

Team Data Science Project Report: Joint and Individual Analysis of Stress Reaction Data

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Abstract

This report is commissioned by Aysenil Belger and Joshua Bizzell from the Department of Psychiatry at UNC School of Medicine to examine the association between brain activation during stress and physiological stress reactivity and vulnerability profile to understand cognitive disorders among adolescents. In particular, we attempt to investigate the joint signals between stress response profile and brain region response during a stress test. Then we implement a similar analysis where we use fMRI data during the working memory task rather than during the stress test. Finally, we analyze the joint signals in the previous two cases while adding demographics information as another data block. Angle-based Joint and Individual Variance Explained (AJIVE) is utilized for these analyses. For each analysis, we have discovered that the joint subspace of multiple data blocks is one-dimensional, and that the relationship between cortisol and brain activation is different for the two tasks. The code to reproduce our analysis may be found at https://github.com/amysong21/STOR765_Spring2023_TeamDS.

1 Introduction

Our clients Aysenil Belger and Joshua Bizzell from the Department of Psychiatry at UNC School of Medicine aim to enhance the understanding of cognitive disorders in adolescents. Their focus is on examining the relationships between brain activation, psychological responses, and stress vulnerability. To achieve their objective, the project addresses these three research questions:

1. What is the relationship between stress response profile and brain region response during a stress test?
2. Is there a joint signal between the stress response profile and brain region response during a working memory task?
3. How do the joint signals in the previous two questions alter with the inclusion of demographic information?

In this report, we explore multiple types of data: Demographic, Cortisol, fMRI, Clinical-Psychological, Working Memory, and Autonomic data. Our primary focus is on the Cortisol data block to study stress response in subjects and its association with brain connectivity, as measured by the fMRI block or brain activation during Working Memory tasks. We also utilize Demographic data to uncover any new findings and address missing value issues in the data.

We address these research questions using Angle-based Joint and Individual Variation Explained (AJIVE) [1] which captures statistical signals shared across different data blocks. For question 1, we used the Cortisol and fMRI data blocks for AJIVE analysis. Then for question 2, the Cortisol and Working Memory data blocks were employed. Finally, for question 3, we added demographics as a third block to each of the two AJIVE analyses mentioned above.

The AJIVE model fitted with the Cortisol block and fMRI block showed that the activation of certain parts of brain such as VMPFC was highly associated with the cortisol level.

On the other hand, the joint signal of the cortisol level and working memory was weighted towards other regions such as DLPFC. For both cases, different states of cortisol level had approximately equal weights on the joint signals.

The report is organized as follows. In Section 2, we examine the datasets given by the clients. In Section 3, we provide an overview of PCA and AJIVE. The findings of our AJIVE analyses are discussed in Section 4. Finally, we conclude the report with a discussion in Section 5.

2 Data

2.1 Data Blocks

The client provided a data set that includes data for around 100 children/adolescents. The data set is divided into 6 blocks, with varying numbers of observations in each block.

Block	Data	Dimension ($n \times p$)	Measurement
1	Demographic	130×6	sex, age, puberty level, education
2	Cortisol	118×7	cortisol level (stress response)
3	fMRI	116×9	brain functional connectivity
4	Clinical Psychology	130×6	anxiety, anhedonia etc.
5	Working Memory	64×16	working memory brain activation
6	Autonomic	174×10	heart rate, autonomic nervous system

Table 1: Data Overview

Table 1 gives an overview of the data. The data blocks are linked to each other through the unique SubjectID assigned to each participant.

2.1.1 Demographic block

First, the demographic block contains 130 participants, and the following six variables are briefly described below.

1. **SubjectID**: subject identifier, which is a string, e.g. *cnt_101_bl*
2. **Sex**: gender of the subject, e.g. *M*(Male) or *F*(Female)
3. **AgeInMonths**: age of the subject in months
4. **PubertyTannerSelf**: self-reported puberty level (*1* to *5*, *1* = very early/before puberty, *5* = end of puberty)
5. **PubertyTannerParent**: parent-reported puberty level of their child
6. **ParentalEducationAvg**: average education level of the subject's parent

2.1.2 Cortisol block

The Cortisol data block contains measurements of cortisol hormone levels for 118 participants, which capture their stress response. The measurements are recorded at 6 different time points, labeled as `M_S1`, `M_S2`, `M_S3`, `M_S4`, `M_S5`, and `M_S6`, and can be linked to each participant through their unique `SubjectID`.

2.1.3 fMRI block

The third block, fMRI data, measures the functional connectivity of the brain in 116 participants. In raw form, this data consists of a time series of 8 brain regions. The client averaged this over time and provided us with a single value for each region, which was given in the form of a 928×3 matrix, with columns for `SubjectID`, `ROI` (region of interest), and `MeanPerSigChg` (Mean per signal change). We reorganized it into a 116×9 matrix where each `SubjectID` has a value of `MeanPerSigChg` for each of the 8 regions.

2.1.4 Clinical-Psychological block

The fourth block contains the clinical and psychological profiles of 130 participants, with 6 variables measuring anxiety, disorganized communication, anhedonia, and other factors. These variables include:

1. `SubjectID`: subject identifier, which is a string, e.g. *cnt_101_bl*
2. `STAITrait`: a measure of trait anxiety
3. `STAIPost-Pre`: the difference between self-reported stress scores before and after a stress task
4. `CogDisScore`: score measuring disorganized communication, reflecting thought disorder and speech problems
5. `Anhedonia`: a measure of social anhedonia, including lack of close friends, preference for solitude, and disinterest in social activities
6. `CsopsNegative`: a summary score measuring negative symptoms

2.1.5 Working Memory block

The fifth block contains working memory data, collected in a long format similar to the fMRI block. This dataset includes measurements of brain activation changes during *N-back* working memory tasks, specifically comparing the *2-back* task to the *0-back* task. In order to compare the brain activation during stress, measurements are taken twice - before and after the stress task.

It has dimensions of 1024×4 , and includes the following variables:

1. `SubjectID`: subject identifier, which is a string, e.g. *cnt_101_bl*
2. `ROI`: region of interest, with 8 regions specified

3. **Status:** pre- or post-stress status (before and after the stress task)
4. **Mean:** mean percentage of signal change in the specified region of interest (ROI) comparing the *2-back* task to the *0-back* task

To simplify the data, we transformed it into a wider version, creating a separate column for each of the 8 regions of interest and its 2 statuses. This resulted in a new data dimension of 64×17 , where the first column contains the subject IDs. Each column represents the **Mean** variable for a specific combination of ROI and status.

2.1.6 Autonomic block

The final block in the dataset is the Autonomic data block, which includes information on heart rate and the autonomic nervous system. The heart rate is measured as a time series over three time points: `HRV_MIST1`, `HRV_MIST2`, and `HRV_MIST3`. Salivary alpha-amylase (SAA) is also measured as a time series over six time points: `AA_S1`, `AA_S2`, `AA_S3`, `AA_S4`, `AA_S5`, and `AA_S6`. This gives us a 174×10 matrix for this block. To examine the correlations between variables in this block and the other blocks, please refer to Appendix A.

2.2 Missing Data

After checking each block for missing data, the Cortisol data block, fMRI data block, and Working Memory data block do not have missing data.

2.2.1 Demographic block

For the Demographic data block, there are 45 missing values. This is shown in Figure 1. On the top of the figure, you see each variable and its corresponding percentage of missing values in parentheses. In the box below, the black color indicates the observation with missing data and the grey color shows that the observation has a valid value. We can easily see that two of these missing values are either from puberty-related variables, `PubertyTannerSelf` (22%) or `PubertyTannerParent` (16%), or from parent education-related variables, `ParentalEducationAvg` (5%).

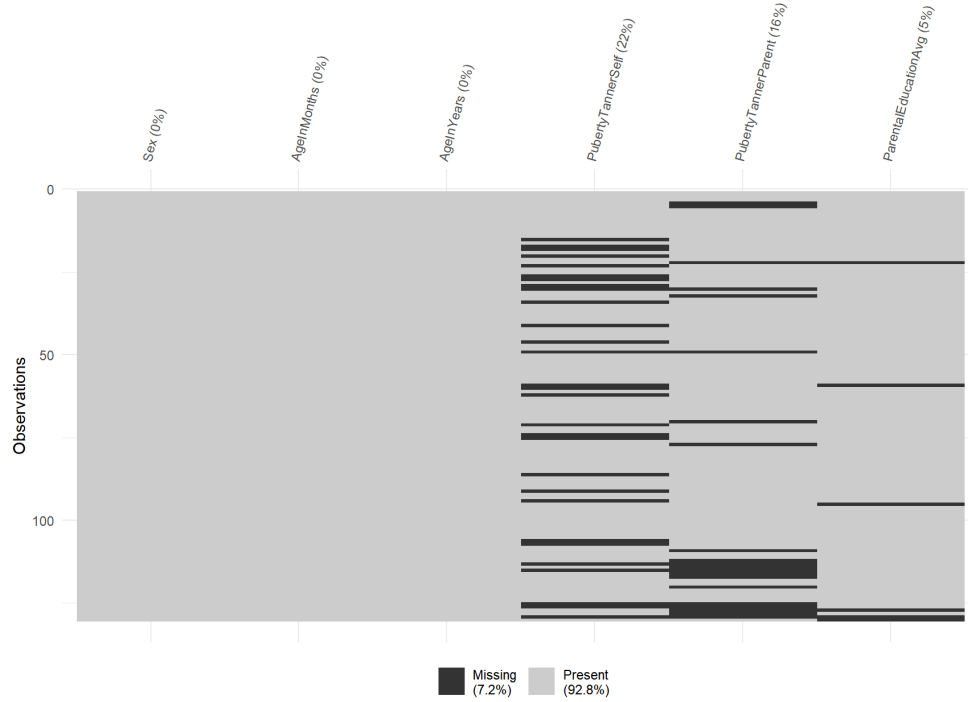


Figure 1: Heatmap of Missing Data in Demographic Data Block. Missing values are puberty-related or parent education-related variables; `PubertyTannerSelf`, `PubertyTannerParent`, and `ParentalEducationAvg`.

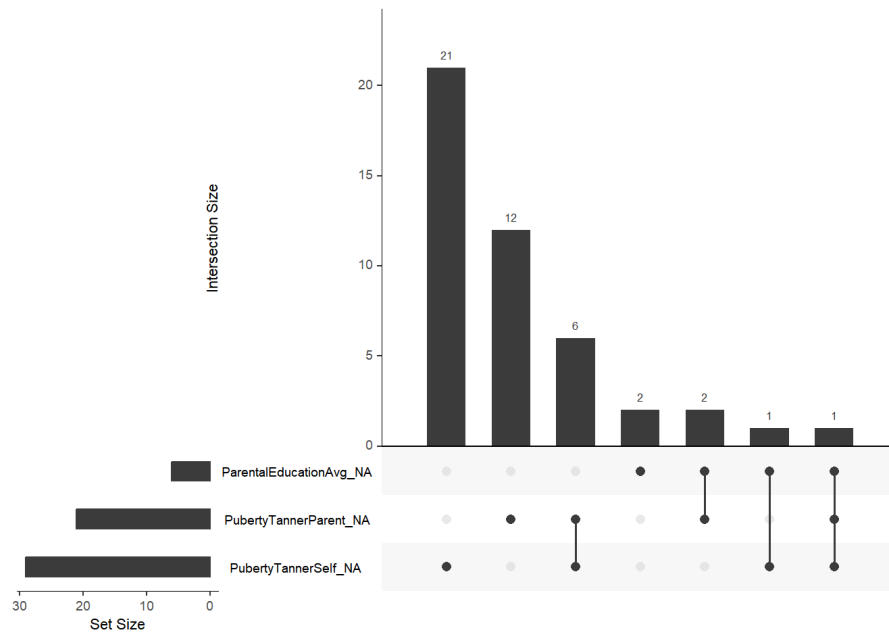


Figure 2: Missing Data in Demographic Data Block by Variable. Most missing values are coming from `PubertyTannerSelf` either by itself or in combination with other puberty-related or parent education-related variables.

Figure 2 shows the number of observations with different combinations of missing values in the Demographic block. In the bottom left corner, we can see the number of observations that have missing values for each of the variables. From this, we can substantiate our finding from above that `PubertyTannerSelf` has the highest number of missing values. This is followed by `PubertyTannerParent`, and `ParentalEducationAvg`. To the right, the black circles indicate the combination of variables with missing values, and the bar plot above shows the frequency of that combination. For instance, the bar plot on the far left with a black dot only on `PubertyTannerSelf` indicates that there are 21 observations with only `PubertyTannerSelf` variable value missing. To the right, we can see that there are 12 observations with only the `PubertyTannerParent` variable missing. The third from the left with `PubertyTannerParent` and `PubertyTannerSelf` black dots shows that 6 observations have missing values only for these two variables. We remove the rows with at least one missing value, leaving 85 rows out of 130.

The clients remarked that the two Tanner scores are very similar measurements, and that in the future, a missing value in one variable might be able to be imputed using the other variable. It might also be more succinct to merge the two variables in some way.

2.2.2 Clinical-Psychological block

The Clinical-Psychological data block has a low fraction of missing values, which can be seen in Figure 3. This figure can be interpreted similarly to Figure 1. The `STAI_Trait` variable has 5 missing values (3%), and `STAI_Post-Pre` has 4 missing values (4%)

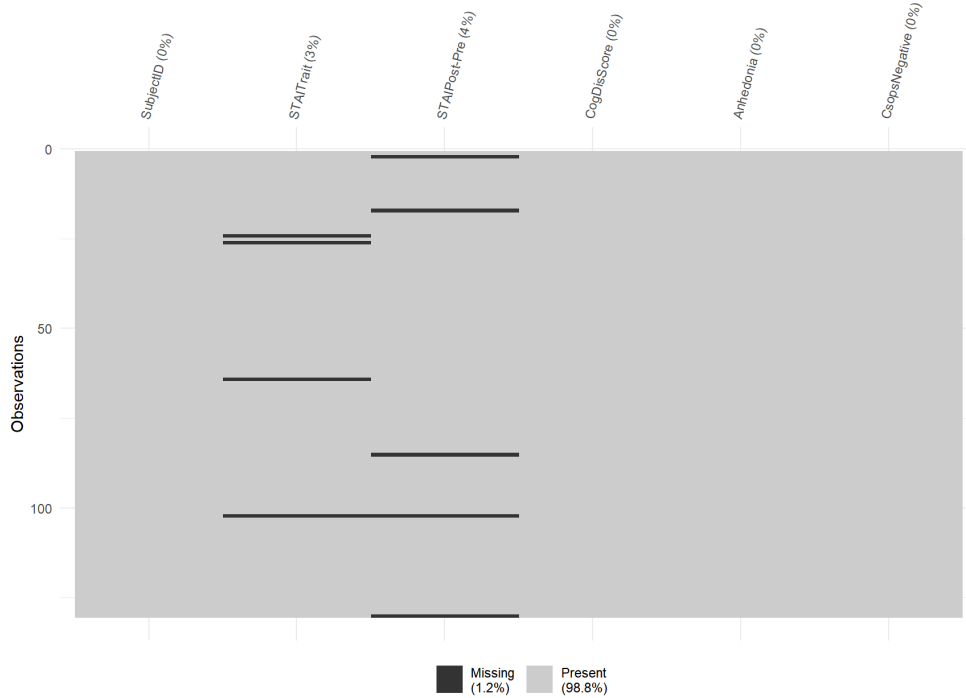


Figure 3: Heatmap of Missing Data in Clinical Psychology Data Block. Missing data is found in `STAI_Trait` and `STAI_Post-Pre`.

Figure 4 displays the missing data *combinations* for the Clinical-Psychological data block. Similarly from above, we see that the combination with the most missing data is missing a single variable, **STAIPost-Pre**, with 4 rows. It is followed by 3 data points only missing **STAITrait**. There is 1 row where both variables are missing. After removing the rows with missing data, the block contains 122 rows.

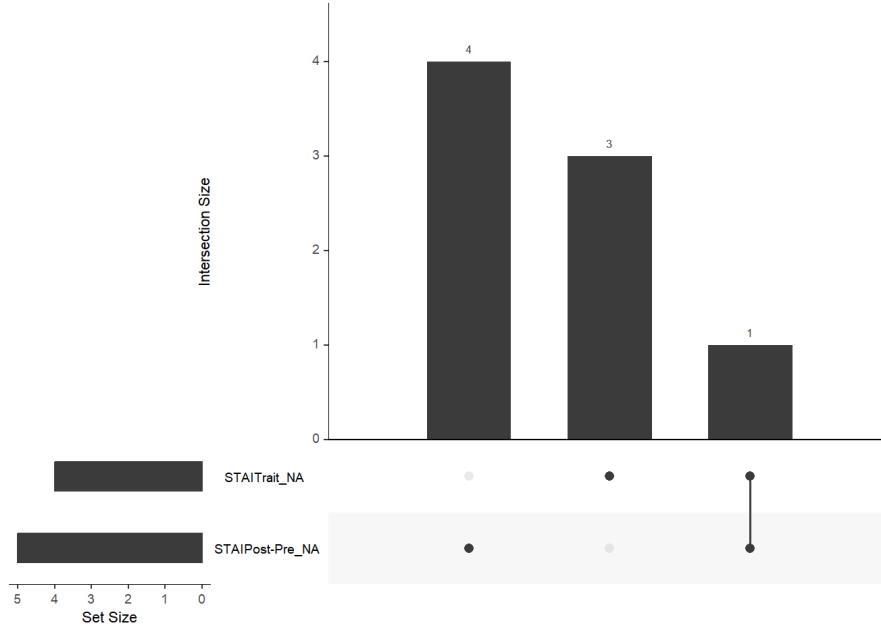


Figure 4: Missing Data in Clinical Psychology Data Block by Variable. The observations with missing values are either missing **STAITrait** or **STAIPost-Pre**. Only 1 observation is missing both.

The clients remarked that some ‘STAI’ variables are also measured during the EEG session, and that in the future, missing STAI values in this block could possibly be imputed using the values taking during the EEG.

2.2.3 Autonomic block

The Autonomic data block has by far the most missing values. Out of 174 observations, 137 observations have at least one variable with a missing value, which accounts for around 80% of the data block. Figure 5 clearly shows that there is a high percentage of missing values for all variables. The variables related to heart rate, **HRV_MIST1**, **HRV_MIST2**, and **HRV_MIST3**, all have missing data over 40%. The variables related to **SAA**, **AA_S1**, **AA_S2**, **AA_S3**, **AA_S4**, **AA_S5**, and **AA_S6**, all have missing data of over 50%.

that 53 participants have missing values for all variables, followed by 26 participants with no information about SAA and 7 without any information about HRV. This indicates that the problem of missing values in this block is widespread across all variables, not limited to a few variables. After careful consideration, we exclude this entire block from further analysis due to the missing value issue, and none of the research questions directly is related to this data block. To utilize this data block in future studies, we suggest conferring with the client on how to handle the missing data issue in this block.

3 Methodology

The first step of AJIVE analysis is determining initial signal ranks of data blocks. This can be done by examining scree plots obtained from Principal Components Analysis (PCA) as described in [1]. PCA is done for each of the data blocks, and the signal ranks of the data blocks are determined using scree plots, which depict the percentage of variance explained by each principal component.

3.1 Principal Component Analysis (PCA)

PCA is used to find a lower dimensional structure from the high dimensional data. For data with correlated variables, principal components allow us to summarize the set of variables with a relatively small number of linear combinations of the variables that collectively explain most of the variability in the original set [2].

Each of the given data blocks is in the form of a matrix, $X \in \mathbb{R}^{n \times p}$, where n is the number of subjects and p is the number of features. When p is large, a lower-dimensional representation of the data matrix may be enough to capture a lot of information from the original data. “PCA finds a small number of dimensions that are interesting as possible, where the concept of *interesting* is measured by the amount that the observations vary along each dimension. Each of the dimensions found by PCA is a linear combination of the p features” [2].

To perform PCA, the variables in the data are centered to have a mean of zero. In blocks that contain non-commensurate variables, i.e. when multiple measurement scales were present, the variables were scaled to have a standard deviation of 1. Among the data blocks used for PCA, data blocks on demographics and clinical psychology are scaled because these two data blocks consist of variables with different measurement units. On the other hand, the data blocks related to cortisol measure, fMRI signals, and working memory were not scaled because the variables are commensurate within each block.

The *loading vectors*, $\phi_j \in \mathbb{R}^p$, for each principal component $j = 1, \dots, p$ define the directions in feature space along which the data vary the most. The *scores*, $z_{1,j}, \dots, z_{n,j}$, with $j = 1, \dots, p$ for principal component j are the values when the data with n observations are projected onto the direction of the loading vector. A *biplot* visualizes the loading vectors and scores for two selected principal components. Figure 7 displays the biplot for the Cortisol data block. The points on the plot depict the score of each observation from the first and second principal components, and the red arrows are the loading vector for each variable. In the biplot, the loading vectors of the variables for PC1 direction are all positively associated.

In addition, although we can say that the six features from this data block have similar weights in this principal component, the variables related to first three time points: `M_S1`, `M_S2`, and `M_S3`, show relatively lower weights than the variables related to the latter three time points. Similar interpretation can be made for the loading vectors of the variables for PC2 direction. The variables from the first three time points: `M_S1`, `M_S2`, and `M_S3`, are positively associated while the variables related to the latter three time points are negatively associated. The biplot also indicates an outlier of the scores in the biplot, but in this analysis, none of the outliers caused from the PCA are removed.

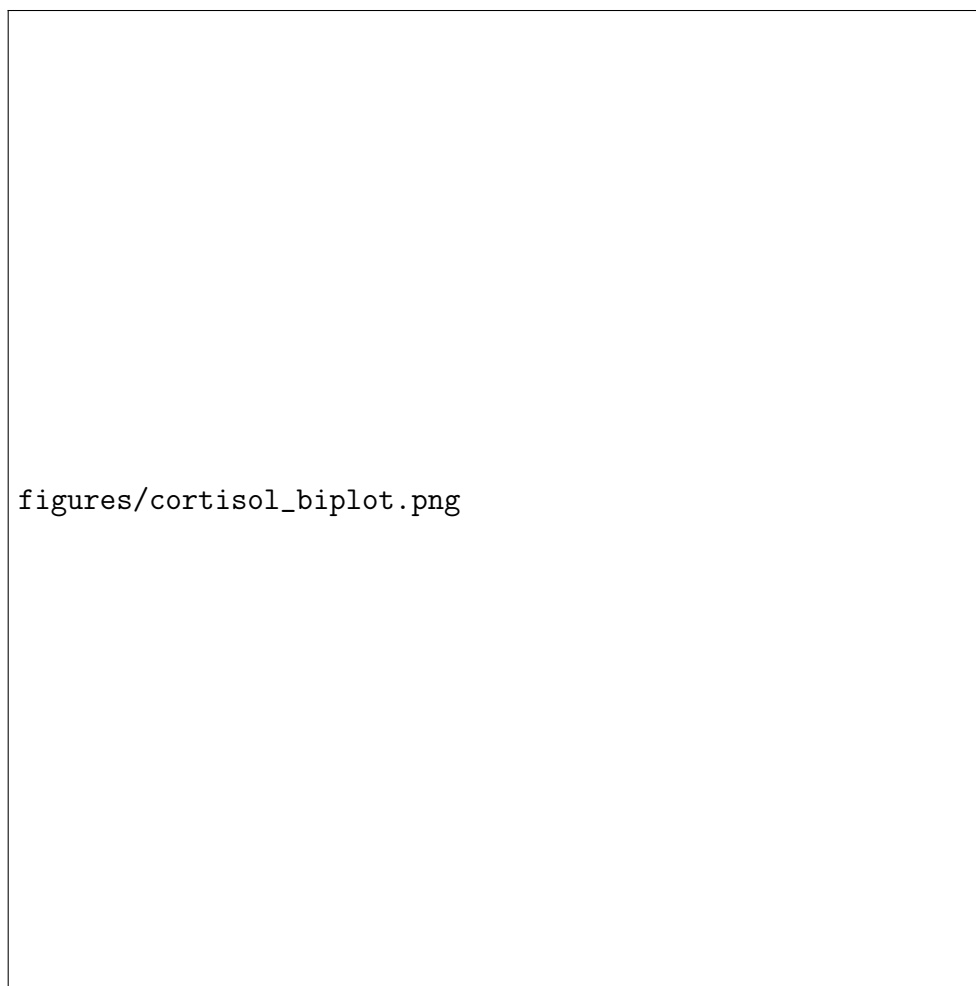


Figure 7: biplot from PCA on Cortisol Data Block. The first two principal components for Cortisol data block. The black points indicate the scores for each subject and the red arrows indicate the loading vectors for the first two principal components.

In PCA, the proportion of variance explained is used to measure how much the selected principal components can explain the variance in the data. The scree plot visualizes the proportion of variance explained by each principal component. One chooses the smallest number of principal components that are required to explain a sizable amount of variation in the data [2]. For this project, the smallest number of principal components that explained 95% of the variation in the data is chosen for each data block.

Figure 8 displays the scree plot of PCA performed on the Cortisol data block. The bars on the plot depict the percentage of variance explained by each of the principal components in the Cortisol data block. The gray line depicts the cumulative percentage of variance explained by the principal components. As shown in the scree plot, the first three principal components explain about 95.5% of the variation in the data. We therefore decided to use 3 principal components for this data block.

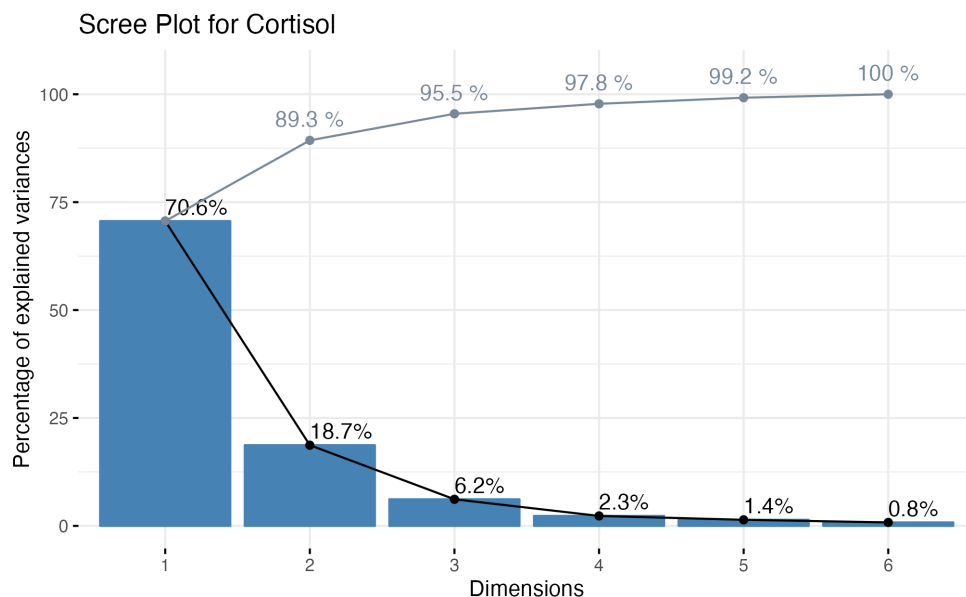


Figure 8: scree plot from PCA on Cortisol Data Block. First three principal components explain about 95% of the variance in the data.

The number of principal components for the remaining data blocks are selected similarly. Figure 9 shows the scree plot from the PCA on fMRI data block and 5 principal components are chosen for about 95% of the variance in the data is explained.

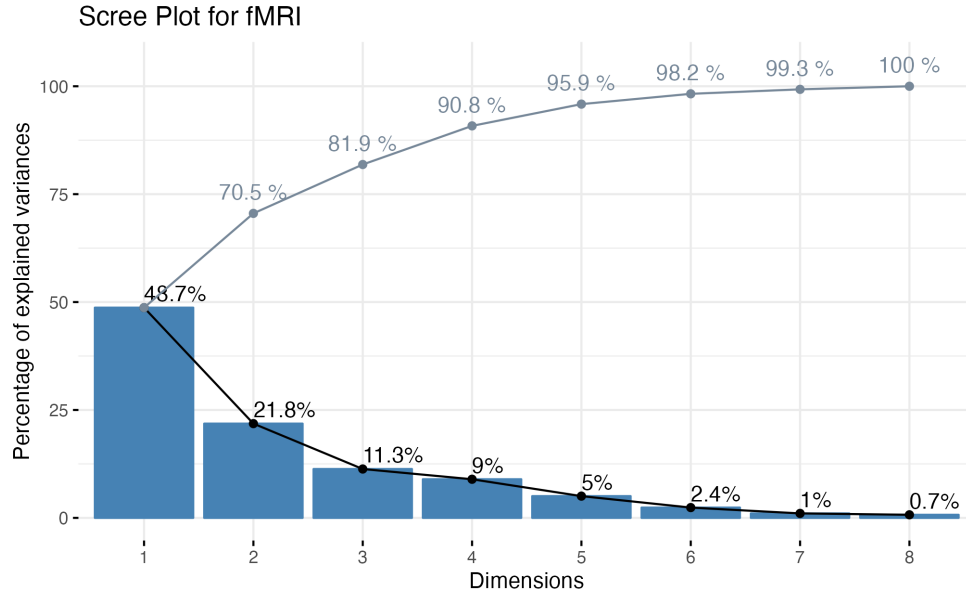


Figure 9: scree plot from PCA on fMRI Data Block. First five principal components explain about 95% of the variance in the data.

Figure 10 is the scree plot from the PCA on the working memory data block. As shown in the plot, the first nine principal components explain about 95% of the variance in the data; thus 9 principal components are used for this data block.

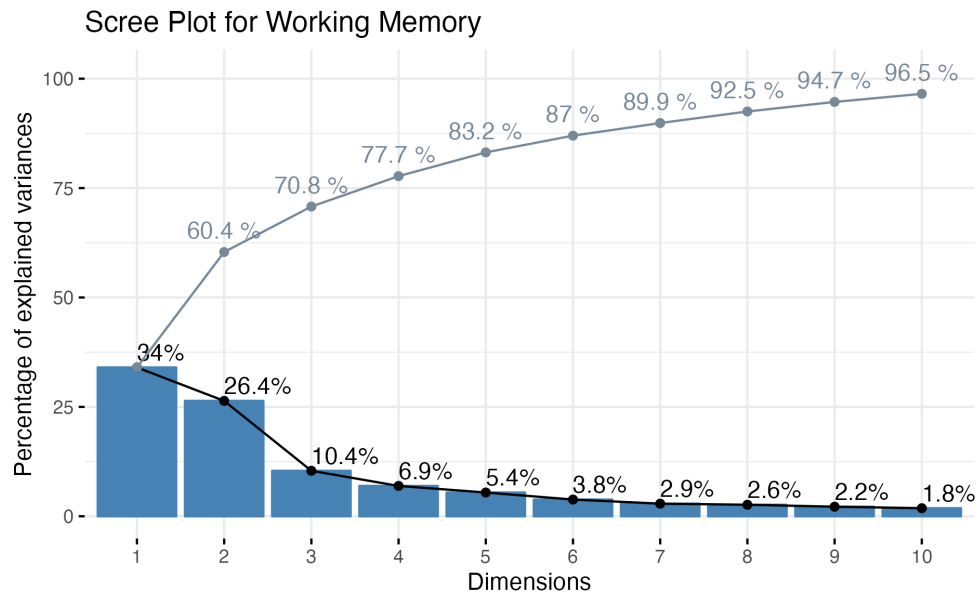


Figure 10: scree plot from PCA on Working Memory Data Block. The first 10 principal components out of 16 principal components are visualized in the plot. First nine principal components explain about 95% of the variance in the data.

Figure 11 is the scree plot from the PCA on the demographics data block. The first four

principal components explain more than 95% of variance in the data, so this is selected for the further analysis.

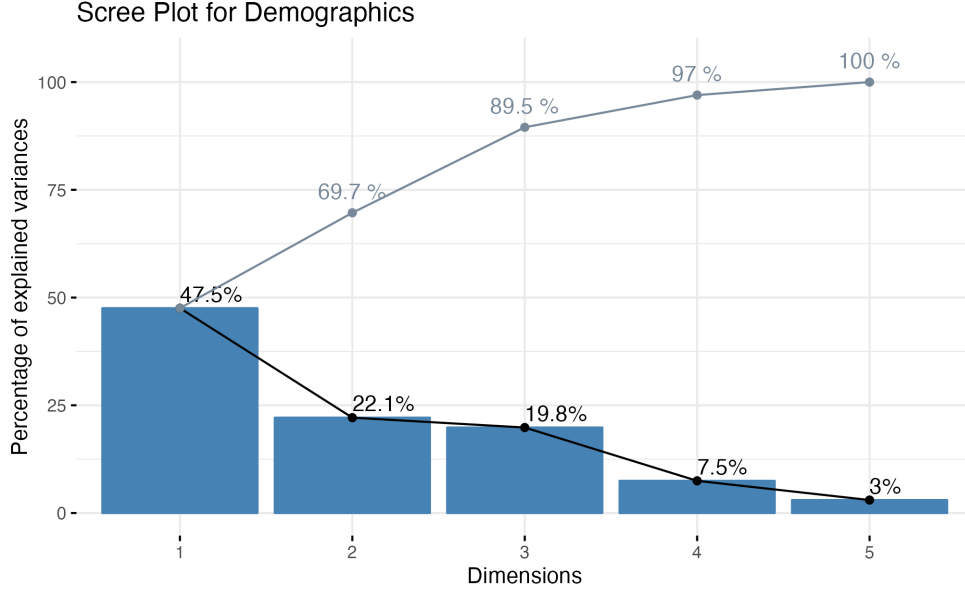


Figure 11: scree plot from PCA on Working Memory Data Block. First four principal components explain about 97% of the variance in the data.

3.2 Angle-Based Joint and Individual Variation Explained

AJIVE [1] is a procedure for extracting statistical features and reducing dimensionality in multi-block data. Its main objective is to identify joint signals across all data blocks, as well as independent signals unique to each block.

To simplify our overview of the method, let us assume that we have two data blocks named $X \in \mathbb{R}^{n \times d_x}$ and $Y \in \mathbb{R}^{n \times d_y}$ with the same number of observations n . The AJIVE algorithm is used to determine the shared variation between these two data blocks as well as the variation unique to each block. Specifically, the algorithm decomposes each matrix into the joint (J), individual (I), and error (E) terms (with corresponding subscripts) as

$$X = J_x + I_x + E_x, \quad Y = J_y + I_y + E_y,$$

under the conditions

$$\begin{aligned} \text{col}(J_x) &= \text{col}(J_y) \subseteq \mathbb{R}^n \\ \text{col}(J_x) &\perp \text{col}(I_x), \quad \text{col}(J_y) \perp \text{col}(I_y) \\ \text{col}(I_x) \cap \text{col}(I_y) &= \emptyset. \end{aligned}$$

This allows us to estimate how much of the variation in X and Y is shared between the two blocks, and how much is specific to each block. The joint matrices from the two data blocks span a common joint subspace. In contrast, the individual matrices from each block span subspaces that are orthogonal to the joint subspace. The joint rank refers to the

dimensionality of the joint subspace, while the individual ranks refer to the dimensionality of the individual subspaces of X and Y , respectively.

The process of AJIVE analysis is as follows. First, an initial signal rank are determined for each data block by investigating the PC scree plots. Then we fit an AJIVE model following the steps in [1]. Finally, we analyze the joint loading vectors provided by the fitted AJIVE model.

4 Results

Based on the PC scree plots presented in Section 3.1, we chose initial signal ranks of 3, 5, 9, and 4 for the Cortisol, fMRI, Working Memory, and Demographic data blocks, respectively. We conducted the AJIVE analysis using the R package contained in the GitHub repository: https://github.com/taebinkim7/r_jive. It is a revised version of the package in https://github.com/idc9/r_jive where some errors in the code are fixed. To address the research questions in Section 1, we fitted AJIVE models with four combinations of blocks:

1. Cortisol and fMRI (addressing Q1)
2. Cortisol and Working Memory (Q2)
3. Cortisol, fMRI, and Demographics (Q3)
4. Cortisol, Working Memory, and Demographics (also Q3)

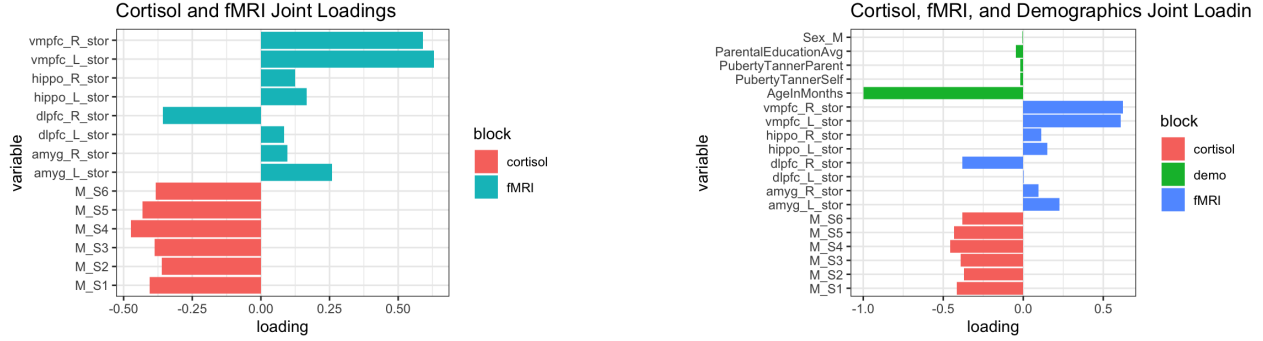
For each of these models, the joint rank of the fitted AJIVE model was 1. This means that there is only one transformed feature that captures the joint signals between multiple data blocks. Hence, we focus on the joint loading vectors to examine the weights of the features on the joint signals.

4.1 AJIVE analysis of Cortisol and fMRI blocks, with and without Demographics block

In this subsection we examine the loadings of the cortisol, fMRI, and demographic variables on the discovered joint component from the AJIVE analysis. We start with the AJIVE model that included all three blocks. The loadings for this model are shown in Figure 12b. The cortisol loadings (red bars) have around the same magnitude and point in the negative direction, while the fMRI loadings (blue bars) are large and positive for VMPFC and moderate-size and negative for right DLPFC. The only large demographic loading (green bars) is for age. The interpretation of this result is that below-average cortisol is associated with younger age, above-average activation in both sides of the VMPFC, and below-average activation in the DLPFC, and that above-average cortisol is associated with higher age and the opposite brain activation patterns. The other brain regions of interest in the figure also had positive loadings, but much smaller in magnitude. We conclude that activation in these areas is less associated with cortisol level.

When we remove the Demographics block, the Cortisol and fMRI loadings hardly change. This can be seen in Figure 12a, where where the pattern of blue and red bars is nearly the

same as in Figure 12b. This indicates that we are still finding approximately the same joint direction when we remove that block. The only appreciable difference is in the Left DLPFC loading, which is negligible when the Demographics block is included, and positive when the Demographics block is excluded.



(a) Loadings without Demographics block.

(b) Loadings with Demographics block.

Figure 12: Joint loadings plots for Cortisol-fMRI AJIVE analysis, with and without the Demographics block. The inclusion of the Demographics block does not affect the Cortisol and fMRI loadings.

4.2 AJIVE analysis of Cortisol and Working Memory blocks, with and without Demographics block

The loadings for the AJIVE model with Cortisol, Working Memory, and Demographics are shown in Figure 13a. The Cortisol and Demographics loadings showed the same patterns in this analysis as they did in the analysis in the previous subsection: the cortisol loadings are around equal magnitude and point in the negative direction, and the only large demographic loading is for the age variable. However, the brain activation patterns in this joint mode of variation are not the same as in the other analysis, indicating a difference in brain activation for the two cognitive tasks. Lower cortisol levels and lower ages were associated with:

- substantially higher right-side pre-stress VMPFC activity;
- moderately lower left-side post-stress VMPFC activity;
- moderately higher hippocampus activity, both pre- and post-stress, except for the left-side pre-stress hippocampal measure, which was small;
- substantially lower DLPFC activity, except for the pre-stress right DLPFC measure, which was moderately lower;
- moderately higher pre- and post-stress left and right amygdala activity.

Higher cortisol levels and ages were associated with the opposite brain activity patterns.

When we remove the Demographics block, the Cortisol and the Working Memory loadings do not change much as a whole, indicating that we are finding nearly the same joint direction.

However, there are some noteworthy changes in the Working Memory loadings. These can be seen in Figure 13b and are listed below:

- The right-side pre-stress VMPFC loading drops from substantial to moderate, while the right-side *post-stress* VMPFC loading increases from small to moderate.
- The left-side pre-stress VMPFC loading changes sign, going from moderately positive to slightly negative.
- The left and right pre-stress amygdala loadings become more positive, while the left and right post-stress amygdala loadings become less positive.



(a) Including Demographics block.

(b) Not including Demographics block.

Figure 13: Joint loadings plots for Cortisol-Working Memory AJIVE analysis, with and without the Demographics block. The inclusion of the Demographics block does not affect the Cortisol loadings, but has a small effect on the Working Memory loadings.

A possible reason for finding slightly different Working Memory loadings is that when we included the Demographics block, we had to exclude some subjects who were missing one or more Demographics variables. When we excluded the entire block, these missing values were no longer an issue, giving us more subjects to work with. Therefore, the difference in observations may be the reason for the slightly different loadings.

We remark that while we chose to use bar graphs to visualize the loadings, some users use *parallel-coordinates plots* for this purpose.

5 Discussion

In this research, we obtained a one-dimensional joint subspace for each research question presented in Section 1, and we found that the relationship between cortisol and brain activation differed for the two tasks. For future work, the data blocks left out in this analysis can be investigated with information provided in Section 2. In our AJIVE analysis, we utilized four out of the six data blocks: Demographic, Cortisol, fMRI, and Working Memory blocks. Since there were no research questions that required the use of the Clinical Psychology and the Autonomic data blocks, we do not include this block in the AJIVE analysis and believe

that this could be valuable for future research. Second, alternative methods can be explored for handling missing data. The Autonomic data block had a high number of missing values. We also dropped the columns and rows with missing data issues. The missing values can be replaced with mean substitution or regression imputation as described in [3]. Future researchers should consult the clients about the appropriate imputation method, as a non-standard statistical method may be appropriate for a given data block. Furthermore, other state-of-the-art data integration methods such as Data Integration Via Analysis of Subspaces (DIVAS) [4] can also be utilized for the analysis of multiple data blocks.

References

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Appendix

A Correlation among variables

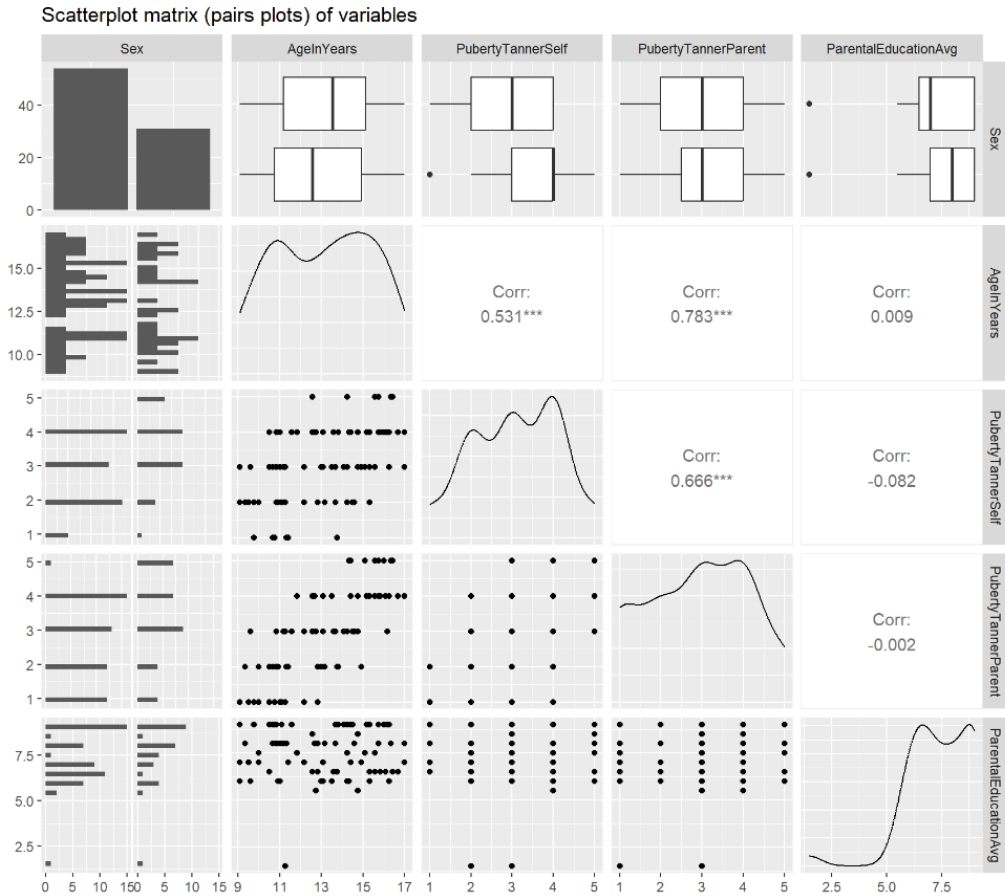


Figure A1: Correlation of Demographic data block by Variable

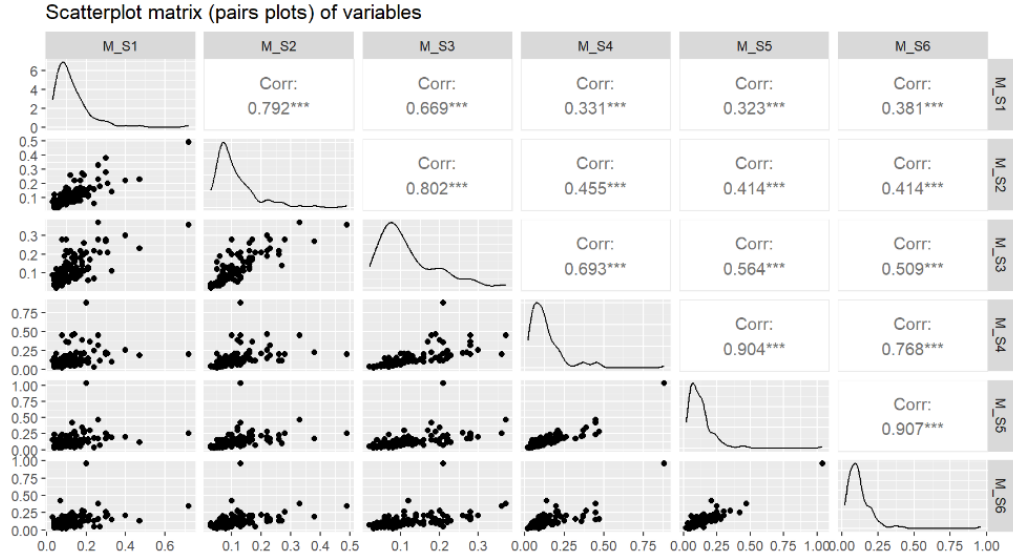


Figure A2: Correlation of Cortisol data block by Variable

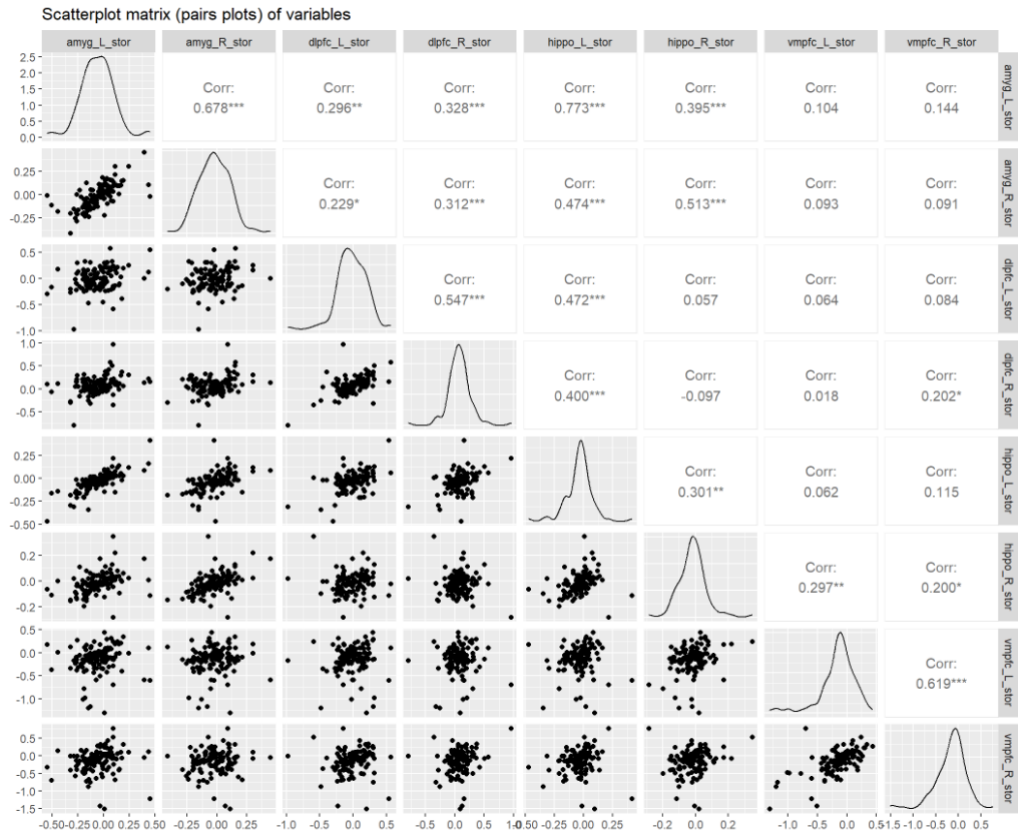


Figure A3: Correlation of fMRI data block by Variable

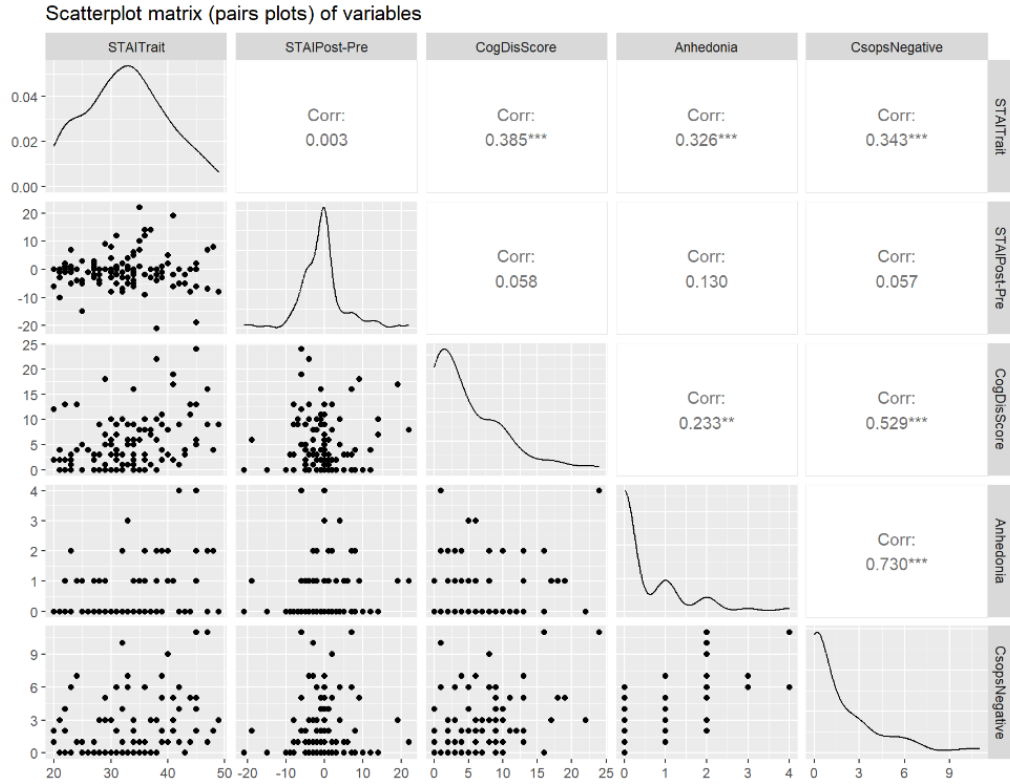


Figure A4: Correlation of Clinical Psychology data block by Variable

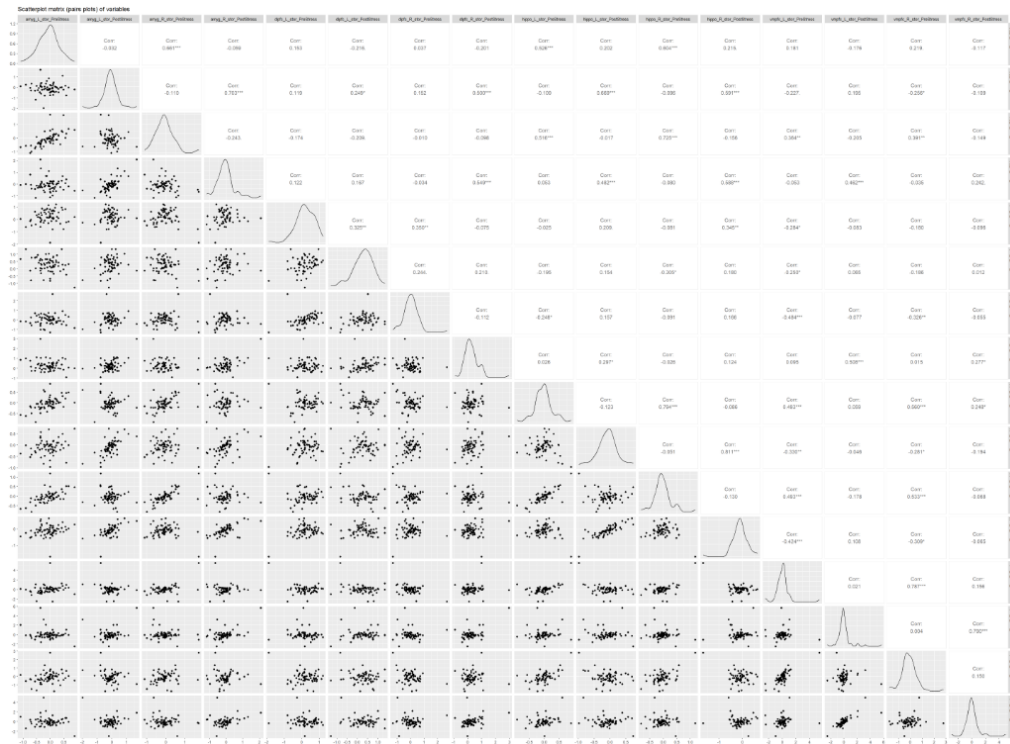


Figure A5: Correlation of Working Memory data block by Variable

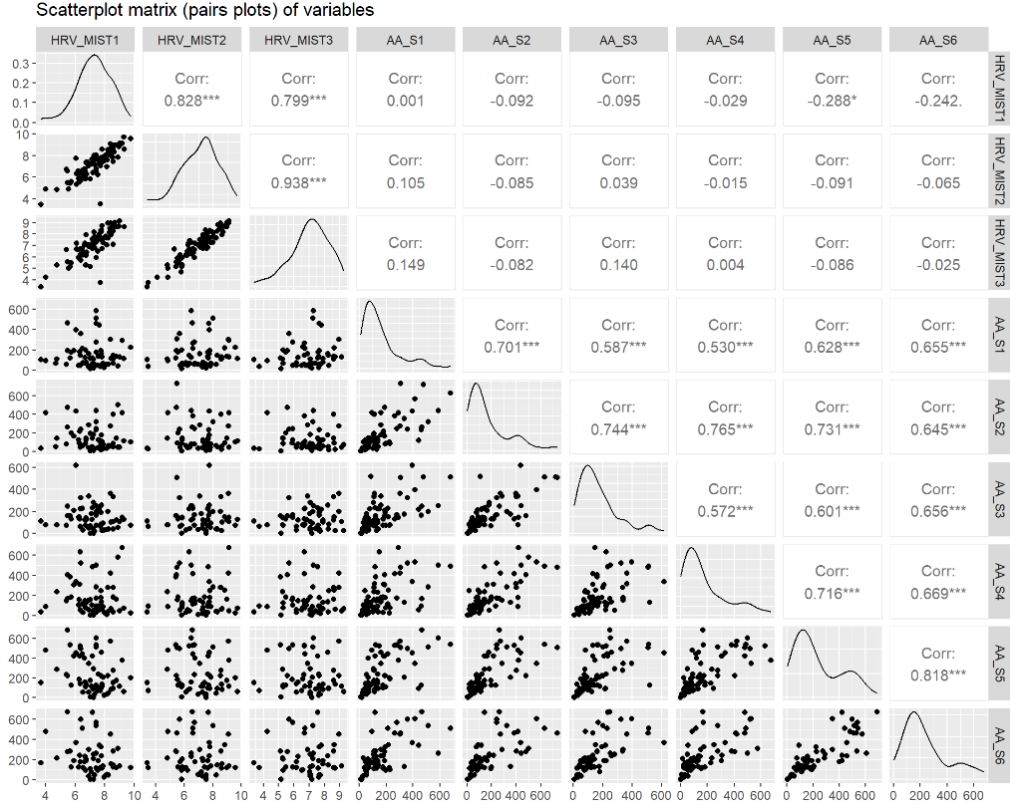


Figure A6: Correlation of Autonomic data block by Variable

B PCA: scree plots and biplots

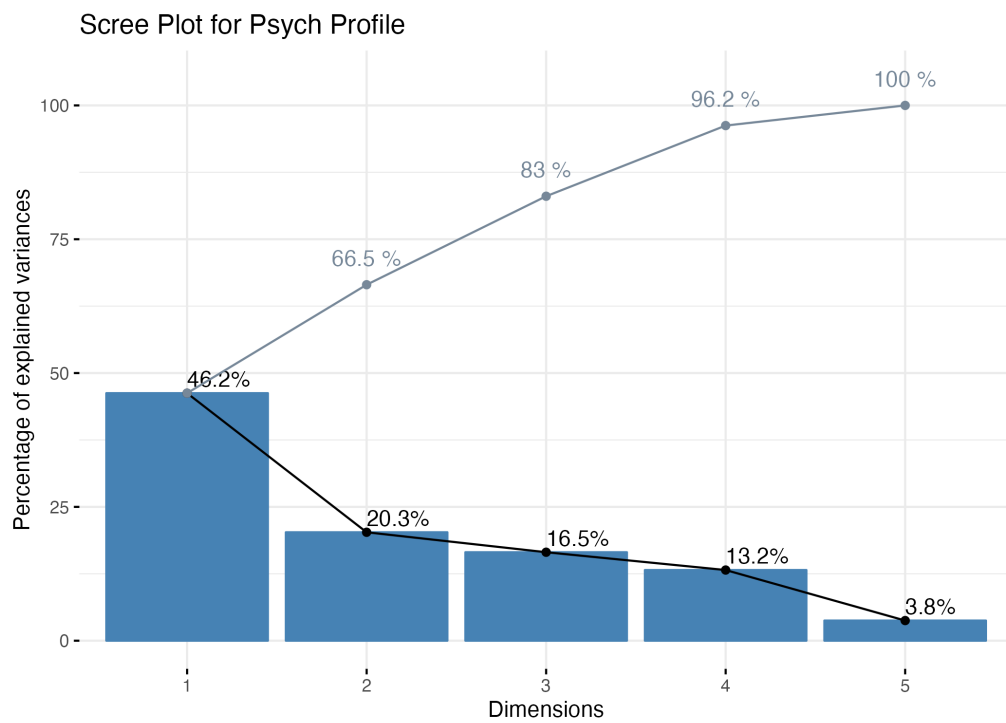
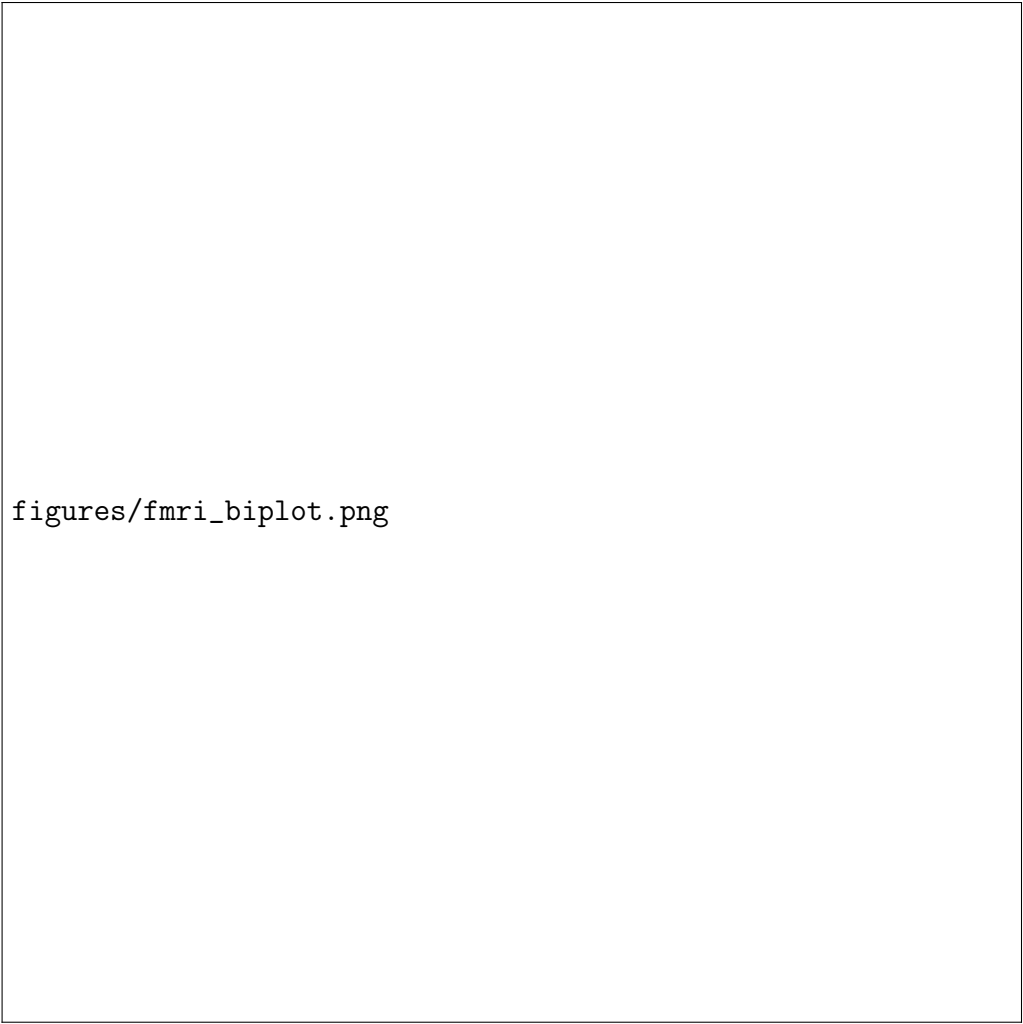


Figure B1: scree plot from PCA on Clinical Psychology data block



figures/fmri_biplot.png

Figure B2: biplot from PCA on fMRI data block

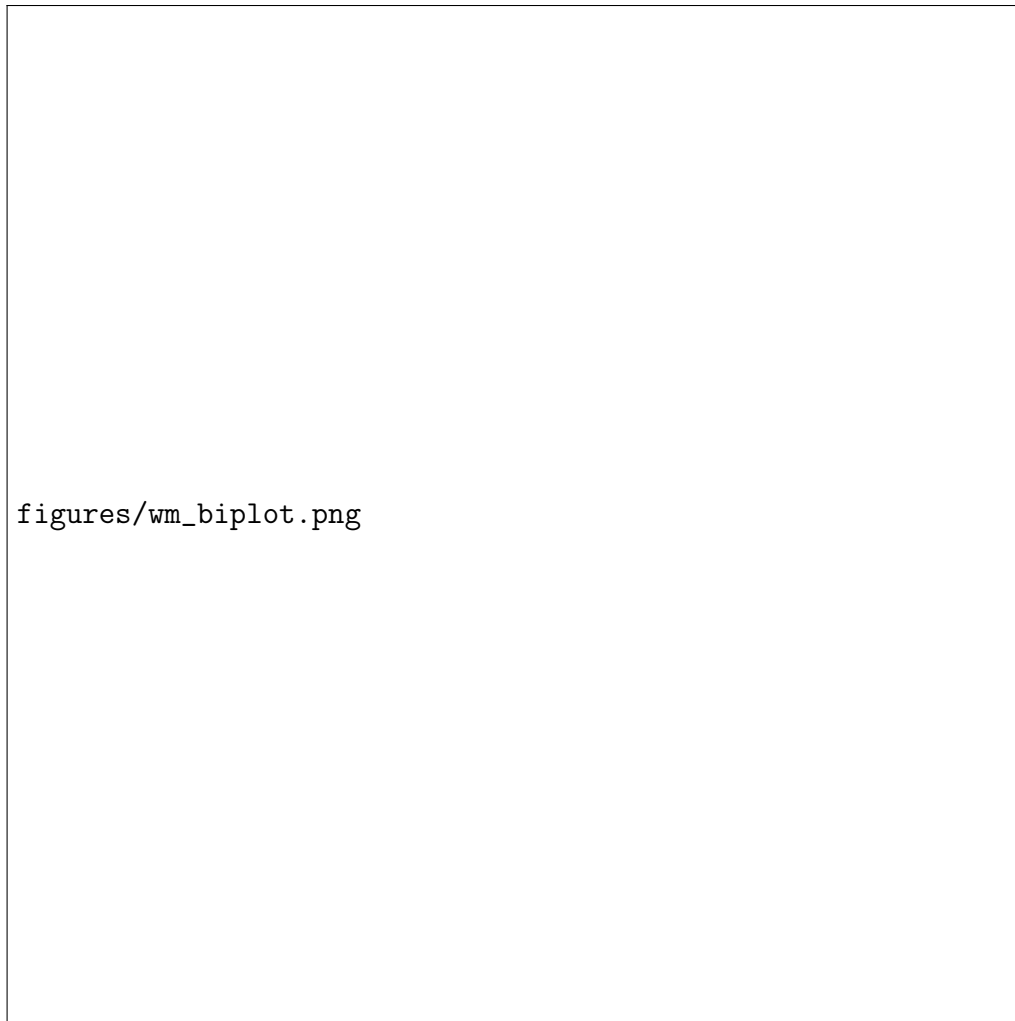
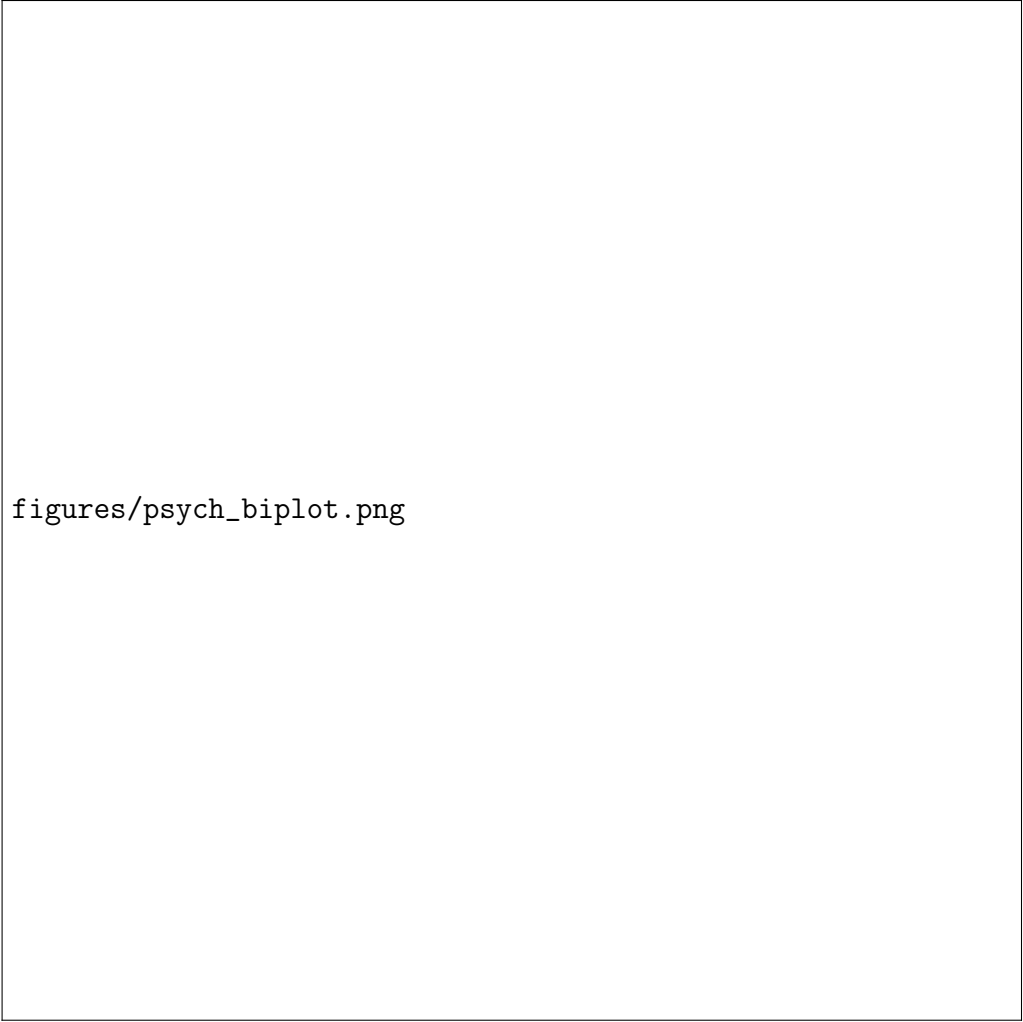


Figure B3: biplot from PCA on Working Memory data block



Figure B4: biplot from PCA on Demographics data block



figures/psych_biplot.png

Figure B5: biplot from PCA on Clinical Psychology data block