THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF PSYCHOLOGY

ASSESSING THE ROLE OF LESION VOLUME AND CINGULATE GYRUS WITHIN THE DEFAULT MODE NETWORK ON EXECUTIVE FUNCTION IN MODERATE-SEVERE TRAUMATIC BRAIN INJURY PATIENTS

RIDDHI DILIPKUMAR PATEL
SPRING 2018

A thesis
submitted in partial fulfillment
of the requirements
for baccalaureate degrees
in Psychology and Biology
with honors in Psychology

Reviewed and approved* by the following:

Frank G. Hillary
Associate Professor of Psychology
Thesis Supervisor and Honors Advisor

Jeff Love
Associate Teaching Professor of Psychology
Faculty Reader

* Signatures are on file in the Schreyer Honors College.

ABSTRACT

Traumatic Brain Injury (TBI) is a major health and socioeconomic issue that affects over 1.5 million people every year resulting in cognitive impairment and reduced quality of life. Cutting-edge neuroimaging technology such as 3T MRI scanners have facilitated research investigating the role of specific brain structures, lesion volume and different neural network connectivity dynamics which may enhance medical interventions and targeted therapies. The recently evolved structure of the limbic system, cingulate gyrus is involved in the attention, executive processes, word generation, memory and emotion. Due to its functional significance in TBI, examining behavioral effects on task switching and other executive functions post-injury can be give some beneficial insight. Default Mode Network (DMN) is a neural network that includes the posterior cingulate cortex and maintains ongoing resting brain activity. The current study examines total lesion volume, parcellated cingulate gyrus volumes, interconnectivity among the cingulate cortex within the DMN and correlates them with neuropsychology test scores to examine their role in cognitive deficits post injury. Results indicate a statistically significant decrease in the posterior cingulate cortex volume and lower neuropsychological tests scores in TBI participants compared to their healthy controls. Higher total lesion volumes in TBI modestly correlate with poorer neuropsychological performance. Lastly, greater interconnectivity among the CC-DMN was associated with better performance on Digit Span and Trails Making tests among the TBI sample. Future studies should include a larger sample to provide more statistical power between the volumetric, connectivity and behavioral findings.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to thank Dr. Frank Hillary for being the most wonderful mentor one could ask for and the unwavering support and guidance throughout the past two and a half years. I would also like to thank Dr. Love for being an amazing professor and for being willing to read my thesis. A special thank you goes to Emily Grossner who has always welcomed my hundreds of questions and queries with a smile, personally guided me and gone out of her way to help me throughout my time in the lab. Thank you to Rachel Bernier and Einat Brenner for all the advice and kind, loving support. I am forever indebted to the Brain and Behavior Lab for their help and allowing me to get hands-on learning research experience in my field of interest.

I am grateful to Nick Gilbert, without whom, I wouldn't have been a part of this lab in the first place; he has been a total delight and a constant source of support to me in terms of research and medical school application process. I would also like to thank Jon Richards for his guidance and assistance in working with the lesion data. I would like to thank my best friends, Sahil Mishra and Vasudev Vohra, for their precious time and boundless efforts in helping me run the R code, helping me fix the formatting issues, but more importantly, for constantly criticizing me, teaching me important things like Ctrl + T/W and pushing me to reach my highest potential throughout the past four years.

Thank you to my family for always supporting me and having faith in me. I would like to give a special shout out to my soul mate Sanyukta Baluni for always willing to spend hours next to me studying as I work on my thesis, for all the moral support and for entertaining me through the pain. I am also thankful to all my close friends and my professors for helping me learn and grow over the last four years and molding me in the person I am today. I appreciate all of your support more than I can express.

Chapter 1

INTRODUCTION

Traumatic Brain Injury

Traumatic Brain Injury is one of the leading causes of death and disability in the United States, contributing up to 30% of all injury deaths. TBI causes a dysfunction of the brain due to a blow, bump, penetrating head injury or a jolt to the head. Symptoms include confusion, visual disturbance, memory impairment, auditory problems, personality disorders and more (Mcinnes et al. 2017). These can be temporary or can last a lifetime, interfering with the person's quality of life. The goal of this project is to evaluate the effects of lesion volume and cingulate gyrus' role in the Default Mode Network's functionality on behavior. The hypothesis is that TBI participants with a higher lesion volume and higher Cingulate Gyrus connectivity in the Default Mode Network will correlate with better performance on neuropsychological tests testing associated cognitive functions.

Previous studies have shown the role of volume loss in the Posterior Cingulate, and of lack of coordination between Anterior Cingulate and Prefrontal Cortex can result in cognitive deficits (Johnston, et al., 2007). Further research on how the lesion volume and location affects the various hub networks in the brain and subsequently one's cognitive functioning can better help predict the behavioral long-term outcomes for Traumatic Brain Injury patients through more comprehensive treatment and therapy.

Clinical Indicators in TBI

Once admitted to a hospital, patients are administered a Glasgow Coma Score (GCS) to describe their level of consciousness; the GSC assesses verbal responses, attentiveness, and motor responses on a scale from 3 to 15, with a lower GSC suggesting a greater impairment of consciousness (higher severity).

With advancements in neuroimaging and higher performance computing to conduct brain volumetric analysis, has begun to investigate how certain brain regions are affected by TBI, and how changes in volume of certain subcortical structures affect specific functional outcomes (Lin, Pan, et al., 2017). Although the cingulate gyrus is easily visible in magnetic resonance imaging, it is under-studied with much of the research to date focusing on decreased gray matter volume as it relates to task switching, working memory and executive function deficits. Less research has focused on the cingulate gyrus and its role in the dynamic DMN and how it links to performance on the neuropsychological battery tests (Johnston, et al., 2007).

Increased brain activations are typically observed in survivors of TBI which could represent injury-specific compensatory adaptations also utilized in everyday-life situations (Olsen et al., 2014). Traumatic brain injury (TBI) can produce both focal brain damage and diffuse axonal injury (DAI). Patients often have disabling problems in the domains of attention, memory and executive function. These ‘high-level’ cognitive functions require the integration of information processing across spatially distinct brain regions. Impairments in these domains can result from the effects of DAI on long-distance white matter tracts that connect nodes in distributed brain networks (Iadipaolo, et al., 2017). This is why evaluating the DMN’s interconnectivity alongside behavioral data can provide valuable insight on the link between the cingulate cortex and various cognitive deficits.

Cingulate gyrus and Volume Changes

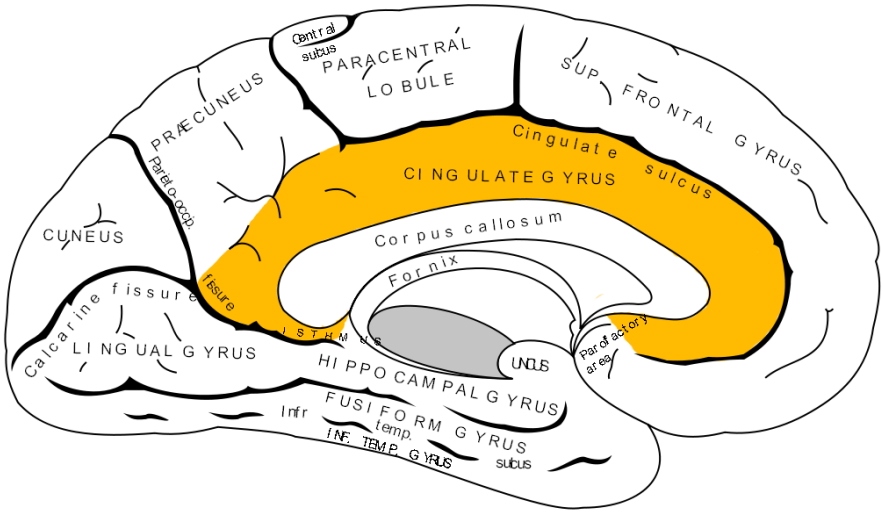

Figure 1. Schema of sagittal view of the location of Cingulate gyrus

Reprinted from "Anterior Cingulate Gyrus" by Brodmann, M. on 11 Nov. 2009 and retrieved from https://, en.wikipedia.org/wiki/Anterior_cingulate_cortex by Wikipedia: The Free Encyclopedia

The cingulate gyrus is the largest and most recently evolved structure of the limbic system. It is located medially in each hemisphere and plays important role in diverse processes such as integration of cognition and emotion, modulation of emotion-related autonomic activity, and emotional responses to pain. But, more importantly it is involved in attention, executive processes, word generation, and memory. Despite the functional significance of the cingulate gyrus in TBI, few studies have examined its effect on behavior. Significant atrophy, primarily in the posterior CG, was found in TBI patients. Degree of atrophy was related to severity of injury (Yount, et al., 2002).

Theories of the regulation of cognition suggest a system with two necessary components: one to implement control and another to monitor performance and signal when adjustments in control are needed (MacDonald et al., 2000). A remarkable aspect of human behavior, and in fact all primates, is the ability to switch rapidly between different tasks. Task switching is commonly

considered to be an example of executive processing, and as such, a large body of psychological research has investigated this behavior in human subjects. Human fMRI studies have reported increased activation of the Prefrontal Cortex (PFC) and Anterior Cingulate Cortex (ACC) on trials following a task switch (Johnston, et al., 2007). In addition, lesion and inactivation studies in monkeys have demonstrated impairments in task switching following both PFC and ACC lesions. Moreover, the ACC (Brodmann's areas 24 and 32) is found to be active when responding to incongruent stimuli, consistent with a role in performance monitoring.

Cognitive control has frequently been operationalized as the provision of top-down support for task-relevant processes. ACC activates when participants are required to hold increasingly long sequences of items in working memory such as in Digit Span test or when two tasks are performed at once, compared to when they are performed one at a time. ACC activity has been more consistently observed when tasks require divided attention, novel or open-ended responses, or the overcoming of a prepotent response. For example, the traditional Stroop task involves naming the ink color of colored words. Sometimes the word and ink color are congruent (the word "RED" printed in red ink) and sometimes they are incongruent (the word "RED" printed in blue ink). Because participants automatically read the word, they are slower to name the color in the incongruent condition, which is also when greater ACC activation is observed. Thus, Stroop task is one of the neuropsychological battery tests included in the current study to assess the degree of involvement of cingulate gyrus in the behavioral or cognitive deficits associate with moderate-to-severe traumatic brain injury (MacDonald et al., 2000).

ACC may be involved in evaluative processes, such as monitoring the occurrence of errors or the presence of response conflict, which occurs when two incompatible responses are both compelling. Individuals who showed the largest Stroop interference effect tended to have

more ACC activation since ACC monitors conflict and larger reaction time interference effects indicate high conflict. ACC was selectively activated during the response period, more for incongruent than for congruent color-naming trials which is consistent with conflict monitoring.

Patients with injuries to this region have shown a great deal of difficulty on the Stroop task, as well as other tasks that require the representation and maintenance of the attentional demands of the task. ACC activity increases when top-down control is low, whether control is reduced from trial to trial or across a number of trials (MacDonald et al., 2000). This study suggests anterior cingulate cortex's role in evaluative processes indicating when control needs to be more strongly engaged and TBI participants who have lesions in these areas have compromised the ability to exhibit control in situations presenting response conflict. In ACC neurons, task selectivity was strongest after the task switch and declined throughout the task block and These results demonstrate that the ACC is recruited when cognitive demands increase and suggest a role for both areas in task maintenance and the implementation of top-down control (Johnston, et al., 2007).

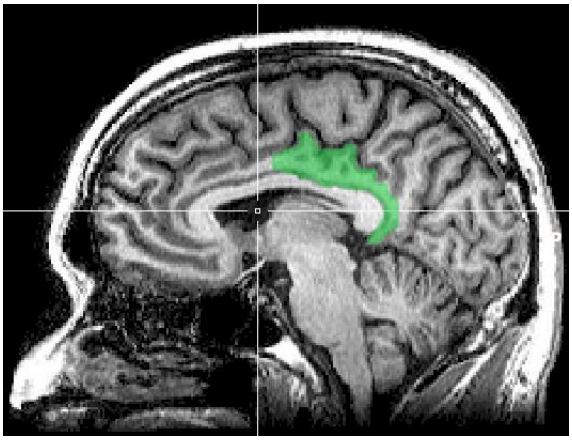

Figure 2. FSL view of a human brain highlighting the sagittal Posterior CingulateT1_MNI.nii.gz

Event-related functional magnetic resonance imaging and a task switching Stroop task indicated that the anterior cingulate cortex (Broadman's areas 24 and 32) was more active when

responding to incongruent stimuli, consistent with a role in performance monitoring (MacDonald et al., 2000).

Default Mode Network and Connectivity

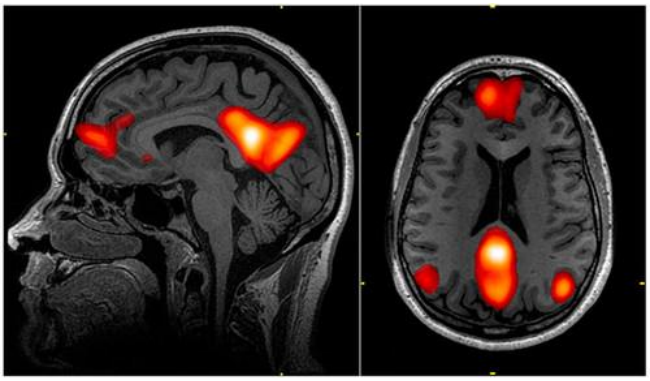

Figure 3. FSL view of the Default Mode Network activity

Reprinted from John Graner, Neuroimaging Department, National Intrepid Center of Excellence, Walter Reed National Military Medical Center, 8901
http://www.frontiersin.org/Neurotrauma/10.3389/fneur.2013.00016/full

The default mode network (DMN) is a set of functionally and structurally connected brain regions that exhibit deactivation during the performance of an externally oriented attention-demanding task and high cerebral blood flow and oxygen consumption during the resting state (Fallon, et al., 2016). It has been largely linked to self-referential thought, autobiographical memory, internal-oriented cognition and mind wandering (Lin et al., 2017). Research has found that DMN topology changes over time and those different patterns are associated with different brain states. Various neuroimaging techniques used for stationary functional connectivity have revealed DMN spatial-temporal properties even during anesthesia, in vegetative patients, during different stages of sleep and thus can be altered due to traumatic brain injuries. Therefore, characterizing the dynamics of brain functional connectivity is thought to be important for gaining a more profound understanding of brain function and behavioral performance.

The DMN regions encompass the posterior cingulate cortex, dorsal medial prefrontal cortex, ventral medial prefrontal cortex, left and right parahippocampal gyri, left and right superior frontal cortices and left and right inferior temporal cortices (Fallon, et al., 2016). The DMN is found to be the most active when the brain is in the resting state and the least active or rather de-active during task performance; it shows a similar spatial architecture across rest and a variety of tasks and clinical studies have shown that reshaping of the DMN topology is associated with neuropsychiatric diseases such as schizophrenia, Alzheimer's disease and alcoholism (Iadipaolo, et al., 2017). Hence, characterizing the adaptive reconfiguration of the DMN and its dynamic topology may provide greater understanding of both the fundamental properties of normative brain cognition, DMN function and pathophysiology of mental illnesses (Lin et al., 2017).

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a widely used clinical diagnostic tool for brain tumors, stroke, infections, hemorrhage, multiple sclerosis, brain injury, and more. MRI uses a powerful magnetic field to produce very detailed pictures of the brain and body. With a 3.0T MRI scanner, very clear images are attained that can be used for volume measurements of different subcortical structures, such as the cingulate gyrus (Magnetic Resonance Imaging, 2017). It is a non-invasive imaging technology that produces three dimensional detailed anatomical images without the use of damaging radiation. It is based on sophisticated technology that excites and detects the change in the direction of the rotational axis of protons found in the water that makes up living tissues.

To obtain an MRI image, a patient is placed inside a large magnet and must remain very still during the imaging process in order not to blur the image. Contrast agents may be given to a patient intravenously before or during the MRI to increase the speed at which protons realign with the magnetic field and to brighten up the image. MRI scanners are particularly well suited to image the non-bony parts or soft tissues of the body (Magnetic Resonance Imaging, 2017). They differ from computed tomography (CT), in that they do not use the damaging ionizing radiation or X-rays. The brain, spinal cord and nerves, as well as muscles, ligaments, and tendons are seen much more clearly with MRI than with regular X-rays or with CT.

In the brain, MRI can differentiate between white matter and gray matter and can also be used to diagnose aneurysms and tumors. Because MRI does not use x-rays or other radiation, it is the imaging modality of choice when frequent imaging is required for diagnosis or therapy, especially in the brain. However, MRI is more expensive than x-ray imaging or CT scanning. One kind of specialized MRI is functional Magnetic Resonance Imaging (fMRI.) This is used to observe brain structures and determine which areas of the brain "activate" (consume more oxygen) during various cognitive tasks or where the blood is flowing. It is used to advance the understanding of brain organization and offers a potential new standard for assessing neurological status and neurosurgical risk.

Goals of the Current Study

Decreased total cingulate gyrus volume and higher total lesion volume could explain some of the cognitive deficits following moderate-severe Traumatic Brain Injury. If TBI subjects have smaller cingulate gyrus volumes and lower VSAT, Digit Span and Stroop scores, it can add to our understanding of the role of the cingulate gyrus as a part of the Default Mode Network and

its contribution to the increased cognitive deficits of moderate to severe TBI patients. While different parts of the cingulate may be responsible for different deficits such as cognitive control while task switching and altered DMN connectivity, the analysis was conducted for the structure as a whole.

Current Study

Hypothesis 1: TBI subjects will have a lower overall cingulate gyrus (including both anterior and posterior) and gray matter volume compared to HC subjects.

Hypothesis 2: Total lesion volume will have a negative correlation with scores on Neuropsychological battery tests related to attention and task switching when comparing TBI to HC subjects.

Hypothesis 3: Cingulate Gyrus plays a major role in the DMN network and greater connectivity among the cingulate cortex ROIs within the DMN in TBI patients will be associated with less cognitive impairment.

Chapter 2

METHODS

Subjects

The study includes 23 individuals between the ages of 19 and 60, including 13 individuals who suffered moderate- severe TBIs and 12 healthy controls (HC) comparable in education and age. All of the TBI participants were diagnosed and given a Glasgow Coma Scale (GCS) score to quantify the injury severity. Glasgow Coma Scale is a neurological scale used to gauge an objective and reliable measure of one's level of consciousness at initial and during subsequent assessments following a traumatic brain injury. A GCS score of 9-12 is considered moderate TBI and a score between 3 and 8 is classified as a result of severe TBI.

Table 1. Healthy Control and Traumatic Brain Injury Subject Group Demographic means and standard deviation (SD)

	HC (mean, SD)	TBI (mean, SD)
	N= 17	N= 16
Gender	7 M, 5 F	9 M, 7 F
Age (years)	36.78, 12.53	31.30, 13.04
Education (years)	13.46, 1.39	13.25, 1.89
GCS	N/A	5.92, 3.60

MRI Data Acquisition and Analysis in FSL

All subjects were scanned on a Siemens Magnetom trio 3T scanner in the Imaging Center at the Pennsylvania State University in University Park, PA, or in the Department of Radiology at Hershey Medical Center in Hershey, PA, or on a Philips Achieva 3T scanner in the Department of Radiology at Hershey Medical Center in Hershey, PA. T1-

Weighted Magnetization-Prepared Rapid Acquisition with Gradient Echo Structural data were acquired with 1 mm × 1 mm × 1 mm voxels, a repetition time (TR) of 2,300 ms, and an echo time (TE) of 2.98 ms, and slices were collected interleaved. In the Resting State Scan, all participants were presented with the same stimulus, were instructed to fixate on the white cross on the center of the screen and were reminded not to fall asleep. The 34–35 slices collected were interleaved with 3 mm × 3 mm × 4 mm voxels and acquired with a TR of 2,000 ms and an TE of 30 ms (Hillary et al., 2014).

Anatomical Analysis with FreeSurfer

The software FreeSurfer was used for anatomical and volumetric analysis of specific structures of the brain, namely the Anterior, Mid-Anterior, Central, Mid-Posterior and Posterior parts of the Cingulate Cortex. Freesurfer analysis is performed on MP-RAGE images to create the gray-white matter surfaces. Freesurfer segments gray-white matter into different cortical regions based on sulci and gyri pattern and also segments major subcortical regions in the brain (Zhou et al., 2012). Freesurfer parcellates the brain into left and right hemispheres, and further into other structures such as the Left Hippocampus, Right Putamen, Left Inferior Lateral Ventricle and many others. It generates volumetric data for each of the structures, total gray and white matter volume as well as cortical thickness. All cortical and subcortical regions of interest (ROIs) are then transformed to the diffusion space using FSL's Flirt package. The processing stream comprises of T1 Weighted Input, Skull Stripping, Volumetric Labeling, Intensity

Normalization, White Matter Segmentation, Surface Atlas Registration, Surface Extraction, Gyral Labeling which extracts Statistical data.

Lesional Data Analysis using 264 POWERs ROI

Each individual's resting state data were slice-timed corrected, realigned, normalized to a standard T1 template from the Montreal Neurological Institute in order to minimize signal-to-noise ratio. SPM8 was used to process the data, and subjects with greater than 25% volumes requiring interpolation due to motion were discarded from analyses. As a result, 3 of the original 16 eligible subjects with TBI were discarded due to motion during rest (Bernier, et al., 2017).

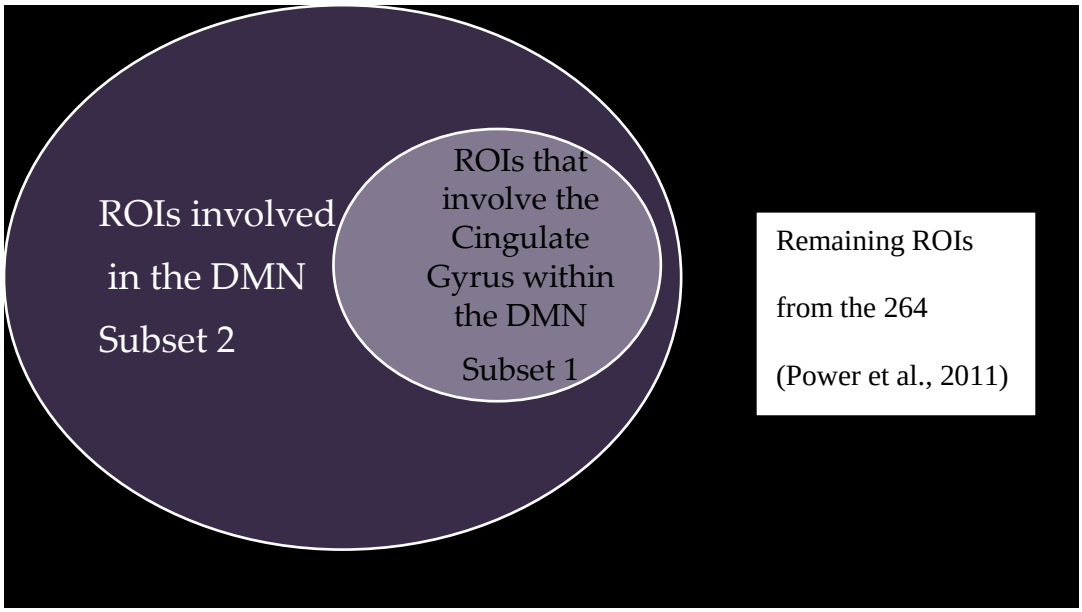

Figure 4. Venn Diagram representing the 264 POWERs ROIs segmentation into the three subsets for analysis.

ROI Selection Power's 264 functionally defined atlas was used to define ROIs (Power et al., 2011). Whole brain connectivity was examined across these 264 ROIs using graph theoretical methods. Power and colleagues' functional labels (Power et al.,

2011) for each ROI were then used to group these ROIs into three functional networks including the default mode network ROIs that mainly comprised of the cingulate cortex, DMN ROIs that did not comprise of the cingulate cortex and the remaining ROIs as one large group. The primary goal of grouping these ROIs into networks was to be able to determine whether connectivity changes in the DMN can be observed between individuals with TBI and linked to behavior.

Similar to other work in this laboratory, graph theory was used to examine whole brain connectivity and determine patterns of response. Power ROIs (34) were correlated with each other to form an adjacency matrix using a code written in R [R.3.1.1 (42)] [e.g., N ROIs will produce N*(N − 1)/2 undirected connections]. Out of these N*(N − 1)/2 correlation values only those that survived FDR test at 0.05 were chosen and the remaining connections were set to 0. To test our hypothesis, between and within network strength was calculated for the DMN network during rest for only positive connectivity (Bernier, et al., 2017). In order to assess whether functional connectivity differences were associated with better or worse recovery, several metrics, were correlated with cognitive functioning using two tailed T-statistical tests.

Neuropsychological Testing

The Visual Search and Attention Test (VSAT), Digit Span, Trails making A and B, and Stroop task were administered to each subject following the MRI scan. The neuropsychology battery tests were double scored for both the TBI and HC subjects and recorded from which the means and standard deviations were calculated (Table 4) and correlations were made. Tasks involving response conflict and error processing operate

within a rapid adaptive temporal scale and thus, Stroop Color task and VSAT fall under this category (Olsen et al., 2014).

The VSAT consists of four visual cancellation tasks that require the respondent to cross out letters and symbols that are identical to a target. It yields an overall attention score. The Stroop Color and Word Test (SCWT) is extensively used to assess the ability to inhibit cognitive interference that occurs when the processing of a specific stimulus feature impedes the simultaneous processing of a second stimulus attribute, well-known as the Stroop Effect. During Digit Span test, subjects are read a sequence of numbers and asked to repeat the same sequence back to the examiner in order (forward span) or in reverse order (backward span). Lastly, Trails making test assesses how long one takes to join the dots in a sensible manner and how many errors are made during the process.

Chapter 3

Results

Testing Hypothesis 1, an independent-sample-t-test was completed to compare the total gray matter, white matter and cingulate gyri subparts' volume in TBI and HC participants.

Table 2. Cingulate Gyri, Gray and White Matter Volumes for Healthy Control and Traumatic Brain Injury Subject Group Demographic means and standard deviation (SD)

	TBI (mean)	HC (mean)	T statistic
Total Gray Matter Volume	624814.66	632022.65	0.181
Total White Matter Volume	457503.95	471516.70	0.746
Post Dorsal Cingulate Gyri**	2.831	2.849	0.030
Post Ventral Cingulate Gyri and Sulci**	2.263	2.328	0.003
Mid-post Dorsal Cingulate Gyri and Sulci**	2.470	2.520	0.047

There was not a significant difference in the total gray or white matter volumes for TBI participants. However, there was a statistically significant decrease in gray matter volume from the right hemisphere of the post-dorsal gyri, post-ventral gyri and sulci and mid-post dorsal gyri and sulci following traumatic brain injury.

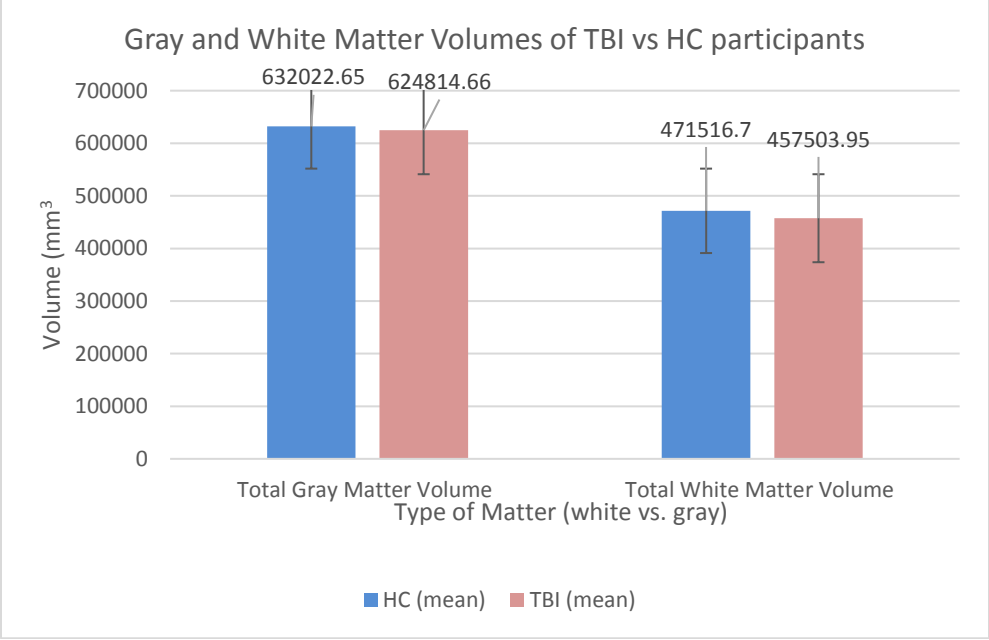

Figure 5. White and Gray Matter Volume Means for HC and TBI

Volumetric analysis using Freesurfer software was conducted to yield the following data, parcellating the cingulate cortex into four main subparts, Posterior, Mid Posterior, Central and Anterior. As illustrated in Table 3, only CC Posterior held statistically significant difference between the average volume of the TBI sample and HC group.

Table 3. Comparison of the average volumes of the subparts of the Cingulate Cortex between HC and TBI participants

Structure Name:	Average TBI volume (mm^3)	Average HC volume (mm^3)	T-statistic
CC Posterior**	110.52	113.80	0.0101
CC Mid Posterior	105.72	106.09	0.6167
CC Central	105.86	105.80	0.9363
CC Mid Anterior	105.89	106.32	0.6146

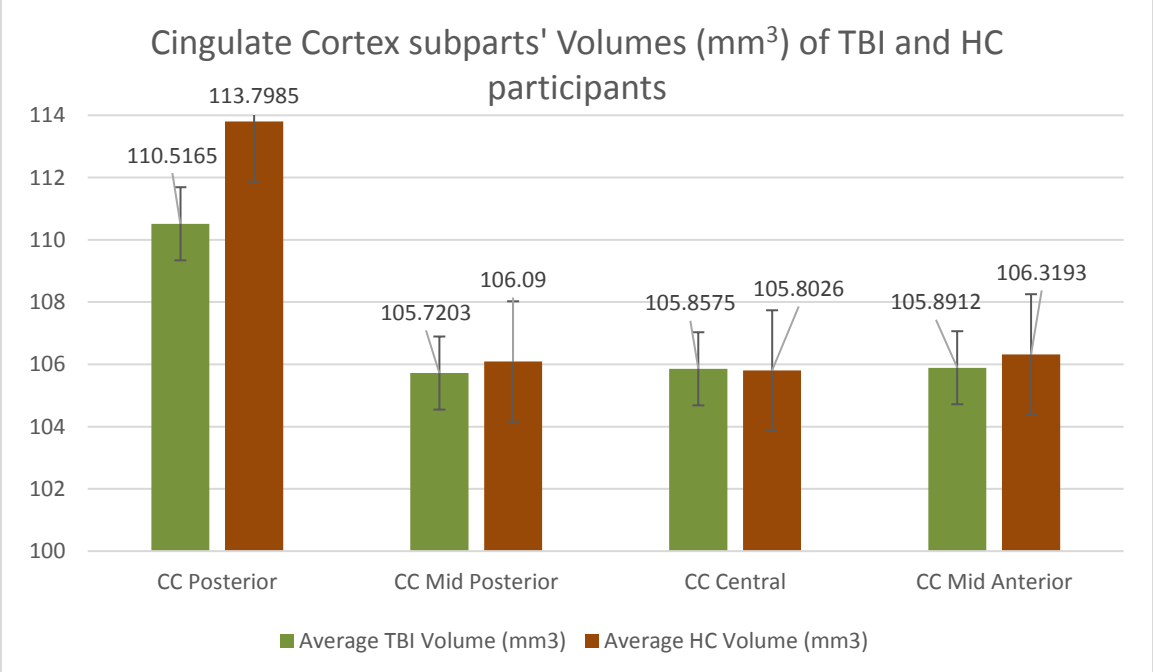

Figure 6. Volume Means for subparts of the Cingulate Cortex for HC and TBI

Of all the various components of the cingulate cortex analyzed as shown in Table 3 and Figure 6, only the posterior cingulate cortex indicated statistically significant reduction in volume among TBI sample as compared to the HC sample. However, mid-posterior and anterior cingulate cortex volumes were found to be slightly higher in healthy controls compared to TBI, just not statistically significant.

Testing Hypothesis 2, an independent-sample-t-test comparing VSAT, Digit Span, Trails making A and B, and Stroop task scores in TBI and HC participants was conducted. Next, the scores of TBI participants were correlated with their total lesion volume and depicted in terms of bar graphs and scatter plots.

Table 4. Cingulate gyrus Volumes and Neuropsychology Battery Tests Mean Scores and Standard Deviations (SD) for TBI and HC Groups

	HC (mean, SD)	TBI (mean, SD)	T statistic
Total Lesion Volume (voxels)	0 (theoretically)	17698.08, 14478.84	N/A
VSAT Letter	59.50, 9.00	57.83, 13.56	0.669
VSAT Symbol	59.00, 11.01	58.88, 13.69	0.976
VSAT Total	118.50, 18.32	116.71, 25.70	0.811
Stroop Color Time	58.31, 12.52	69.74, 22.00	0.069
Stroop Color Total	111.75, 1.00	109.91 , 6.28	0.255
Stroop CW Time	110.50, 10.60	112.70 , 13.51	0.590
Stroop CW Total	104.00, 12.08	94.09, 23.35	0.128
Digit Span Forward	10.88, 2.03	10.54, 2.27	0.638
Digit Span Backward	6.56, 2.03	6.92, 2.28	0.619
Trails making A time	26.38, 20.90	31.43, 19.53	0.444

Trails making A errors	0.25, 0.45	0.35, 0.57	0.571
Trails making B time	57.94, 27.16	65.67, 34.97	0.460
Trails making B errors	0.25, 0.58	0.38, 0.71	0.562

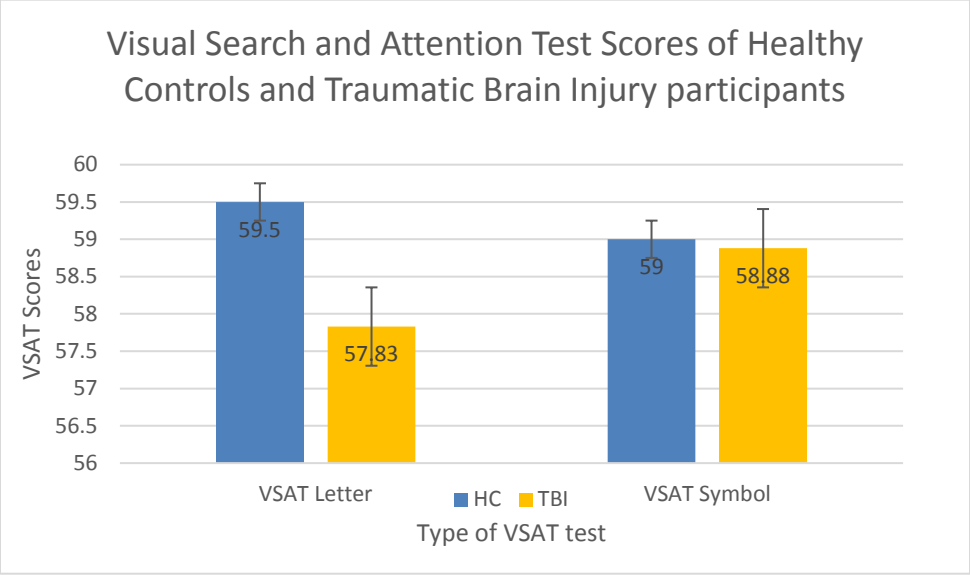

Figure 7. Mean VSAT Scores for HC and TBI

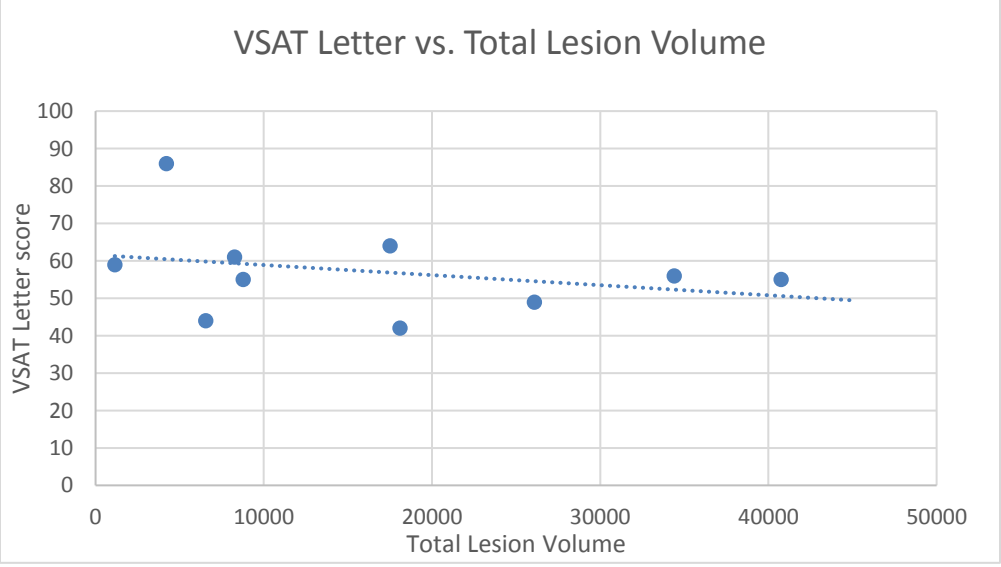

Figure 8. Mean VSAT Scores correlated with Lesion Volume in TBI participants

As illustrated in Figure 7, the mean VSAT scores were lower for the TBI sample with statistically significance for the VSAT Letter test in particular. Furthermore, as shown in Figure 8, correlating the VSAT letter scores with total lesion volumes of TBI participants yielded a negative correlation between the two variables.

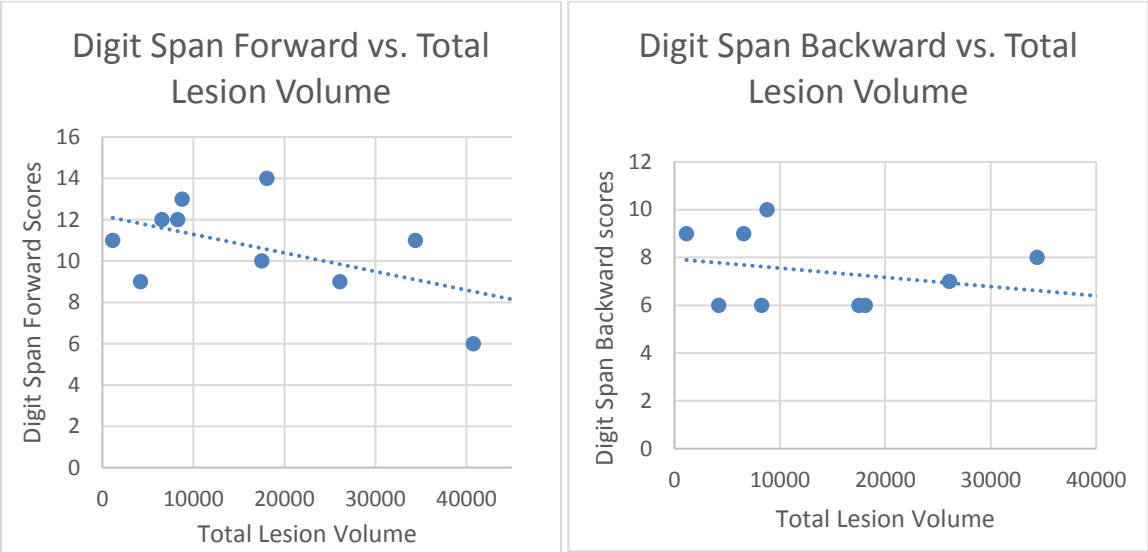

Figure 9 a and b. Digit Span Forward and Backward Scores correlated with Lesion Volume in TBI participants, respectively

The difference in scores for Digit span forward and backward between TBI and HC was found to be close to negligible However, in Figures 9a and 9b, substantial negative correlation is observed between total lesion volume and performance on Digit Span Forward and Backward.

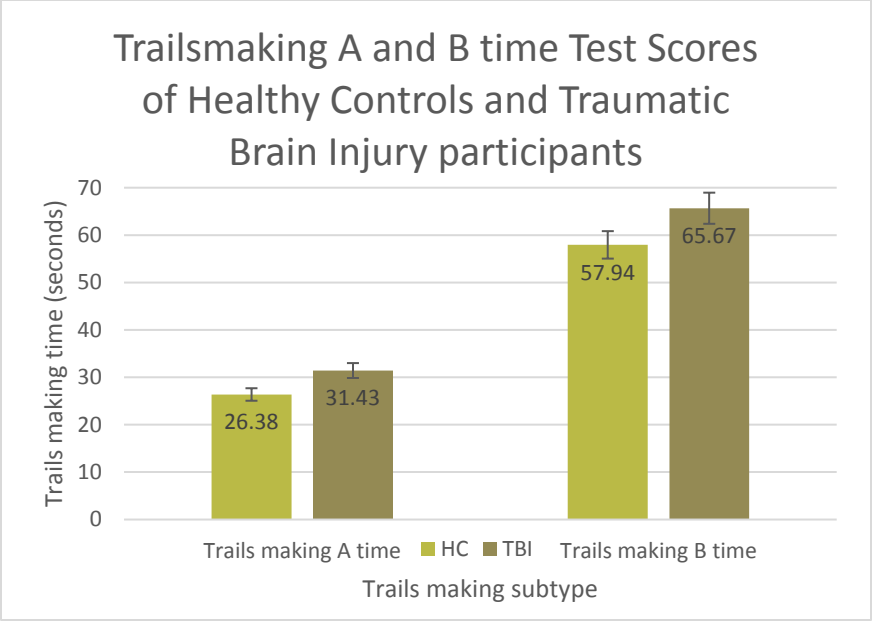

Figure 10. Trails making A and B times for HC and TBI

Figure 10 demonstrates the difference in response/completion times on Trails making tests A and B between TBI and HC groups such that TBI take longer on both tests on average. No reliable correlation was detected between total lesion volume and Trails. This could indicate that not all cognitive deficits have to be related to lesion volume.

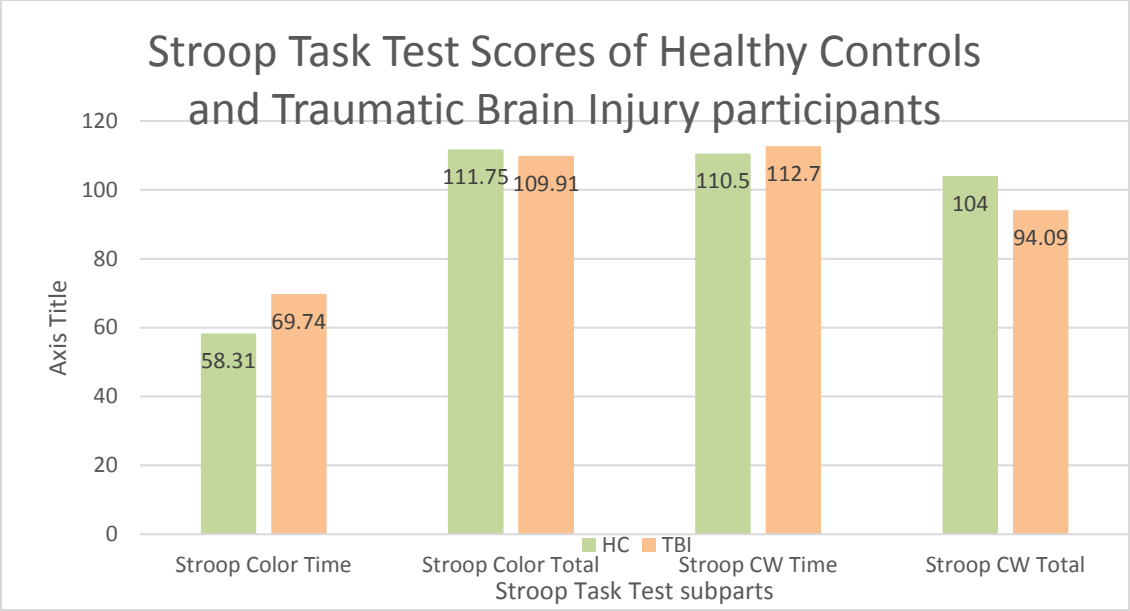

Figure 11. Stroop Task Scores for HC and TBI

As shown above in Figure 11, TBI sample scored slightly lower in both the Stroop color total and Stroop Color Word total compared to HC and took longer as well. No logical deductions could be made the correlation between Stroop test scores and lesion volume among TBI.

Testing Hypothesis 3, subsystem connectivity code was run in R and the level of interconnectivity among the three ROI subgroups, namely Cingulate Gyri of the DMN, rest of DMN and the rest of the functional ROIs are shown in Table 5 below.

Table 5. Sub-connectivity mean data from POWER 264 ROIs for TBI and HC Groups

ROI groups connected with one another	Mean Degree strength
Among Cingulate gyri ROIs (1_1)	12.32
Cingulate gyri ROIs with rest of the DMN ROIs (1_2)	70.44
Cingulate Gyri ROIs with the rest of the ROIs outside the DMN (1_3)	337.67
Among the DMN ROIs (2_2)	94.00
DMN ROIs with the rest of the ROIs outside the DMN (2_3)	931.98
Among the ROIs outside of the DMN (3_3)	2206.44

*__Note__: Cingulate Gyri ROIs (subset 1) include only the ROIs located in the cingulate gyri and involved in the Default Mode Network. ROIs involved in the DMN excluding the cingulate gyrus constitute subset 2 and the rest of the ROIs outside of the DMN collectively constitute subset 3.

The connectivity data seems logical taking the size and number of ROIs into account. Without comparison with HC group, inferences about how TBI affected the DMN interconnectivity cannot be drawn. However, the interconnectivity values for each subject can be correlated with their behavioral data to observe the effect of cingulate cortex's connections on working memory and attention.

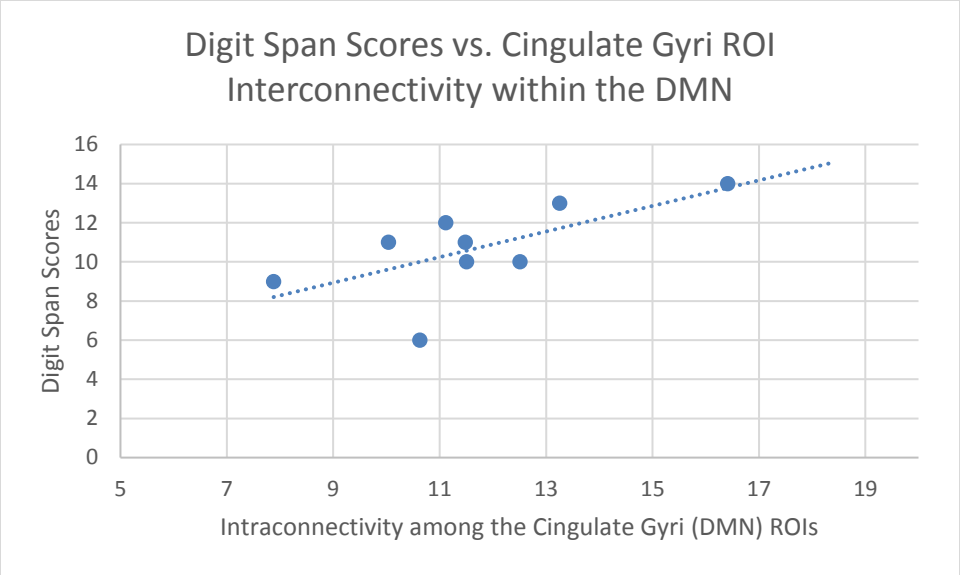

Figure 12. Correlation between Digit Span performance scores and level of interconnectivity among the Cingulate gyri ROIs involved in the DMN

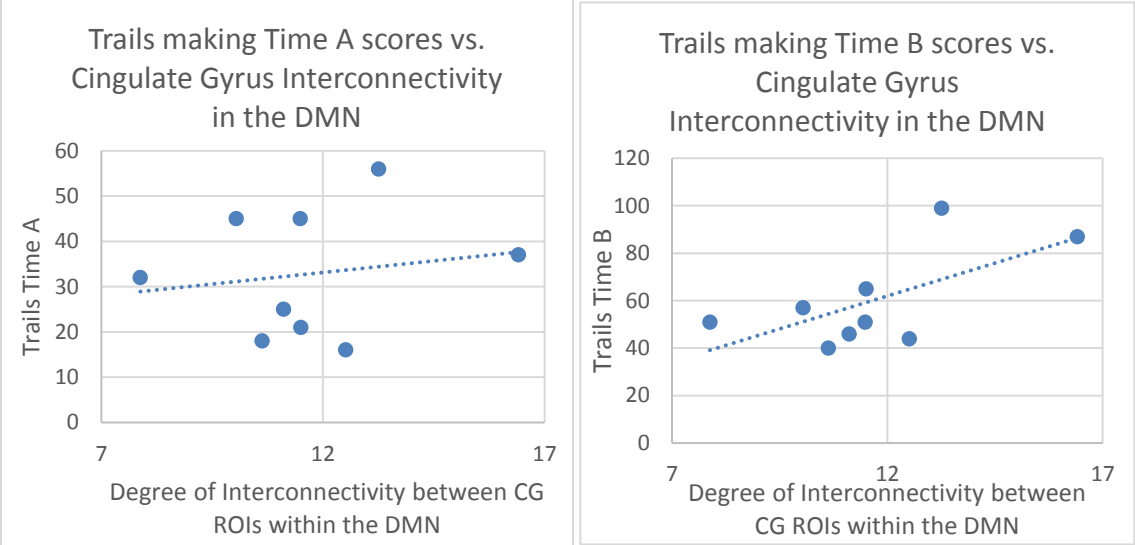

Figure 13 a and b. Correlation between Trails making Time A and B performance scores and level of interconnectivity among the Cingulate gyri ROIs involved in the DMN

According to the correlation depicted in Figures 12, 13a and 13b, between Digit Span scores, Trails making time A and B and the degree of interconnectivity among the DMN ROIs constituting of the cingulate gyrus, it seems that the greater activity and

connectedness in the cingulate gyrus is associated with better performance on tasks involving working memory and executive function such as in Digit Span and Trails making tests, in patients who have suffered moderate-to-severe Traumatic Brain Injury.

Chapter 4

DISCUSSION

Primary Findings

The goal of the current study was to determine cingulate gyrus volume interacts with total lesion volume after TBI to predict poor performance on neuropsychological battery tests. It was also a goal to evaluate the role cingulate cortex ROIs play in the DMN and its correlation with behavior on Digit Span and Stroop task scores. There were three major hypotheses: TBI would result in decreased cingulate gyrus volumes, higher total lesion volumes would correlate with greater decline in cognitive performance and that greater interconnectivity in the cingulate gyrus involved in the DMN would result in better neuropsychological performance. The primary findings generally support the hypotheses; findings outlined below.

A statistically significant decrease was found in the posterior cingulate cortex volume (post-dorsal gyri, post-ventral gyri and sulci and mid-post dorsal gyri and sulci) in TBI participants compared to their healthy controls (HC). No significant difference was found in the total white or gray matter volume between the TBI and HC. As only TBI participants were assumed to have lesions and thus lesion volumes, higher total lesion volumes correlated with poorer neuropsychological performance among the TBI sample but no statistical significance was established. This is found to be consistent with the current literature findings that lesion volume does not explain or constitute as the source of all the cognitive and behavioral deficits that result following Traumatic Brain Injuries.

Overall, TBI sample had lower scores and slower reaction times across the four neuropsychological battery tests used for the most part (although only the difference in VSAT letter scores was found to be statistically significant) compared to the healthy controls. The lack of statistical power stems from the relatively small sample size. And the discrepancy in the scores between the two samples is justified as the tests involve functions such as planning, exercising the working memory, switching tasks and managing response conflicts, which are often compromised in TBI patients.

Lastly, greater interconnectivity among the cingulate cortex regions of interest (ROI) within the DMN was associated with better performance on Digit Span and Trails Making tests among the TBI sample. The other two tests, Stroop and VSAT, were missing data on some of the TBI participants involved in the DMN analysis and hence had to be discarded.

The current study has added to and reinforced our understanding of Traumatic Brain Injury through findings that suggest an association between loss of gray matter volume of the posterior cingulate cortex, lowered connectivity among the cingulate ROIs within the DMN and cognitive deficits in terms of executive function. Studying the anatomical and functional dynamics of certain brain structures post injury can help predict cognitive outcomes and enhance treatment approaches for Traumatic Brain Injury patients.

Limitations

This study was largely limited by the small sample size. Some of the participant files had trouble extracting data when the total lesion volume code and the sub-connectivity R code were being run which reduced the original participant pool.

Moreover, only data from subjects with VSAT, Digit Span, Trail making and Stroop test scores could be used in this study, which limited the TBI group. The smaller sample could contribute to a lack of statistical power for detecting relationships between lesion volume and neurological performance and/or between the DMN connectivity and test performance. But, consistent with the literature, lesion volume shows modest correlation with neuropsychological performance (Yuan et al., 2017). This indicates that lesion volume independently and out of context does not fully elucidate the cognitive and behavioral deficits of Traumatic Brain Injury patients.

A larger sample could provide greater sensitivity for detecting the relationship between cingulate gyrus and executive dysfunction in the TBI population. However, considering the wide spectrum of functions different regions of the cingulate contribute to and the different structures they work in conjunction with such as the prefrontal cortex, it is hard to characterize or correlate the behavioral deficits directly to the overall decrease in its volume. Also, the inherently complex nature of network analysis may give rise to confounds (connections from other regions) affecting the role of cingulate gyrus (anterior and posterior) in the DMN. Moreover, it is difficult to discern whether the intra-connectivity strength results from the sheer number of connections due to the wider area encompassed by the regions or from higher activity between the regions.

Future Studies

Due to the results of the current study, future research needs to investigate the role of the cingulate gyrus more closely by dividing it into anterior and posterior and witnessing which functions are more severed when the anterior portion of the gyrus is

atrophied versus the posterior. Future studies should parcellate gray and white matter volumes more precisely to verify if there are any significant discrepancies between the TBI and HC population.

The current study suggests the DMN and anterior cingulate cortex are involved in task switching and planning, and a study with a larger sample would be able to further understand the effects of TBI on the overall executive functioning by assessing the activity of the cingulate subparts in combination with structures such as the prefrontal cortex and subcortical regions of the limbic system such as hippocampus and amygdala.

APPENDIX A

1_POWERS264_functional_network.R

```
#Author: Arnab Roy, Ph.D. Binghamton University, NY-13902
#Post-Doctoral Researcher, Penn. State University, State College-16801
#Date: 24 July 2015

#-----------------------------------------------------------------------------------------------------------------

#Objective: The objective of this code is to make connectivity network using powers 264 ROI

#*****************************************************************************************************************


#xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

corr_matrix <- function(sig_file,op_name,p_threshold) #corr_matrix.begins
{

library("lsr")

 cormat <- correlate(sig_file,corr.method="pearson",p.adjust.method="fdr")
 cormat$correlation[is.na(cormat$correlation)] <- 0 #for NA cases set correlation to 0
 cormat$p.value[is.na(cormat$p.value)] <- 10000 #For NA cases set the p-value to very large number

 #The NA cases will anyways get excluded as p-value will be large, we will only choose for p-value < 0.05

 #-------------------------------------------------------------------------------

 #Save only the edges that qualify the p-threshold

 op_table <- vector('list',(nrow(cormat$correlation)*nrow(cormat$correlation)+1))
 op_table <- list(c('vox_col_id_A','vox_col_id_B','weight','p_value')) #this is the file header

 counter <- 1 #initialize the counter to 1

 for(c4 in 1:(nrow(cormat$correlation)-1)) #For.c4.begins
   {
    for(c5 in (c4+1):ncol(cormat$correlation)) #For.c5.begins
```

```
        {
         if(cormat$p.value[c4,c5] < p_threshold)
          {
           vox_col_id_a1 <- c4
           vox_col_id_a2 <- c5

           op_table[[counter+1]] <-
c(vox_col_id_a1,vox_col_id_a2,cormat$correlation[c4,c5],cormat$p.value[c4,c5])

           counter <- counter + 1

           }

        } #For.c5.ends

     } #For.c4.ends


 #-----------------------------------------------------------------------------------

 file.create(op_name)

 for(filecounter in 1:counter)
    {
     write(c(unlist(op_table[[filecounter]])),file=op_name,append=TRUE,ncol=100)
    }

} #corr_matrix.begins

#xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxxxxxx


F_powers264_functional_network <-
function(IP_f_path,IP_s_path,IP_subject_folder,IP_c_file,IP_bm_file,IP_powers_coordin
ate,IP_output_file_tag,IP_p_val_threshold)#the main funtion begins
{

#Load the fmri library

library("fmri")

#-------------------------------------------------------------------------------------------------------

#c1 controls the subjects
for(c1 in 1:length(IP_subject_folder)) #for.c1.begins
   {
    #the functional nifti file
    f_nifti_file_name <- paste(IP_f_path,IP_subject_folder[c1],"/",IP_c_file,sep="")
```

```
    print(f_nifti_file_name)
    x <- read.NIFTI(f_nifti_file_name, level = 0.75,setmask=FALSE)
    BOLD_data <- extract.data(x, what = "data")

    #-------------------------------------------------------------------------------------------------------

    #the structural nifti file
    s_nifti_file_name <- paste(IP_s_path,IP_subject_folder[c1],"/",IP_bm_file[c1],sep="")
    print(s_nifti_file_name)
    mask <- read.NIFTI(s_nifti_file_name, level = 0.75,setmask=FALSE)
    mask_data <- extract.data(mask, what = "data")

    #-------------------------------------------------------------------------------------------------------

    #if mask dimensions do not match the data dimension exit

    if(x$dim[1] != mask$dim[1] && x$dim[2]  != mask$dim[2] && x$dim[3]  !=
mask$dim[3])
      {system("echo \"mask dimensions not equal to data dimensions\" >> error ");quit();}


    print(c(x$dim[1],mask$dim[1],x$dim[2],mask$dim[2],x$dim[3],mask$dim[3]))

    #-------------------------------------------------------------------------------------------------------

    #first read powers coordinate file

    p_cood <- read.table(IP_powers_coordinate,header=TRUE)

    #define empty array for storing the ROI signals
    signal_data <- vector('list',264)  #PARA

    #now iterate through all 264 powers coordinates and find out which voxels belong to
each coordinate.
    for(c2 in 1:264)#for.c2.begins  #PARA
      {

        #find the voxel closest to this power's coordinate
        vox_x_cood <- round((91 - p_cood$x[c2])/3)
        vox_y_cood <- round((107 + p_cood$y[c2])/3)
        vox_z_cood <- round((89 + p_cood$z[c2])/3)

        #print(c(p_cood$x[c2],p_cood$y[c2],p_cood$z[c2],paste(p_cood$system[c2])))
        #print(c(p_cood$x[c2],p_cood$y[c2],p_cood$z[c2],vox_x_cood,vox_y_cood,vox_z_
cood))


        #now check all 27 voxels around it and see which ones belong to grey matter.
        #and then create an averge signal using these voxels
```

```
      voxel_count <- 0
      signal <- rep(0,145)  #PARA
      for(c3x in -2:2)#for.c3x.begins
        {
         for(c3y in -2:2)#for.c3y.begins
           {
            for(c3z in -2:2)#for.c3z.begins
              {

                if(mask_data[vox_x_cood+c3x,vox_y_cood+c3y,vox_z_cood+c3z,1] >
153)
                  {
                   voxel_count <- voxel_count + 1
                   signal <- signal +
BOLD_data[vox_x_cood+c3x,vox_y_cood+c3y,vox_z_cood+c3z,1:145]
                  }

              }#for.c3z.ends
           }#for.c3y.ends
        }#for.c3x.ends

      #print(c(c2,voxel_count))


      #store the average signal
      if(voxel_count == 0)
        {signal_data[[c2]] <- rep(0,145)}  #PARA
      else
        {signal_data[[c2]] <- signal/voxel_count}

     }#for.c2.ends

   #-------------------------------------------------------------------------------------------------------

   #now create the correlation matrix
   #please note that the signal for each ROI is store across columns.
   #that is col-1 is time-1, col-2 is time-2, and so on.
   #for correlation to work properly we need to transpose this matrix

   signal_data_transposed <- t(do.call(rbind,signal_data))

   corr_matrix(signal_data_transposed,paste(IP_output_file_tag,"_",IP_subject_folder[c
1],sep=""),IP_p_val_threshold)
   print("Correlation matrix created.")


  }#for.c1.ends
```

```
#-------------------------------------------------------------------------------------------------------

}#the main funtion ends

#-------------------------------------------------------------------------------------------------------
#-------------------------------------------------------------------------------------------------------
#-------------------------------------------------------------------------------------------------------
#-------------------------------------------------------------------------------------------------------
#-------------------------------------------------------------------------------------------------------


functional_path <-
'/gpfs/group/nad12/legacy/fgh3/Users/Emily/final_masters_data/new_TBI/REST_DATA/
REST/'

structural_path <-
'/gpfs/group/nad12/legacy/fgh3/Users/Emily/final_masters_data/new_TBI/REST_DATA/
T1/'

subject_folder <- c('LBRITNE.UP.1.013', 'LBRITNE.UP.1.014', 'LBRITNE.UP.1.015',
'LONG.HMC.1.021.TIME3', 'LONG.HMC.1.022.TIME3', 'LONG.HMC.1.024.TIME3',
'LONG.HMC.1.026.TIME3', 'LONG.HMC.1.027.TIME3', 'LONG.HMC.1.030.TIME3',
'LONG.HMC.1.032.TIME3', 'LONG.HMC.1.033.TIME3', 'LONG.HMC.1.036.TIME3',
'LONG.UP.1.038.TIME3', 'LONG.UP.1.039.TIME3')


conn_output_file<-
'conn_project1_new/results/preprocessing/niftiDATA_Subject001_Condition000.nii'  #P
ARA

binary_mask_file <- c('resample_wc1cr_coT1MPRageSagittal.nii',
'resample_wc1cr_coT1MPRageSagittal.nii', 'resample_wc1cr_coT1MPRageSagittal.nii',
'resample_wc1cr_co20100603_175443T1MPRAGEIsos007a1001.nii',
'resample_wc1cr_co20100610_170305T1MPRAGEIsos007a1001.nii',
'resample_wc1cr_cos012a1001.nii', 'resample_wc1cr_coT1MPRAGEIsos002a1001.nii',
'resample_wc1cr_co20120222_180702T1MPRAGEIsos003a1001A.nii',
'resample_wc1cr_co20120620_171657T1MPRAGEIsos002a1001A.nii',
'resample_wc1cr_co20121016_161545T1MPRAGEIsos002a1001.nii',
'resample_wc1cr_co20121016_161545T1MPRAGEIsos002a1001.nii',
'resample_wc1cr_coT1MPRAGEIsos002a1001.nii',
'resample_wc1cr_coT1MPRageSagittal.nii', 'resample_wc1cr_coT1MPRageSagittal.nii')


powers_coordinate <- './powers_MNI_coordinate.dat'  #PARA

output_file_tag <- 'powers_264_conmat_TBI1'  #PARA
```

```
p_val_threshold <- 0.05 #PARA

F_powers264_functional_network(functional_path,structural_path,subject_folder,conn_
output_file,binary_mask_file,powers_coordinate,output_file_tag,p_val_threshold)
```

APPENDIX B

CC_and_Pathlength_igraph_code.R

```
#Author: Arnab Roy
#Department of Psychology, PSU
#Date: 29-Jan-2016

      #apl <- average.path.length(g1,unconnected = TRUE)
      #please note these are unweighted transitivities
      #tl <- transitivity(g1,type="localaverage")
      #tg <- transitivity(g1,type="global")
      #tw <- mean(transitivity(g1,type="weighted"))
      #t1_apl <- c(t1_apl,apl)
      #t1_tl <- c(t1_tl,tl)
      #t1_tg <- c(t1_tg,tg)
      #t1_tw <- c(t1_tw,tw)
      #print(c(apl,tl,tg,tw))

#The following code find the degree of each node in a network and saves it to a file

#---------------------------------------

function_graph_metrics <- function(path,FL1)
{

library("igraph")


  #t1_apl <- c()
  #t1_tl <- c()
  #t1_tg <- c()
  #t1_tw <- c()

  for(c1 in 1:length(FL1)) #for.c2a.begins
    {

      #read the tbi file
      g <- read.table(paste(path,FL1[c1],sep=""),header=TRUE)
      g1 <- graph.data.frame(abs(g),directed=FALSE)

      write(c("ROI","Degree"),file=paste("Degree_",FL1[c1],sep=""),ncol=2,append=FALS
E)
      node_degree <- degree(g1,v=V(g1))
      nodes <- unlist(V(g1)$name)
      print(nodes)
      for(c2 in 1:length(node_degree))
        {
```

```
          #print(nodes[c2])
          write(paste(nodes[c2],node_degree[c2],sep="
"),file=paste("Degree_",FL1[c1],sep=""),ncol=2,append=TRUE)
         }

       #print(length(V(g1)))

      }


   print("--------------------------------")

}



#---------------------------------------------------------------------

path1 <-
"/gpfs/group/nad12/legacy/fgh3/Users/Emily/final_masters_data/new_TBI/Analysis/RES
T/1_createnetwork/positive/"
#PARA

file_list1 <- c('powers_264_conmat_TBI1_LBRITNE.UP.1.013',
'powers_264_conmat_TBI1_LBRITNE.UP.1.014',
'powers_264_conmat_TBI1_LBRITNE.UP.1.014',
'powers_264_conmat_TBI1_LBRITNE.UP.1.015',
'powers_264_conmat_TBI1_LONG.HMC.1.021.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.022.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.024.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.026.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.027.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.030.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.032.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.033.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.036.TIME3',
'powers_264_conmat_TBI1_LONG.UP.1.038.TIME3',
'powers_264_conmat_TBI1_LONG.UP.1.039.TIME3')


function_graph_metrics(path1,file_list1)
```

APPENDIX C

Subsystem_analysis.R

```
function_subsystem_analysis <- function(path,FL1)
{
library("gplots")
pdf("heatmap.pdf")

meta_ROI_table <-
read.table("recoded_power_ROIs_10_20.csv",header=TRUE,sep="|")
total_meta_regions <- length(unique(meta_ROI_table$Network))

#the following loop is reading the power_conn_mat file subject by subject
for(c1 in 1:length(FL1)) #for.c1.begins
  {

   #clean the output files

   write(file=paste("link_count_summary_",c1,".txt",sep=""),"", append=FALSE)
   write(file=paste("link_weight_summary",c1,".txt",sep=""),"", append=FALSE)
   write(file=paste("link_weight_positive_summary",c1,".txt",sep=""),"", append=FALSE)
   write(file=paste("link_weight_negative_summary",c1,".txt",sep=""),"", append=FALSE)


   #read the power_conn_mat file of the c1th subject
   g <- read.table(paste(path,FL1[c1],sep=""),header=TRUE)

   meta_network <- matrix(rep(0,(total_meta_regions^2)), nrow=total_meta_regions,
ncol=total_meta_regions)
   meta_network_weight <- matrix(rep(0,(total_meta_regions^2)),
nrow=total_meta_regions, ncol=total_meta_regions)
   meta_network_weight_positive <- matrix(rep(0,(total_meta_regions^2)),
nrow=total_meta_regions, ncol=total_meta_regions)
   meta_network_weight_negative <- matrix(rep(0,(total_meta_regions^2)),
nrow=total_meta_regions, ncol=total_meta_regions)

   #c2 goes into the g object line by line
   for(c2 in 1:nrow(g))#for.c2.begins
     {

      ROI1 <- g$vox_col_id_A[c2]
      ROI2 <- g$vox_col_id_B[c2]
      link_weight <- (g$weight[c2])

      #now we will find out what is the meta-ROIs of the current ROIs
      meta_ROI1 <- meta_ROI_table$Network[ROI1]
```

```
        meta_ROI2 <- meta_ROI_table$Network[ROI2]

        #print(c(ROI1,ROI2,meta_ROI1,meta_ROI2))

        if(meta_ROI1 < meta_ROI2)#if.meta_ROI1.begins
          {
           meta_network[meta_ROI1,meta_ROI2] <-
meta_network[meta_ROI1,meta_ROI2] + 1
           meta_network_weight[meta_ROI1,meta_ROI2] <-
meta_network_weight[meta_ROI1,meta_ROI2] + abs(link_weight)

 if(link_weight>0)

            {
   meta_network_weight_positive[meta_ROI1,meta_ROI2] <-
meta_network_weight_positive[meta_ROI1,meta_ROI2] + link_weight
             }

if(link_weight<0)
            {
   meta_network_weight_negative[meta_ROI1,meta_ROI2] <-
meta_network_weight_negative[meta_ROI1,meta_ROI2] + link_weight
             }
  }
        else
          {
           meta_network[meta_ROI2,meta_ROI1] <-
meta_network[meta_ROI2,meta_ROI1] + 1
           meta_network_weight[meta_ROI2,meta_ROI1] <-
meta_network_weight[meta_ROI2,meta_ROI1] + abs(link_weight)

if(link_weight>0)
            {
   meta_network_weight_positive[meta_ROI2,meta_ROI1] <-
meta_network_weight_positive[meta_ROI2,meta_ROI1] + link_weight
             }

if(link_weight<0)
            {
   meta_network_weight_negative[meta_ROI2,meta_ROI1] <-
meta_network_weight_negative[meta_ROI2,meta_ROI1] + link_weight
             }

        }#if.meta_ROI1.ends


       }#for.c2.ends
```

```
  print(meta_network)
  print(meta_network_weight)


  for(c3 in 1:total_meta_regions)#for.c3.begins
    {
    for(c4 in 1:total_meta_regions)#for.c4.begins
      {
       write(file=paste("link_count_summary_",c1,".txt",sep=""),c(c3,c4,meta_network[c3
,c4]), append=TRUE,ncol=1000)
       write(file=paste("link_weight_summary",c1,".txt",sep=""),c(c3,c4,meta_network_w
eight[c3,c4]), append=TRUE,ncol=1000)
  write(file=paste("link_weight_summary_positive",c1,".txt",sep=""),c(c3,c4,meta_networ
k_weight_positive[c3,c4]), append=TRUE,ncol=1000)
       write(file=paste("link_weight_summary_negative",c1,".txt",sep=""),c(c3,c4,meta_n
etwork_weight_negative[c3,c4]), append=TRUE,ncol=1000)
      }#for.c4.ends
    }#for.c3.ends



  heatmap(meta_network,dendrogram = "none")


  }#for.c1.ends



dev.off()

}

#---------------------------------------------------------------------------

path1 <-
"/gpfs/group/nad12/legacy/fgh3/Users/Emily/final_masters_data/new_TBI/Analysis/RES
T/1_createnetwork/positive/"
#PARA

file_list1 <- c('powers_264_conmat_TBI1_LBRITNE.UP.1.013',
'powers_264_conmat_TBI1_LBRITNE.UP.1.014',
'powers_264_conmat_TBI1_LBRITNE.UP.1.015',
'powers_264_conmat_TBI1_LONG.HMC.1.021.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.022.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.024.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.026.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.027.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.030.TIME3',
```

```
'powers_264_conmat_TBI1_LONG.HMC.1.032.TIME3',
'powers_264_conmat_TBI1_LONG.HMC.1.033.TIME3')



function_subsystem_analysis(path1,file_list1)
```

BIBLIOGRAPHY

Bernier, Rachel Anne et al. "Dedifferentiation Does Not Account for Hyperconnectivity after Traumatic Brain Injury." *Frontiers in Neurology* 8 (2017): 297. *PMC*. Web. 31 Mar. 2018.

Fallon, Nicholas et al. "Functional Connectivity with the Default Mode Network Is Altered in Fibromyalgia Patients." Ed. Satoru Hayasaka. *PLoS ONE* 11.7 (2016): e0159198. *PMC*. Web. 30 Mar. 2018.

Hillary, Frank G., et al. "The Rich Get Richer: Brain Injury Elicits Hyperconnectivity in Core Subnetworks." *PLoS ONE*, vol. 9, no. 8, 2014, doi:10.1371/journal.pone.0104021.

Iadipaolo, Allesandra S., et al. "Behavioral Activation Sensitivity and Default Mode Network-Subgenual Cingulate Cortex Connectivity in Youth." Behavioural Brain Research, Elsevier, 27 June 2017.

Johnston, Kevin, et al. "Top-Down Control-Signal Dynamics in Anterior Cingulate and Prefrontal Cortex Neurons Following Task Switching." *Neuron*, vol. 53, no. 3, 2007, pp. 453–462., doi:10.1016/j.neuron.2006.12.023.

Lin, Pan, et al. "Dynamic Default Mode Network across Different Brain States." *Scientific Reports*, vol. 7, June 2017, p. 46088., doi:10.1038/srep46088.

MacDonald, Angus W., et al. "Dissociating the Role of the Dorsolateral Prefrontal and Anterior Cingulate Cortex in Cognitive Control." *Science*, American Association for the Advancement of Science, 9 June 2000, science.sciencemag.org/content/288/5472/1835.

"Magnetic Resonance Imaging (MRI)." National Institute of Biomedical Imaging and Bioengineering, U.S. Department of Health and Human Services, 2 Feb. 2017, <www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri>

Mcinnes, Kerry, et al. “Mild Traumatic Brain Injury (MTBI) and Chronic Cognitive Impairment: A Scoping Review.” *Plos One*, vol. 12, no. 4, Nov. 2017, doi:10.1371/journal.pone.0174847.

Olsen, Alexander, et al. “Altered Cognitive Control Activations after Moderate-to-Severe Traumatic Brain Injury and Their Relationship to Injury Severity and Everyday-Life Function.” *Cerebral Cortex*, vol. 25, no. 8, 2014, pp. 2170–2180., doi:10.1093/cercor/bhu023.

Power, Jonathan D., et al. “Functional Network Organization of the Human Brain.” Neuron, vol. 72, no. 4, 2011, pp. 665–678., doi:10.1016/j.neuron.2011.09.006.

Yount, Ryan, et al. “Traumatic Brain Injury and Atrophy of the Cingulate Gyrus.” The Journal of Neuropsychiatry and Clinical Neurosciences, vol. 14, no. 4, 2002, pp. 416–423., doi:10.1176/jnp.14.4.416.

Yuan, Binke, et al. “Brain Hubs in Lesion Models: Predicting Functional Network Topology with Lesion Patterns in Patients.” *Scientific Reports*, vol. 7, no. 1, 20 Dec. 2017, doi:10.1038/s41598-017-17886-x.

Zhou, Yongxia, et al. “Default-Mode Network Disruption in Mild Traumatic Brain Injury.” *Radiology*, vol. 265, no. 3, 2012, pp. 882–892., doi:10.1148/radiol.12120748.

ACADEMIC VITA

Academic Vita of Riddhi Patel
Email: rvp5292@psu.edu

Education

The Pennsylvania State University, Schreyer Honors College
Bachelor of Science in Biology Neuroscience
Bachelor of Science in Psychology Neuroscience
Honors in Psychology

Thesis Title: Assessing the effect of lesion location on executive function in patients with Moderate-Severe Traumatic Brain Injury.
Thesis Supervisor: Dr. Frank Hillary

Research Experience:

Institute for Environmental Medicine
Summer Research Intern
June 2015 – August 2015
Perelman School of Medicine at the University of Pennsylvania
Under the supervision of Dr. Sheldon Feinstein
Designed and performed PCR and Gel Electrophoresis on DNA obtained from rat tail tips to identify mutations in the mouse colonies; trained a high school student in the lab; analyzed and presented data/findings at the department's biweekly meetings.

Neuro-Genetics Lab
Undergraduate Research Student
October 2015 – May 2016
Biochemistry and Molecular Biology Department, University Park, PA
Under the supervision of Dr. Scott Selleck
Conducted experiments independently on Drosophila flies: crossed, collected, dissected, immunostained NMJ and imaged larvae using confocal microscopy and the Imarus software.

Brain and Behavior Lab
Undergraduate Research Student
June 2016 – Present
Clinical Neuropsychology Department, University Park, PA
Under the supervision of Dr. Frank Hillary
Assist with data lesion analysis, literature reviews, MRI scan studies, Neuropsychological battery tests scoring and subject recruitment.

Clinical Experience:

Abington Lansdale Hospital Medical Center, *Abington, Lansdale, PA*
Volunteer/Allied Health Program
September 2013 – June 2014
Shadowed the doctors in the OR, ER, Radiology, Cardiology, Lab, Acute rehab, Pharmacy and assisted with patient care.

Mount Nittany Medical Center, *State College, PA*
Emergency Department Volunteer
June 2016 – December 2017
Assisted patients to their respective CT, MRI and X-ray scans, helped with discharge, stocked linen, snacks and any other service that may be required in the Emergency department.

Children's Hospital of Philadelphia
Aspiring Medical Student/Shadowee
Summer 2017
Shadowed neurosurgeon and cardiothoracic surgeons in the Operating Room performing surgeries, in the clinic and on the floors interacting with patients and their families.

Scholarships:

Schreyer Honors College Academic Excellence Scholarship
Van Dyke Memorial Scholarship
Homer Braddock Scholarship
Joe Paterno Renaissance Scholarship
Gelet Trustee Scholarship
Chaiken Trustee Scholarship
Provost 5K Fund Scholarship

Presentations:

Patel, R., Grossner, E., Bernier, R., Benson, M., Hillary, F.G. (2017, April). Evaluating the effect of White Matter loss and Anterior Cingulate on Planning and Processing Speed in Moderate-Severe TBI patients. Poster presentation at the Pennsylvania State University Psi-chi Research Conference, April 2017, University Park, PA.

Activities and Leadership

Penn State THON – Rules and Regulations Committee member
Mehta Prep Academy – Director of Tutoring
Indian Culture and Language Club – Treasurer/ Vice President
Schreyer Honors College Student Council Member
Global Brigades: Medical, Environmental and Dental – Panama, Spring 2015
Penn State Jadhoom – Co-ed Fusion Dance Team – Oaks City Revolution, 2018