Patterns of Brain Connectivity Associated with Heart Rate Variability

Introduction

Intelligence is like a muscle that can be trained. Studies have shown that working memory, a measure of intelligence, can be increased with training[1]. This training works on healthy individuals as well as individuals diagnosed with ADHD, a disorder characterized by the inability to stay focused[2]. True, working memory is not the only factor involved in intelligence. A study just published a few months ago found that working memory training might neglect fluid intelligence, a measure that is characterized by the ability to apply old learning to new contexts[3]. However, working memory is a reliable predictor of reading comprehension and the ability to focus one's attention on the task at hand, which are two highly valuable skills for students in an academic context[4]. Therefore, training working memory is an important skill for students to hone.

One proven method for increasing working memory is to train one's heart rate variability (HRV). Heart rate variability is a measure of changes in the heart's beat-to-beat (interbeat) timing. Changes on the order of 0.1 Hz are a result of input on the heart coming from the vagus nerve. The vagus nerve is the source of parasympathetic input that slows the heart rate. Increases in the relative contribution of the vagus nerve are associated with increased working memory scores [5, 6] neurovisceral integration model provides an explanation for this technique's effectiveness.

According to the neurovisceral integration model from Thayer et al. (2013)[7], heart rate variability partially reflects the activity of inhibitory input on the amygdala from the ventromedial prefrontal cortex (vmPFC). A meta-analysis of studies of heart rate variability shows that amygdala activity is associated with heart rate variability during emotional tasks. Greater gray matter density in the vmPFC predicts greater fear extinction and regulation, higher self-perceived social status, and also higher HRV. Damage to this region impairs fear regulation in response to threat stimuli and memory of fear extinction[8]. Therefore, vmPFC activity, which is necessary for maintaining information and learned associations in working memory, is associated with the threat response as well as with HRV. Lower vmPFC activity, indexed by a lower HRV, could be a sign that emotional regulation and working memory are impaired. HRV training could help to rectify this problem.

In order to further investigate the neurobiological basis of the interaction between working memory and HRV, we sought to analyze the brains of people who have different degrees of HRV and then to compare the degree of functional connectivity within the brains of these different people. Functional connectivity is a measure of neuronal connections between different regions of the brain that is measured by having someone sit inside of a brain scanner and measuring their activity using functional magnetic resonance imaging (fMRI). The activity

[1] http://www.psycontent.com/content/6n1t126263257274/
[2] http://www.sciencedirect.com/science/article/pii/S0890856709614271
[3] http://pss.sagepub.com/content/early/2013/10/03/0956797613492984
[4] http://www.ncbi.nlm.nih.gov/pubmed/21875246
[5] http://www.ncbi.nlm.nih.gov/pubmed/15338220
[6] http://www.sciencedirect.com/science/article/pii/S0167876003000734
[7] http://wagerlab.colorado.edu/files/papers/Thayer.meta.analysis.heart.rate.variability.pfc.NBR.12.pdf
[8] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1838961/

in various regions of the brain are correlated with one another in order to arrive at the measure of functional connectivity between regions. By doing this analysis, we hope to find more regions, in addition to the vmPFC and amygdala, that are associated with HRV. More information on our techniques is given in the methods section.

Data

Since our goal was to look at the relationship between brain connectivity and heart rate variability, it was necessary to find a data set that included not only functional brain images (measures of changes in brain activity across time), but also heart rate data. Functional magnetic resonance imaging (fMRI) measures brain activity under the assumption that blood oxygenation is a proxy for brain activity. Magnetic pulses cause atoms within the brain to resonate at a certain frequency. Since oxygenated and deoxygenated blood have atoms that resonate at different frequencies, the fMRI scanner can measure levels of blood oxygenation throughout the brain. When neurons fire, they take up oxygen from the blood for their metabolic processes, so the degree of brain activity is correlated with the degree of blood oxygenation. More activity means more oxygenated blood is flowing to the regions that require that blood in order to maintain their activity.

After some searching, we found a data set via the website of the "1000 Functional Connectomes Project", a movement that seeks to make a wide variety of brain imaging data sets open source. The data set consists of 6-minute fMRI scans of 31 adult subjects, males and females, in the age range of 24-60 years old[9]. The brain scans are resting-state brain scans, which means that the subjects were given no instructions other than to simply sit inside of the scanner. In addition to the brain scans, there are heart rate and breathing measurements that were taken while the subjects were sitting inside the scanners, and the ages and sexes of the subjects are also included. Thus, with this data set, it is possible to calculate relationships between heart rate variability and brain activity.

Methods

Because our personal computers have approximately 8 GB of RAM each, it was necessary to download the data set to the computer science department cluster computers. We requested 200GB of project space from the CS department and connected to the cycles.cs.princeton.edu machines via secure shell (ssh). Then, we copied the data onto the CS department project space using a secure transfer protocol (scp). We accessed the Matlab graphical user interface (GUI) running on the CS department clusters through our personal computers and then ran the CONN functional connectivity toolbox via this GUI, downloaded from the NeuroImaging Informatics Tools and Resources Clearinghouse (NITRC), a source for freely shared neuroimaging analysis tools.

[9] http://fcon_1000.projects.nitrc.org/indi/retro/ClevelandCCF.html

Using the CONN toolbox for Matlab

The CONN toolbox for Matlab gives you the option of processing large data sets of neuroimaging data using a simple GUI. In our case, we wanted to find out the functional connectivity between various regions of the brains of 31 subjects. We used the CONN toolbox in order to preprocess the data. Preprocessing fMRI data is necessary for removing noise and smoothing the imaging data. While sitting in an fMRI scanner, people tend to move their heads a few millimeters from time to time. So, the CONN toolbox removes the effects of head motions from the fMRI signal by tracking the head motions and relocating the activities of voxels based on this movement. Furthermore, it is possible that fMRI signals can trend downward or upward overall, regardless of the actual activities that are happening in the brain. The CONN toolbox removes the effects of these longer-term trends on the measured activity as well.

After the data was preprocessed, the CONN toolbox also used anatomical images taken of each subject's brain in order to align the subject's brain with the traditionally recognized anatomical subdivisions of the brain. Different people's brains have different sizes in certain regions. For example, one person's hippocampus, a part of the brain, could be larger than another person's hippocampus. The CONN toolbox aligns each subject's particular activation data with these recognized anatomical brain subdivisions, so that we can make inferences about the possible functions of certain brain activity patterns based on known functions and connections of certain brain areas. In Figure 1 (in the appendix), we show example output from the CONN toolbox.

For the final step of processing the fMRI data, the CONN toolbox correlates activity across brain regions using bivariate analysis. Activity across the anatomical brain regions are averaged and then the time-series of activity of one brain region is correlated with that of all the other regions. This process is repeated across all the brain regions. There are 88 different regions recognized by CONN in total, so in the final analysis, there were approximately 7,500 region pairs for which correlations were calculated.

Processing Raw Oximeter Signal in R

In order to extract the heart rate variability for use in the final analysis, the finger-tip pulse oximeter signals were imported into R using code as attached in the appendix. Oximetry is a measurement of the heart's pulsatile activity, and spikes in the oximetry correlate to contractions of the heart, which is a single heartbeat.

Oximetry is the measurement of the oxygen content of the blood, and it corresponds to the heart’s beating, versus time. We converted this raw signal was converted to interbeat intervals using the code below. The justification for converting from raw signal into interbeat intervals is that in order to calculate heart rate variability, you must calculate the variation in the inter-beat intervals. So, the code below locates the times at which spikes occurred in the oximetry signal and then graphs them on a histogram, so that you can get an intuitive sense of how variable the interbeat intervals are for a typical subject. Another word for interbeat intervals is RR-interval, (as referred to it in our code).

Moreover, we calculated the variance of the interbeat intervals for each subject (RRVar). We used these numbers to represent HRV in the final analysis. Though there are many different ways of calculating HRV we elected to go with this very straightforward method in order to focus on the next section of our project, which is the general linear model.

General Linear Model for Heart Rate Variability in R

After the bivariate correlations were found, these correlations were used as variables in a general linear model for heart rate variability in R. The correlations and heart rate variability were calculated in the ways shown in the code as attached in the appendix. Our model for HRV used the functional connectivity (bivariate correlations) between different brain regions as our inputs. We decided to use glmnet in R for our linear modeling because our data was very high-dimensional (over 7,000 variables). Glmnet limits the numbers of variables in the model by placing a penalty on overfitting due to too many degrees of freedom in a model. Moreover, it is the standard package that is used when the data is high dimensional.

Selected Results

At the conclusion of our analyses, we were able to specify 20 pairs of regions that were significant predictors of HRV. These pairs and their beta coefficients for the cross-validated elastic net model in R are given in the appendix, though we would like to notice that there was a significant drop off in the value of the beta coefficient after the 20th variable. We believe that this is owed to the ability of glmnet modeling to make predictions using sparse parameter spaces, and the conservative approach to predictive modeling that the glmnet's elastic model uses.

Brain Area 1	Brain Area 2	Beta
BA.43 (L). Subcentral Area_1_1	BA.20 (R). Inferior Temporal Gyrus_1_1	-3.46E-02
BA.39 (L). Angular gyrus_1_1	BA.13 (L). Insular Cortex_1_1	-2.42E-02
BA.20 (R). Inferior Temporal Gyrus_1_1	BA.19 (L). Associative Visual Cortex_1_1	-1.46E-02

Discussion of Results

Brodmann area 39, the angular gyrus, comes up a few times in the pairs of regions that predict HRV. This region plays a role in the comprehension and formation of the meanings of words. Brodmann area 40 also comes up a few times in the variables of the final model. This is another region related to the reading and phonology of words. It is not clear why the connections of regions that are related to the meanings of words would be negatively correlated with HRV. It is possible that these regions were not correctly identified by the tools of the Matlab CONN toolbox. For example, since these regions are so small, what may have happened is that the toolbox mistakenly labeled other active regions with these labels. It is impossible to be perfectly precise in labeling regions in functional magnetic resonance imaging at this time because people move their heads around while laying down in MRI scanners, and different people have different sized brain regions, so the exact locations of these regions cannot be perfectly predicted by the CONN toolbox. As a result, we would not rely on these results to make any conclusions about the regions that contribute to HRV. However, it is interesting that we were able to build a sparse model predicting HRV using the functional connectivity of the brain.

Conclusions

Heart rate variability (HRV) is an important indicator of health, so it is imperative to know what brain regions can contribute to increased or decreased heart rate variability. Perhaps, by knowing the functions of the regions that contribute to heart rate variability, we can make inferences about the types of activities to engage in for increasing heart rate variability and becoming healthier and more stress-free. This project was an attempt to build a model of heart rate variability using brain connectivity, and more importantly than finding predictive power from brain data, we were more interested in finding which brain regions show promise in neuroscience. Future studies can improve on this project in the following ways:

1. Including more subjects in the analysis. 31 subjects is too small to build a reliable model. One of the many reasons why our predictive analysis is lacking is due to the fact that the data lends itself to being prone to human error in both measurement and sample size.
2. Using a more complex measure of heart rate variability, other than the overall variance of the interbeat intervals.
3. Attempt to remove more noise from the signal by using more accurate anatomical delineations of the brain.
4. Not pre-assigning anatomical delineations of the brain at all, and instead, assign the delineations after creating a voxel-by-voxel model predicting heart rate variability.

Overall, we were satisfied with this study because our model was moderately successful at predicting HRV after cross-validation. Even though the exact regions of the brain may not be correctly labeled, it proves that there are patterns of brain connectivity that can predict HRV, and this gives hope for future studies to learn more about the relationship between the heart and brain.

Appendix

A. The Data

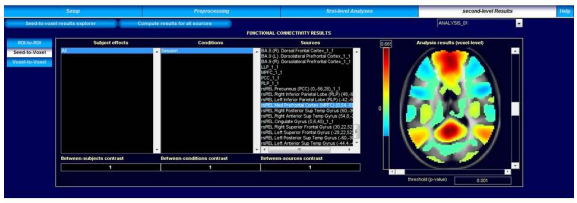
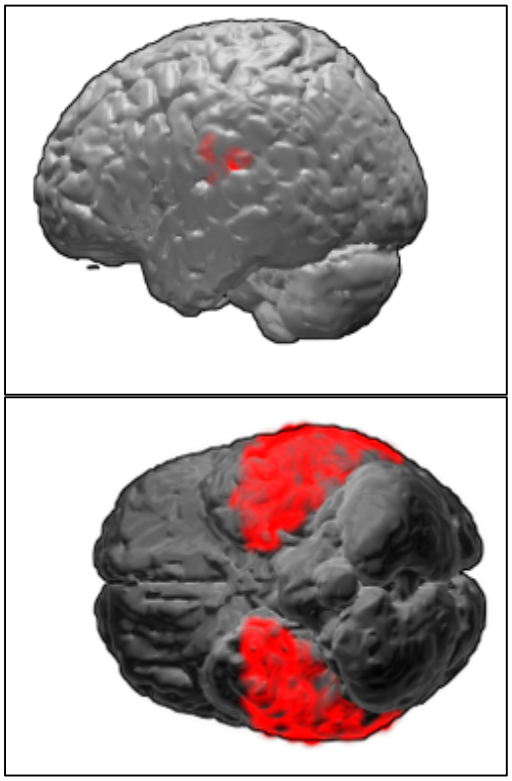


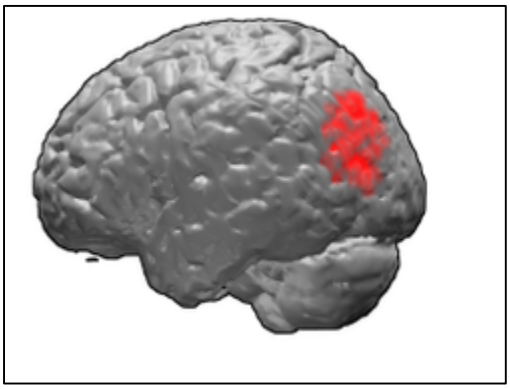
Figure 1: Example usage of the Matlab CONN toolbox for the final processing step, correlating activity across brain regions. Adapted from NITRC.org[10]

Of the regions whose connectivity patterns were shown to significantly contribute to Heart Rate Variability, these are the top 3 pairs. All figures adapted from Wikipedia.

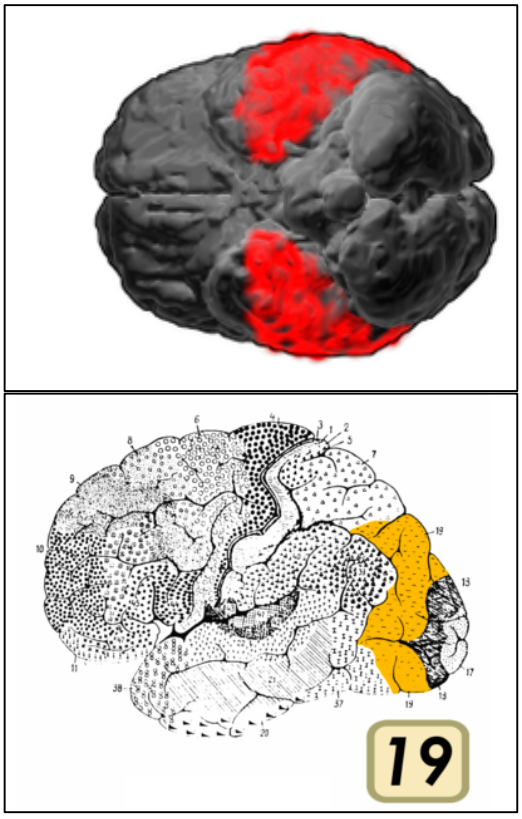
BA. 43 (side view) and BA. 20 (bottom)



BA.39 (side) and BA. 13 (not available)



BA.20 (R) Inferior Temporal Gyrus and BA.19 (L) Associative Visual Cortex



10 https://www.nitrc.org/project/list_screenshots.php?group_id=279&screenshot_id=429

B. Full Results of Regression

Brain Area 1	Brain Area 2	Beta
BA.43 (L). Subcentral Area_1_1	BA.20 (R). Inferior Temporal Gyrus_1_1	-3.46E-02
BA.39 (L). Angular gyrus_1_1	BA.13 (L). Insular Cortex_1_1	-2.42E-02
BA.20 (R). Inferior Temporal Gyrus_1_1	BA.19 (L). Associative Visual Cortex_1_1	-1.46E-02
BA.39 (L). Angular gyrus_1_1	BA.18 (L). Secondary Visual Cortex_1_1	-1.42E-02
BA.43 (L). Subcentral Area_1_1	BA.11 (R). Orbitofrontal Cortex_1_1	-1.26E-02
BA.27 (R). Piriform Cortex_1_1	BA.22 (R). Superior Temporal Gyrus_1_1	-6.25E-03
BA.43 (L). Subcentral Area_1_1	BA.19 (L). Associative Visual Cortex_1_1	-4.62E-03
BA.10 (L). Anterior Prefrontal Cortex_1_1	BA.21 (L). Middle Temporal Gyrus_1_1	-1.58E-03
BA.40 (R). Supramarginal Gyrus_1_1	BA.24 (R). Ventral Anterior Cingulate Cortex_1_1	-1.48E-03
BA.10 (R). Anterior Prefrontal Cortex_1_1	BA.4 (R). Primary Motor Cortex_1_1	-1.23E-03
RLP_1_1	BA.39 (R). Angular gyrus_1_1	-1.22E-03
BA.46 (L). Dorsolateral Prefrontal Cortex_1_1	BA.11 (L). Orbitofrontal Cortex_1_1	-3.72E-04
BA.40 (R). Supramarginal Gyrus_1_1	BA.29 (L). Retrosplenial Cingulate Cortex_1_1	-9.73E-05
BA.40 (R). Supramarginal Gyrus_1_1	BA.9 (R). Dorsolateral Prefrontal Cortex_1_1	-9.65E-05
BA.5 (R). Somatosensory Association Cortex_1_1	BA.6 (R). Premotor Cortex_1_1	-5.11E-05
BA.36 (R). Parahippocampal cortex_1_1	BA.45 (L). IFC pars triangularis_1_1	-3.88E-05
BA.8 (L). Dorsal Frontal Cortex_1_1	BA.47 (L). Inferior Prefrontal Gyrus_1_1	-3.29E-05
BA.21 (R). Middle Temporal Gyrus_1_1	BA.46 (R). Dorsolateral Prefrontal Cortex_1_1	-1.73E-05
BA.42 (R). Primary Auditory Cortex_1_1	BA.7 (R). Somatosensory Association Cortex_1_1	-1.59E-05
BA.45 (L). IFC pars triangularis_1_1	LLP_1_1	-1.04E-05

C. Code

```
# create vector of file paths
paths <- vector()
for (i in 1:9) (paths[i] <-
paste('/Users/payam/Documents/Sprin
g 2014/',
                  'COS 424/HRV
data/Cleveland dataset/',

'INDI_Lite_NIFTI/001700',
as.character(i),
'/session_1/rest_1/',

'physio/card_r1.dat', sep = ""))
for (i in 10:31) (paths[i] <-
paste('/Users/payam/Documents/Sprin
g 2014/',

'COS 424/HRV data/Cleveland
dataset/',

'INDI_Lite_NIFTI/00170',
as.character(i),
'/session_1/rest_1/',

'physio/card_r1.dat', sep = ""))
# import data into list card
# refer to individual subjects in
list by card[[#]]
card <- list()
for (i in 1:length(paths)) (card[i]
<- read.table(paths[i]))
# plot data on graph
time <- seq(0.02, 5, by = 0.02)
plot(time,card[[11]][1:250],
type='l')
```

```
#####################
# Function extracts beat positions
from oximetry signal.
# Sample rate is 50Hz.
# 132 (volumes) * 2.8 (second TR) *
50Hz = 18480 samples.
# 369.6 seconds of data
#####################
# load library
library(quantmod)
# position of heart beat peaks in
time series (s)
peakPosition <- list()
for (i in 1:31) (peakPosition[[i]]
<- findPeaks(card[[i]])/50)
#peakPosition[[]] <-
findPeaks(card_data[,1])*(1/50)
# RR intervals (inter-beat
intervals)
rrIntervals <- list()
for (i in 1:31)
  (rrIntervals[[i]] <-
peakPosition[[i]][2:length(peakPosi
tion[[i]])] -

peakPosition[[i]][1:length(peakPosi
tion[[i]])-1])
# histogram of RR Intervals
hist(rrIntervals[[15]], breaks =
100)
# variance of rrIntervals
RRVar <- vector()
for (i in 1:31) (RRVar[i] <-
var(rrIntervals[[i]]))
mean(rrIntervals)
# plot of RR Intervals vs time
points = 50 # number of data points
to plot
plot(peakPosition[1:points],rrInter
vals[1:points], type='l')
# plot of RR intervals with
interpolation of extra data between
points
rrIntervalsSmooth =
spline(peakPosition[1:points],rrInt
ervals[1:points],
                          n=1000)
plot(rrIntervalsSmooth, type='l')
 library(glmnet)
age <- phenotypic[[2]]
sex <- phenotypic[[3]]
X <- rbind(s01[2:length(s01)],
s02[2:length(s01)],
s03[2:length(s01)],
s04[2:length(s01)],
s05[2:length(s01)],
s06[2:length(s01)],
s07[2:length(s01)],
s08[2:length(s01)],
s09[2:length(s01)],
s10[2:length(s01)],
           s11[2:length(s01)],
s12[2:length(s01)],
s13[2:length(s01)],
s14[2:length(s01)],
s15[2:length(s01)],
s16[2:length(s01)],
s17[2:length(s01)],
s18[2:length(s01)],
s19[2:length(s01)],
s20[2:length(s01)],
           s21[2:length(s01)],
s22[2:length(s01)],
s23[2:length(s01)],
s24[2:length(s01)],
s25[2:length(s01)],
s26[2:length(s01)],
s27[2:length(s01)],
s28[2:length(s01)],
s29[2:length(s01)],
s30[2:length(s01)],
           s31[2:length(s01)])
# fill in nan values
XFill <- X
nan <- is.nan(X)
XFill[nan] <- 0 # replace nan
values with 0
model <- glmnet(XFill, RRVar,
family = 'gaussian', dfmax = 100)
cvmodel <- cv.glmnet(XFill, RRVar)
# best model using CV
# indices of top 30 betas
top30 <- order(coef(cvmodel, s =
cvmodel$lambda.min))[1:30]
# values of top 30 betas, only top
21 are significant
values_top30 <- coef(cvmodel, s =
cvmodel$lambda.min)[top30]
```

```
# ROI pairs corresponding to the
columns of the input matrix
names <- scan(file =
"/Users/payam/ROIconnectivity/names
.txt", what = 'character') ## 88
names2 <- scan(file =
"/Users/payam/ROIconnectivity/names
2.txt", what = 'character') ## 89
ROInames <- vector() # vector of
ROI pair names
dummy <- 0 # counter variable
for (i in 1:88)
  { for (j in 1:89)
    { dummy <- dummy + 1
     ROInames[dummy] <-
paste(names[i], names2[j], sep = "
< - > ") } }
```