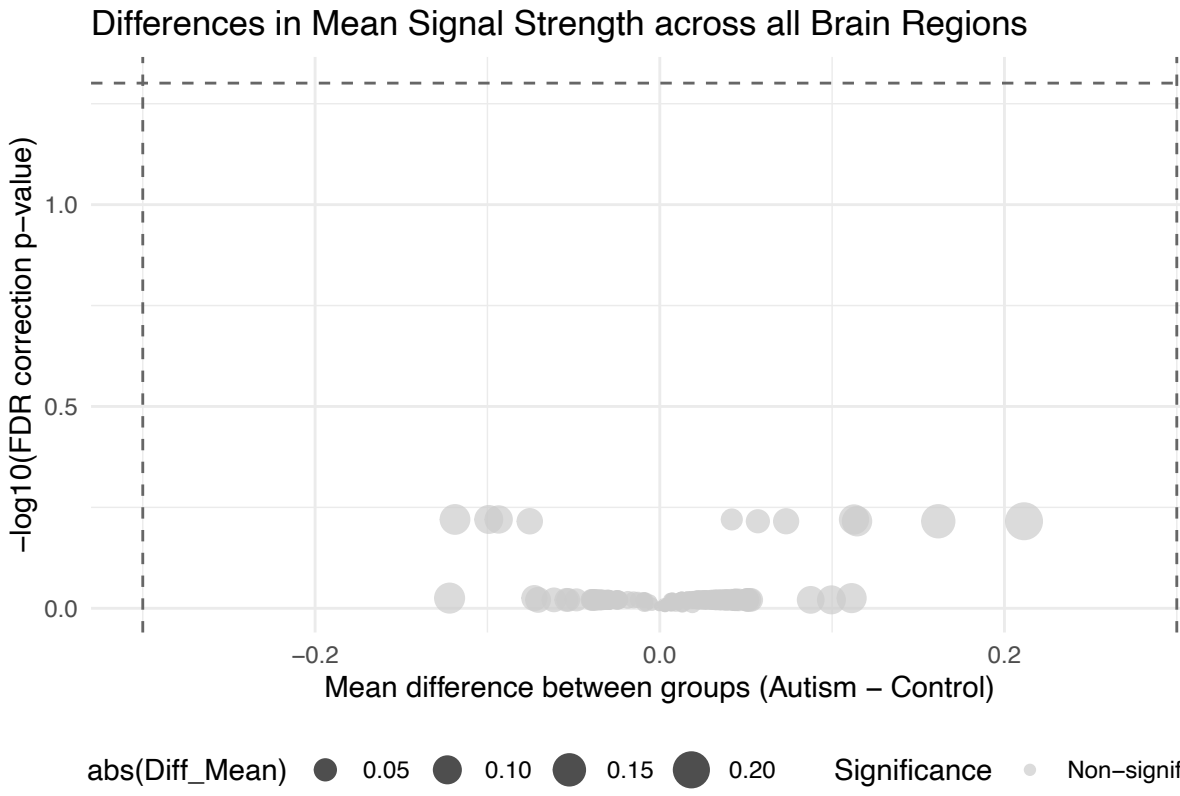
Brain activity was similar between the two groups, however, Autistic group had slightly higher average activity intensity.

3.2.2 Brain Region Compare

```
get_region_mean <- function(mat) {
  data.frame(
    Region = 1:ncol(mat),
    Mean = colMeans(mat, na.rm = TRUE)
  )
}

mean_data <- lapply(YALE_fmri, get_region_mean) %>%
  bind_rows(.id = "SubjectID") %>%
  mutate(SubjectID = as.numeric(SubjectID))

demo_clean <- YALE_demo_var %>%
  mutate(
    SubjectID = row_number(),
    DX_GROUP = factor(DX_GROUP, labels = c("Autism", "Control"))
  ) %>%
  select(SubjectID, DX_GROUP)

mean_data <- mean_data %>%
  left_join(demo_clean, by = "SubjectID")

region_stats <- mean_data %>%
  group_by(Region, DX_GROUP) %>%
  summarise(
    Group_Mean = mean(Mean, na.rm = TRUE),
    Group_SD = sd(Mean, na.rm = TRUE),
    .groups = "drop"
  ) %>%
  pivot_wider(
```

```
    names_from = DX_GROUP,
    values_from = c(Group_Mean, Group_SD),
    names_glue = "{.value}_{DX_GROUP}"
  ) %>%
  mutate(
    Diff_Mean = Group_Mean_Autism - Group_Mean_Control
  )

all_pvalues <- sapply(1:110, function(r) {
  dat <- mean_data %>% filter(Region == r)
  if (nrow(dat) < 2) return(NA)
  t.test(Mean ~ DX_GROUP, data = dat)$p.value
})

region_stats <- region_stats %>%
  mutate(
    p.value = all_pvalues,
    p.adj = p.adjust(p.value, method = "fdr")
  )

region_stats <- region_stats %>%
  mutate(
    Significance = case_when(
      p.adj < 0.05 & abs(Diff_Mean) > 0.3 ~ "FDR < 0.05 & |Diff| > 0.3",
      p.adj < 0.05 ~ "FDR < 0.05",
      TRUE ~ "Non-significant"
    )
  )

ggplot(region_stats, aes(x = Diff_Mean, y = -log10(p.adj))) +
  geom_point(aes(color = Significance, size = abs(Diff_Mean)), alpha = 0.7) +
  scale_color_manual(
    values = c(
      "FDR < 0.05 & |Diff| > 0.3" = "red",
      "FDR < 0.05" = "orange",
      "Non-significant" = "grey80"
    )
  ) +
  geom_vline(xintercept = c(-0.3, 0.3), linetype = "dashed", color = "grey40") +
  geom_hline(yintercept = -log10(0.05), linetype = "dashed", color = "grey40") +
  geom_text_repel(
    data = subset(region_stats, p.adj < 0.05 & abs(Diff_Mean) > 0.3),
    aes(label = Region),
    size = 3,
    max.overlaps = 20,
    box.padding = 0.5
  ) +
  labs(
    x = "Mean difference between groups (Autism - Control)",
    y = "-log10(FDR correction p-value)",
    title = "Differences in Mean Signal Strength across all Brain Regions ",
    caption = "Dashed line: | difference | > 0.3 and FDR < 0.05"
  ) +
```

```
  theme_minimal() +
  theme(legend.position = "bottom")
```



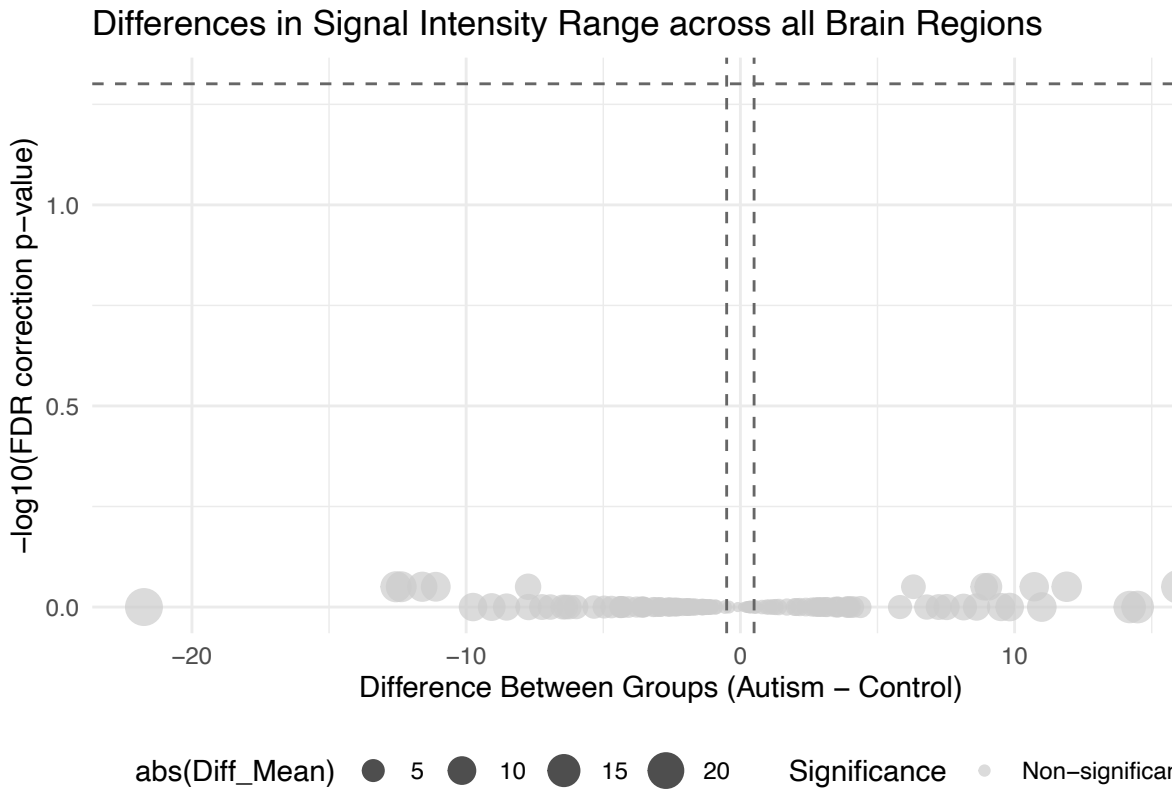
Compare by Mean

Dashed line: | difference | > 0.3 and FDR <

```
get_region_range <- function(mat) {
  data.frame(
    Region = 1:ncol(mat),
    Min = apply(mat, 2, min, na.rm = TRUE),
    Max = apply(mat, 2, max, na.rm = TRUE)
  )
}

range_data <- lapply(YALE_fmri, get_region_range) %>%
  bind_rows(.id = "SubjectID") %>%
  mutate(SubjectID = as.numeric(SubjectID))

demo_clean <- YALE_demo_var %>%
  mutate(
    SubjectID = row_number(),
    DX_GROUP = factor(DX_GROUP, labels = c("Autism", "Control"))
  ) %>%
  select(SubjectID, DX_GROUP)

range_data <- range_data %>%
  left_join(demo_clean, by = "SubjectID")
```

```r
range_data <- range_data %>%
  mutate(Range = Max - Min)

region_diff <- range_data %>%
  group_by(Region, DX_GROUP) %>%
  summarise(
    Mean_Range = mean(Range, na.rm = TRUE),
    SD_Range = sd(Range, na.rm = TRUE),
    .groups = "drop"
  ) %>%
  pivot_wider(
    names_from = DX_GROUP,
    values_from = c(Mean_Range, SD_Range),
    names_glue = "{.value}_{DX_GROUP}"
  ) %>%
  mutate(
    Diff_Mean = Mean_Range_Autism - Mean_Range_Control
  )

all_pvalues <- sapply(1:110, function(r) {
  dat <- range_data %>% filter(Region == r)
  if (nrow(dat) == 0) return(NA)
  wilcox.test(Range ~ DX_GROUP, data = dat)$p.value
})

region_diff <- region_diff %>%
  mutate(
    p.value = all_pvalues,
    p.adj = p.adjust(p.value, method = "fdr")
  )

region_diff <- region_diff %>%
  mutate(
    Significance = case_when(
      p.adj < 0.05 & abs(Diff_Mean) > 0.5 ~ "FDR < 0.05 & |Diff| > 0.5",
      p.adj < 0.05 ~ "FDR < 0.05",
      TRUE ~ "Non-significant"
    )
  )

ggplot(region_diff, aes(x = Diff_Mean, y = -log10(p.adj))) +
  geom_point(aes(color = Significance, size = abs(Diff_Mean)), alpha = 0.7) +
  scale_color_manual(
    values = c(
      "FDR < 0.05 & |Diff| > 0.5" = "red",
      "FDR < 0.05" = "orange",
      "Non-significant" = "grey80"
    )
  ) +
  geom_vline(xintercept = c(-0.5, 0.5), linetype = "dashed", color = "grey40") +
  geom_hline(yintercept = -log10(0.05), linetype = "dashed", color = "grey40") +
  geom_text_repel(
    data = subset(region_diff, p.adj < 0.05 & abs(Diff_Mean) > 0.5),
```

```
    aes(label = Region),
    size = 3,
    max.overlaps = 20,
    box.padding = 0.5
  ) +
  labs(
    x = "Difference Between Groups (Autism - Control)",
    y = "-log10(FDR correction p-value)",
    title = "Differences in Signal Intensity Range across all Brain Regions",
    caption = "Dashed line: | difference | > 0.5 and FDR < 0.05"
  ) +
  theme_minimal() +
  theme(legend.position = "bottom")
```



Compare by Range

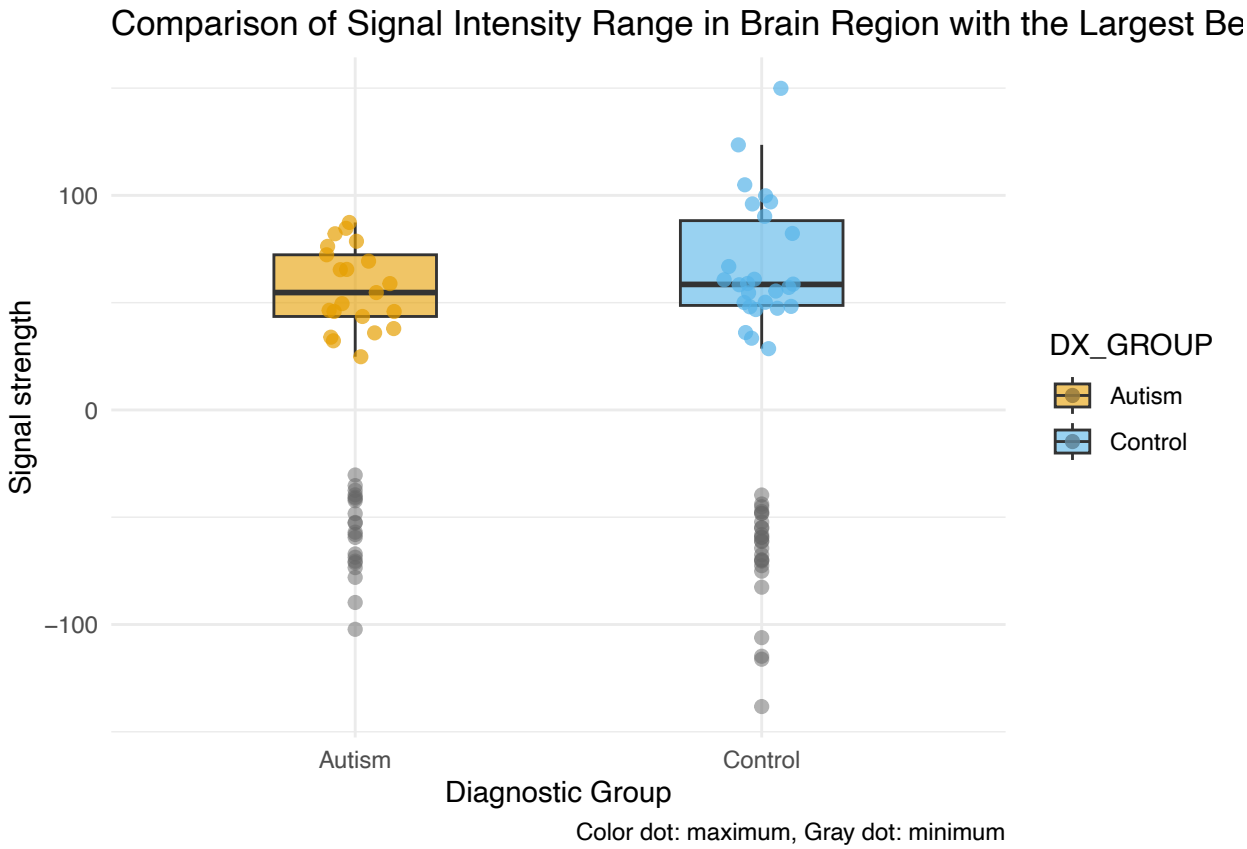
```
range_data <- range_data %>%
  mutate(Range = Max - Min)

region_stats <- range_data %>%
  group_by(Region, DX_GROUP) %>%
  summarise(
    Mean_Range = mean(Range, na.rm = TRUE),
    SD_Range = sd(Range, na.rm = TRUE)
  ) %>%
  pivot_wider(
    names_from = DX_GROUP,
    values_from = c(Mean_Range, SD_Range)
  )
```

```
## `summarise()` has grouped output by 'Region'. You can override using the
## `.groups` argument.
```

```
region_diff <- region_stats %>%
  mutate(
    Diff_Mean = Mean_Range_Autism - Mean_Range_Control,
    Diff_SD = SD_Range_Autism - SD_Range_Control
  ) %>%
  arrange(desc(abs(Diff_Mean)))

head(region_diff, )
```

```
## # A tibble: 6 x 7
## # Groups:   Region [6]
##   Region Mean_Range_Autism Mean_Range_Control SD_Range_Autism SD_Range_Control
##    <int>             <dbl>              <dbl>           <dbl>             <dbl>
## 1     31             115.               136.             36.7              52.1
## 2     64              70.4               54.5            36.8              32.7
## 3    109             136.               122.             29.7              36.0
## 4    107             150.               136.             47.7              44.0
## 5    102              66.5               79.0            15.5              30.5
## 6      6              64.8               77.2            20.2              26.4
## # i 2 more variables: Diff_Mean <dbl>, Diff_SD <dbl>
```

```
region31 <- range_data %>% filter(Region == 31)

ggplot(region31, aes(x = DX_GROUP, y = Max, fill = DX_GROUP)) +
  geom_boxplot(width = 0.4, alpha = 0.6, outlier.shape = NA) +
  geom_jitter(aes(color = DX_GROUP), width = 0.1, size = 2, alpha = 0.7) +
  geom_point(aes(y = Min), color = "grey40", size = 2, alpha = 0.5) +
  scale_fill_manual(values = c("Autism" = "#E69F00", "Control" = "#56B4E9")) +
  scale_color_manual(values = c("Autism" = "#E69F00", "Control" = "#56B4E9")) +
  labs(
    title = "Comparison of Signal Intensity Range in Brain Region with the Largest Between-Group Differe
    x = "Diagnostic Group",
    y = "Signal strength",
    caption = "Color dot: maximum, Gray dot: minimum"
  ) +
  theme_minimal()
```




```
top_region <- region_diff$Region[1]

target_data <- range_data %>% filter(Region == top_region)

wilcox_result <- wilcox.test(Range ~ DX_GROUP, data = target_data)

cat("Statistical Test Results for the Brain Region with the Largest Between-Group Difference\n")
```

```
## Statistical Test Results for the Brain Region with the Largest Between-Group Difference
```

```
print(wilcox_result)
```

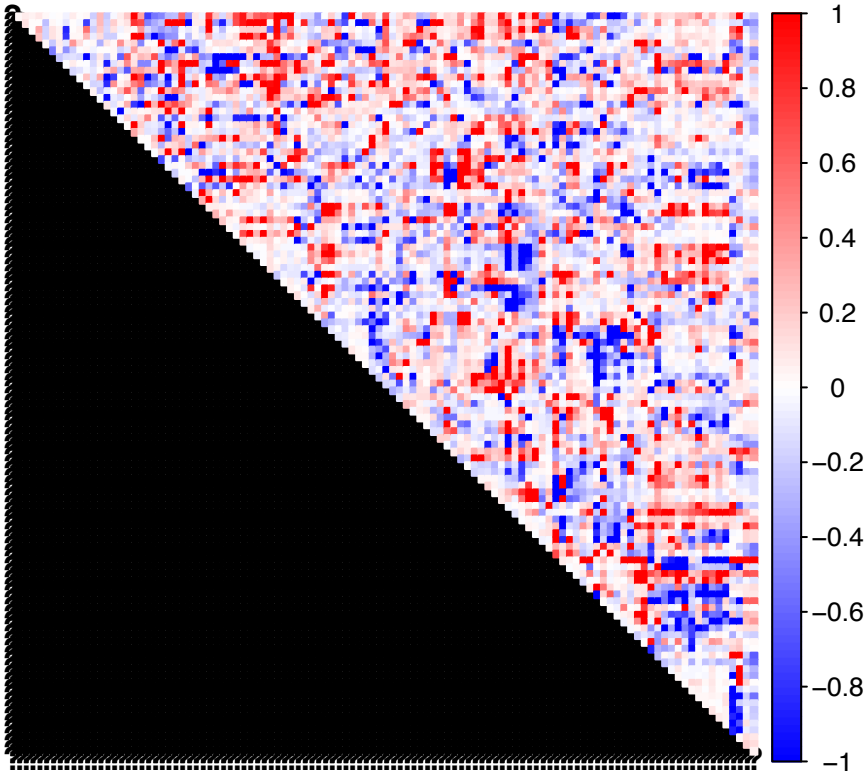
```
##
##  Wilcoxon rank sum exact test
##
## data:  Range by DX_GROUP
## W = 206, p-value = 0.1561
## alternative hypothesis: true location shift is not equal to 0
```

3.2.3 Brain Regions Connection Compare

```
compute_fc <- function(processed_mat) {
  stopifnot(all(abs(colMeans(processed_mat)) < 1e-6))
  stopifnot(all(abs(apply(processed_mat, 2, sd) - 1) < 1e-3))

  cor_mat <- cor(processed_mat)
  z_mat <- 0.5 * log((1 + cor_mat) / (1 - cor_mat))
  diag(z_mat) <- 0
```

```r
  return(z_mat)
}

fc_mats <- lapply(YALE_fmri_processed, compute_fc)

demo_clean <- YALE_demo_var %>%
  mutate(
    SubjectID = row_number(),
    DX_GROUP = factor(DX_GROUP, labels = c("Autism", "Control"))
  ) %>%
  select(SubjectID, DX_GROUP)

autism_mats <- fc_mats[demo_clean$DX_GROUP == "Autism"]
control_mats <- fc_mats[demo_clean$DX_GROUP == "Control"]

autism_mean <- apply(simplify2array(autism_mats), 1:2, mean)
control_mean <- apply(simplify2array(control_mats), 1:2, mean)

epsilon <- 1e-6
relative_diff <- (autism_mean - control_mean) /
                 ((abs(autism_mean) + abs(control_mean))/2 + epsilon)

relative_diff[lower.tri(relative_diff, diag = TRUE)] <- NA

actual_min <- floor(min(relative_diff, na.rm = TRUE))
actual_max <- ceiling(max(relative_diff, na.rm = TRUE))
scale_factor <- max(abs(actual_min), abs(actual_max))
relative_diff_scaled <- relative_diff / scale_factor

col_palette <- colorRampPalette(c("blue", "white", "red"))(100)

corrplot(
  relative_diff_scaled,
  method = "color",
  col = col_palette,
  tl.pos = "n",
  col.lim = c(-1, 1),
  title = "Standardized Differences between Brain Regions Connection",
  mar = c(0, 0, 2, 0))
```

Standardized Differences between Brain Regions Connection




```
compute_fc <- function(mat) {
  cor(mat)
}

fc_mats <- lapply(YALE_fmri, compute_fc)

demo_clean <- YALE_demo_var %>%
  mutate(
    SubjectID = row_number(),
    DX_GROUP = factor(DX_GROUP, labels = c("Autism", "Control"))
  ) %>%
  select(SubjectID, DX_GROUP)

extract_connections <- function(mat) {
  data.frame(
    from = rep(1:110, each = 110),
    to = rep(1:110, times = 110),
    strength = as.vector(mat)
  ) %>%
    filter(from < to)
}

all_connections <- lapply(fc_mats, extract_connections) %>%
  bind_rows(.id = "SubjectID") %>%
  mutate(SubjectID = as.numeric(SubjectID)) %>%
```

```
  left_join(demo_clean, by = "SubjectID")

connection_stats <- all_connections %>%
  group_by(from, to, DX_GROUP) %>%
  summarise(
    mean_strength = mean(strength, na.rm = TRUE),
    sd_strength = sd(strength, na.rm = TRUE),
    .groups = "drop"
  ) %>%
  pivot_wider(
    names_from = DX_GROUP,
    values_from = c(mean_strength, sd_strength),
    names_glue = "{.value}_{DX_GROUP}"
  ) %>%
  mutate(
    diff_strength = mean_strength_Autism - mean_strength_Control
  )

p_values <- sapply(1:nrow(connection_stats), function(i) {
  conn <- connection_stats[i, ]
  autism_vals <- all_connections %>%
    filter(from == conn$from, to == conn$to, DX_GROUP == "Autism") %>%
    pull(strength)
  control_vals <- all_connections %>%
    filter(from == conn$from, to == conn$to, DX_GROUP == "Control") %>%
    pull(strength)
  if (length(autism_vals) < 2 || length(control_vals) < 2) return(NA)
  t.test(autism_vals, control_vals)$p.value
})

connection_stats <- connection_stats %>%
  mutate(
    p.value = p_values,
    p.adj = p.adjust(p.value, method = "fdr")
  )

connection_stats <- connection_stats %>%
  mutate(
    pooled_sd = sqrt(
      (sd_strength_Autism^2 * (sum(demo_clean$DX_GROUP == "Autism") - 1) +
       sd_strength_Control^2 * (sum(demo_clean$DX_GROUP == "Control") - 1)) /
      (sum(demo_clean$DX_GROUP == "Autism") + sum(demo_clean$DX_GROUP == "Control") - 2)
    ),
    cohen_d = diff_strength / pooled_sd
  )

top_connections <- connection_stats %>%
  arrange(p.value, desc(abs(cohen_d))) %>%
  slice_head(n = 10)

print(top_connections %>% select(from, to, diff_strength, cohen_d, p.value))
```

Sorted by uncorrected p-value and effect size

```
## # A tibble: 10 x 5
##     from    to diff_strength cohen_d   p.value
##    <int> <int>         <dbl>   <dbl>     <dbl>
##  1    18    74         0.283    1.44 0.0000111
##  2     3    74         0.246    1.31 0.0000325
##  3    74    95         0.235    1.29 0.0000438
##  4    74    98         0.209    1.20 0.000131
##  5    45    56        -0.189   -1.22 0.000182
##  6    35    74        -0.156   -1.15 0.000234
##  7    81    94         0.183    1.14 0.000253
##  8    40    72         0.213    1.10 0.000446
##  9    12    39         0.141    1.09 0.000498
## 10    74    97         0.198    1.07 0.000572
```

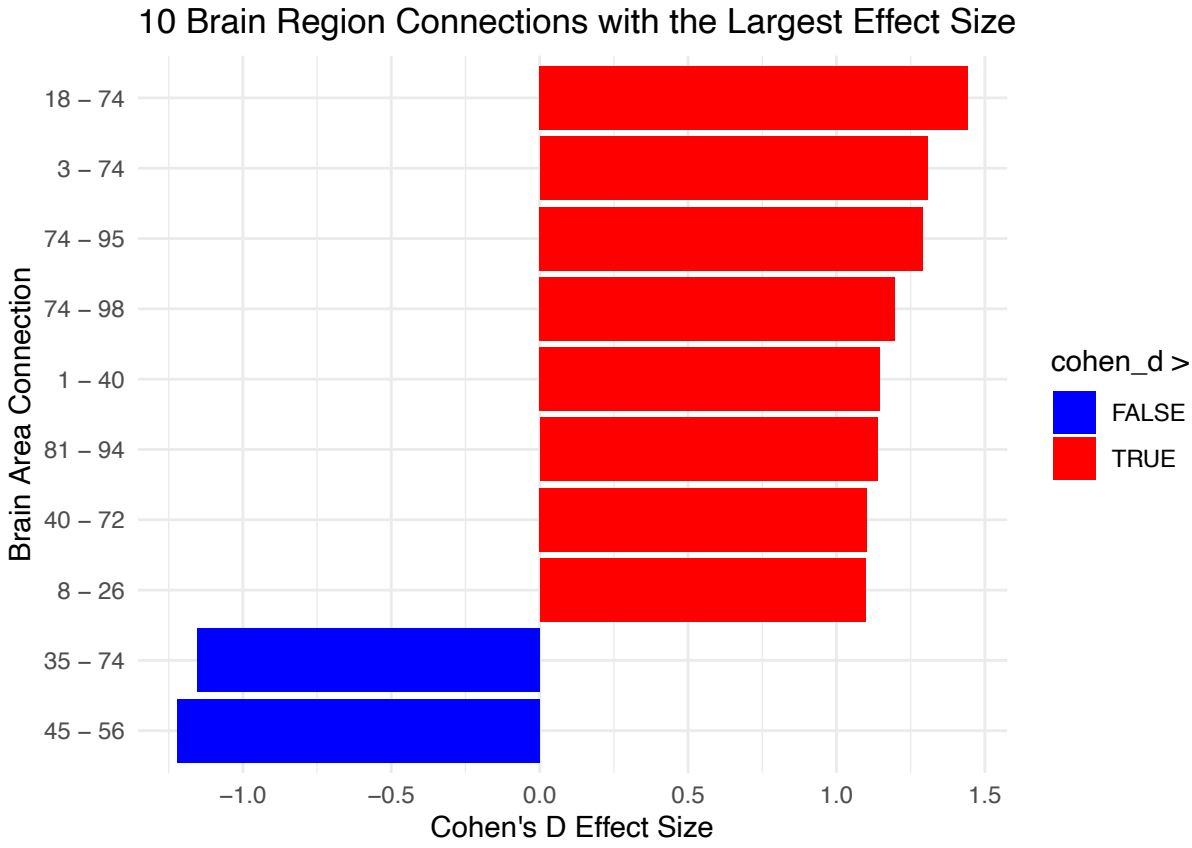
```
top_connections <- connection_stats %>%
  arrange(desc(abs(cohen_d))) %>%
  slice_head(n = 10)

print(top_connections %>% select(from, to, cohen_d, p.value, p.adj))
```

Sorted by effect size

```
## # A tibble: 10 x 5
##     from    to cohen_d   p.value  p.adj
##    <int> <int>   <dbl>     <dbl>  <dbl>
##  1    18    74    1.44 0.0000111 0.0664
##  2     3    74    1.31 0.0000325 0.0875
##  3    74    95    1.29 0.0000438 0.0875
##  4    45    56   -1.22 0.000182  0.216
##  5    74    98    1.20 0.000131  0.196
##  6    35    74   -1.15 0.000234  0.216
##  7     1    40    1.15 0.000588  0.260
##  8    81    94    1.14 0.000253  0.216
##  9    40    72    1.10 0.000446  0.260
## 10     8    26    1.10 0.000645  0.260
```

```
p_values <- sapply(1:nrow(connection_stats), function(i) {
  conn <- connection_stats[i, ]
  autism_vals <- all_connections %>%
    filter(from == conn$from, to == conn$to, DX_GROUP == "Autism") %>%
    pull(strength)
  control_vals <- all_connections %>%
    filter(from == conn$from, to == conn$to, DX_GROUP == "Control") %>%
    pull(strength)
  if (length(autism_vals) < 2 || length(control_vals) < 2) return(NA)
  wilcox.test(autism_vals, control_vals)$p.value
})

connection_stats <- connection_stats %>%
  mutate(
    p.value = p_values,
    p.adj = p.adjust(p.value, method = "fdr")
```

```
  )

top_connections <- connection_stats %>%
  filter(p.adj < 0.1) %>%
  arrange(p.adj, desc(abs(cohen_d))) %>%
  slice_head(n = 10)

top_effects <- connection_stats %>%
  arrange(desc(abs(cohen_d))) %>%
  slice_head(n = 10)

ggplot(top_effects, aes(x = reorder(paste(from, "-", to), cohen_d),
                        y = cohen_d, fill = cohen_d > 0)) +
  geom_col() +
  scale_fill_manual(values = c("blue", "red")) +
  labs(
    x = "Brain Area Connection",
    y = "Cohen's D Effect Size",
    title = "10 Brain Region Connections with the Largest Effect Size"
  ) +
  coord_flip() +
  theme_minimal()
```



Sorted by p-value

4 Verification

```r
all_z <- unlist(lapply(fc_mats, function(mat) mat[upper.tri(mat)]))

ggplot(data.frame(Z = all_z), aes(x = Z)) +
  geom_histogram(aes(y = ..density..), bins = 50, fill = "skyblue") +
  stat_function(fun = dnorm, args = list(mean = mean(all_z), sd = sd(all_z)),
                color = "red", size = 1) +
  labs(title = "Functional Connection Fisher Z value distribution",
       subtitle = "Red curve is normal distribution reference line") +
  theme_minimal()
```

```
## Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
## i Please use `linewidth` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```

```
## Warning: The dot-dot notation (`..density..`) was deprecated in ggplot2 3.4.0.
## i Please use `after_stat(density)` instead.
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_lifecycle_warnings()` to see where this warning was
## generated.
```