Amygdala Connectivity in Patients with Depression After Traumatic Brain Injury

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Abstract
Depression is a common symptom of Traumatic Brain Injury, injury to the brain due to external force. In this study, we analyzed network connectivity of the amygdala and the Default Mode Network (DMN) in patients with depression after TBI. We hypothesized that as the severity in depression of TBI patients increases, there will be an increasing number of alterations in the amygdala connectivity. We also hypothesized that as the severity in depression of TBI patients increases, there will be decreased DMN connectivity within the amygdala region. Using Power 264, we divided the brain into networks: Amygdala-Amygdala, Amygdala-DMN, Amygdala-Else, DMN-DMN, DMN-Else, Else-Else. Using graph theory, a discrete area of mathematics, we were able to visualize the connections that were found statistically and observe if or how network connections were altered.

Introduction

The neurological correlation of depression after Traumatic Brian Injury provides serious complications on patients that could prove to be life altering or threatening. Traumatic Brain Injury (TBI) is- physical injury to the brain tissue that causes temporary or permanent functional damage to individuals (Ghajar, 2000). Due to alterations of area and network connectivity caused by TBI, the development of depressive symptoms in TBI patients is-common. Such symptoms could significantly reduce the ability of individuals with TBI as depression comorbid of TBI results in poor cognitive function, lower quality of life that is health-related, increased functional disability, greater suicide attempts, increased sexual dysfunction, decreased social and physical activity, and more insufficient recovery and rate.

With depression, there is abnormal functionality in the amygdala (Han et al., 2015). The amygdala, part of the brain's limbic system, is known to be the emotional center of the brain, associating with memories and responses to emotion. The part consists of several regions in a connection of the cortical-striatal-pallidal-thalamic circuit, also known as the core neural system in mood disorders (2015). A subgroup of networks divides the amygdala, but three have been studied in particular to psychiatric illness.

These networks are listed as the first one preferentially correlating to -the default mode network (DMN), the second preferentially correlating to the dorsal attention and frontal-parietal network, and the last one, with no preference in what it is correlated to in relativity to the first

two subdivisions. In a resting-state fMRI study, Helm et al. (2018) observed a decrease in DMN connectivity of patients with mood depressive disorder (MDD) compared to healthy controls. Associating the connections between the DMN and the dorsal subdivision is likely to provide information of contributing patterns that ultimately lead to depression. As for the connection in TBI, connecting a part of the DMN with regions of the salience network (SN) shows that the amygdala also holds alterations of the connectivity in the DMN and SN with TBI individuals. There is importance in understanding how the amygdala connectivity is a potential neuroimaging biomarker for patients with depression after TBI. Looking at the DMN may prove to be useful in discovering how severity of depression after TBI affects overall regions of the amygdala, leading to linked symptoms.

Further understanding the neural mechanisms between TBI and depression, as a result of depression after TBI, can help find treatments for the significant symptoms and better understand the clinical outcomes of TBI comorbid with depression severity. In this study, we will utilize fMRI at resting-state to research depression after TBI as depression involves neural processes that occur over more extended periods (minutes or hours) (Han et al., 2015). Using the power 264, we will correlate the activity between the DMN and the Amygdala, which a collection of nodes and edges will then map out to represent the relationship between the nodes, a process of -graph theory (Wang et al., 2010). We hope to examine the strength of the left and right amygdala bilaterally as well as analyze the DMN area of the amygdala to understand what it is doing to modulate the bilateral behavior and if the DMN does predict depression after TBI. We hypothesize that as the severity in depression of TBI patients increases, there will be an increasing number of alterations in the amygdala connectivity. We also expect that as the severity in depression of TBI patients increases, there will be decreased DMN connectivity within the amygdala region.

Materials and Methods

Procedure

This study involved the use of an existing archival dataset, initially collected from functional imaging techniques and neuropsychological testing to analyze. In gathering fMRI data, participants were involved in resting state scan and a block design one-back task. A traditional neuropsychological battery outside of the scan was then administered. A Philips Achieva 3T scanner at Hershey Medical center or a Siemens Magnetom Trio 3T whole-body scanner at the Department of Radiology at Hershey Medical Center, or either a Siemens Magnetom Trio 3T whole-body scanner or a Siemens Prisma 3T whole-body scanner that are both at the Social, Life and Engineering Sciences Imaging Center at The Pennsylvania State University, University Park were used to collect imaging data. The data was gathered and organized in an onsite HW and SW designed to support researchers at The Pennsylvania State University called ICS-ACI.

The data used from this study included 14 individuals with moderate to severe TBI, determined by a Glasgow Coma Scale score of 3-12 (Teasdale and Jennet, 1974) or found by MRI or CT of those who were injured at least approximately a year prior. The ages range from 18-55 years old causes of injury listing as MVC, fall, assault sports, or other.

The participants were recruited as either a cross sectional study after injury or a longitudinal study that examined recovery three months after TBI. In addition, they were informed of the studies prior to consenting, and Penn State IRB approved of the consent form used. Participants were also compensated for participating in the study.

Table 1
Demographics

Sample Size (n)	Age; mean	Gender	BDI-II; mean	GCS; mean	HVLT; mean	Education; mean
13	31.07	3 females 10 males	8	7.83	6.79	12.5

Resting State Scans

For the resting-state scan, all subjects were asked to focus on the white cross at the center of the screen while being reminded to not fall asleep. Data collection included 34-35 slices for whole-brain coverage resulting in 3mm x 3mm x 4mm voxels and taken with a TR of 2,000 ms and a TE of 30ms. After removing the first 3 volumes for T1 equilibration effects, 145 volumes were left for analysis.

Beck Depression Inventory-II (BDI-II)

Participants self-administered a series of 21 items on a survey that measured the existence and severity of depressive symptoms. Each item was scaled from 0 to 3, and the final scores were calculated to determine the measures for each participant.

Data Preprocessing

All of the participants' data were preprocessed using SPM8. Data from resting-state were adjusted and normalized to fit a standard T1 template from the Montreal Neurological Institute and to limit the signal-to-noise ratio. Motion from the scans were examined with the Artifact Repair toolbox to identify large motion and correct any in BOLD signal.

Network Brain Parcellation

The brain is observed through a large-scale network perspective. Through parcellation, pieces of the brain are divided into nodes and analyzed in a network. This methodology assists in the methodology of graph theory, where we studied a graph of functional areas in 264 nodes, or regions of interests. Further, the 264 nodes from the Atlas-Based approach Power 264 were broken into specific nodes for the areas of interest, including the amygdala and the Default Mode Network.

Graph Theory

Graph theory is an area of discrete mathematics that graphs the brain as a complex network. In neuroscience, graph theory can be applied to either functional or effective connectivity (Farahani et al., 2019). A graph is a diagram made up of coordinates that represent relation. In graph theory, these graphs represent the networks through a collection of nodes and edges. Nodes demonstrate the anatomical elements of the brain while the edges show the relationships between the nodes (Wang et al., 2010). In Figure 1, a sample of nodes are pointed at by arrows, representing specific brain regions of interest. A sample of edges is also pointed at in this figure, showing particular connections between nodes.

The degree of a node is the number of edges connected to a node; for example, node D has a degree of three while node C has a degree of two. Figure 2 highlights modules, a cluster of nodes; two clusters are circled in a gold color in Figure 2. Additionally, in this figure, node A is labeled to illustrate a hub, which is a node with a high degree. Compared to the other nodes in

this figure, node A has the highest degree, that being four and therefore a hub of this network. Given these components, graph theory can show the relationship of network connectivity within or across brain regions.

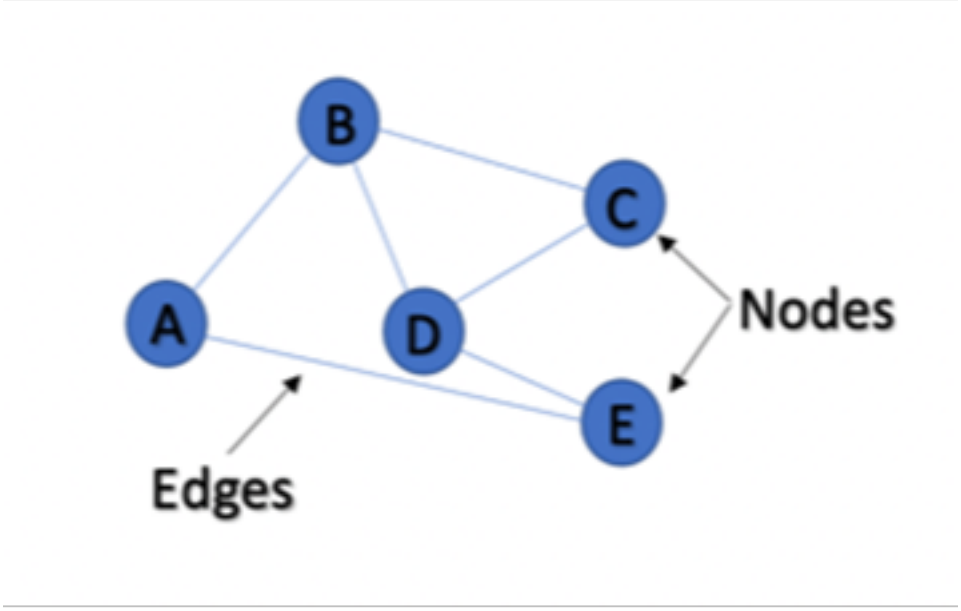

Figure 1
A diagram demonstrating edges and nodes, components seen in graph theory-based approaches.

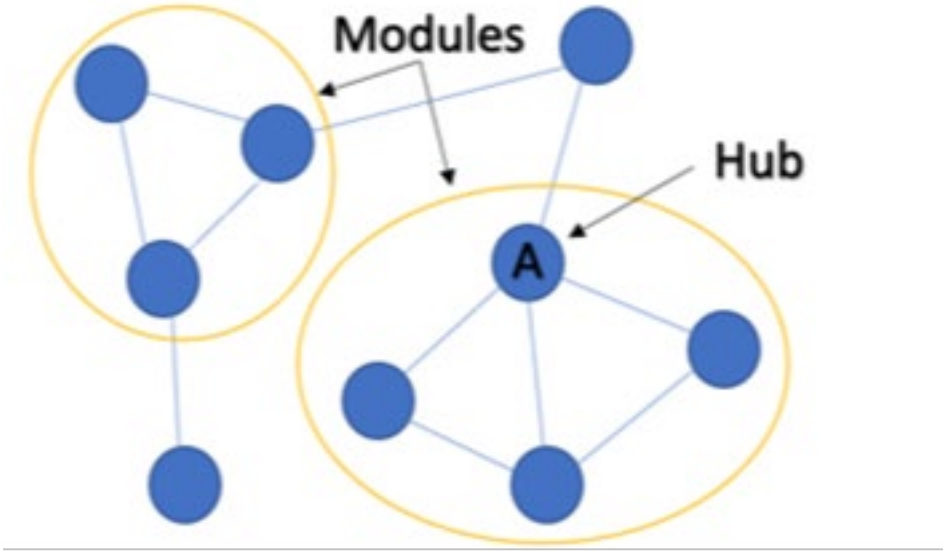

Figure 2
A diagram demonstrating and highlighting modules and hubs, components seen in graph theory-based approaches.

Network Analysis
MNI coordinates for the left and right amygdala were run through the ACI system provided by Penn State. The coordinates used were (right amygdala, 27, 5, −17; left amygdala, −15, −1, −14)

(Feng et al., 2016), and nodes 265 and 266 were added to include the left and right amygdala, respectively. The nodes for the DMN and the rest of the brain were arranged in their respective networks. After the run, we received the strengths of the connections.

Results

Amygdala Connectivity

Amongst the 13 patients totaled, the strength of the network connectivity associated with the amygdala all held a value of 0.00, indicating no connection between each network shown in Table 2.

Table 2

Strength values of amygdala connectivity connected to associated networks

Network	Strength
Amygdala-Amygdala	0.00
Amygdala-DMN	0.00
Amygdala-Else	0.00

BDI-II Scores versus Network Weights

The relationship between BDI-II scores and network weights are shown in figures 3 and 4. The data indicates a non-linear relationship between the two variables amongst the total of the 13 patients. The correlation value (R) of BDI-II Scores vs. DMN-DMN was 0.320 while the R values of BDI-II Scores vs. DMN-Else was 0.280. Both values, considering p-value significance of less than 0.05, were not significant.

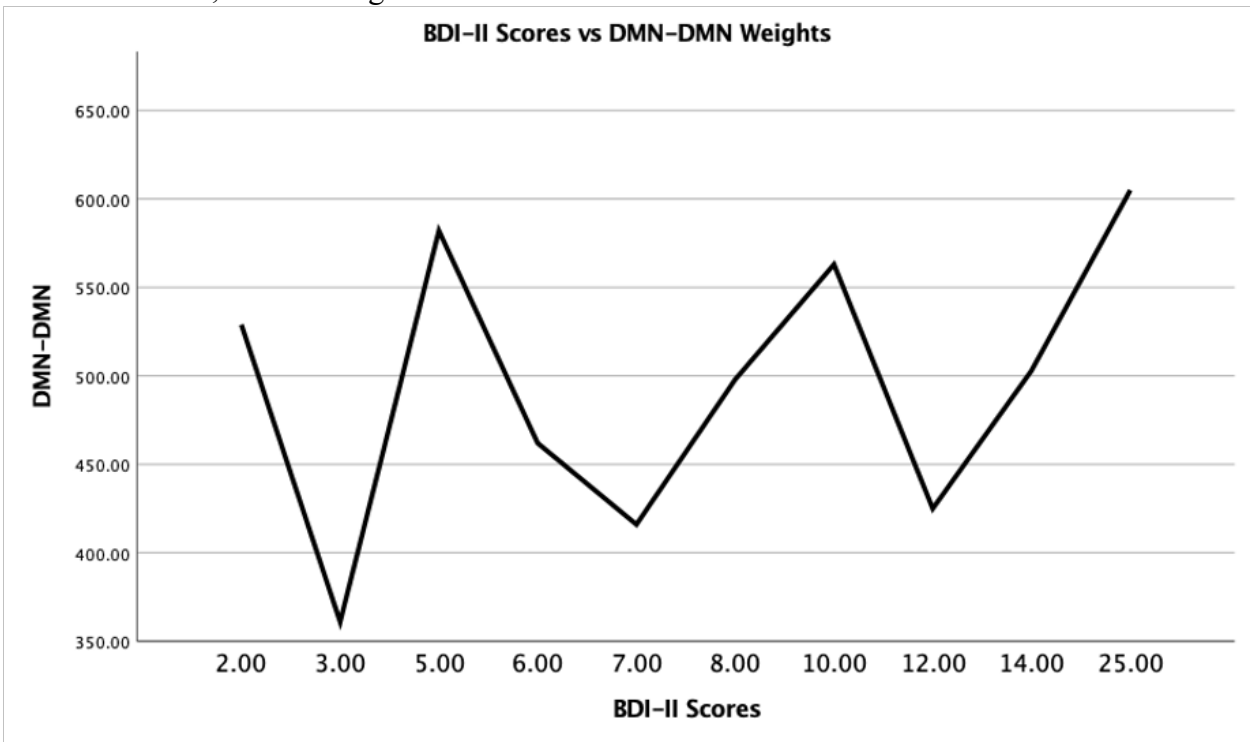

Figure 3: Linear model of relationship between BDI-II Scores, measurement of depression severity, and DMN-DMN weights (values).

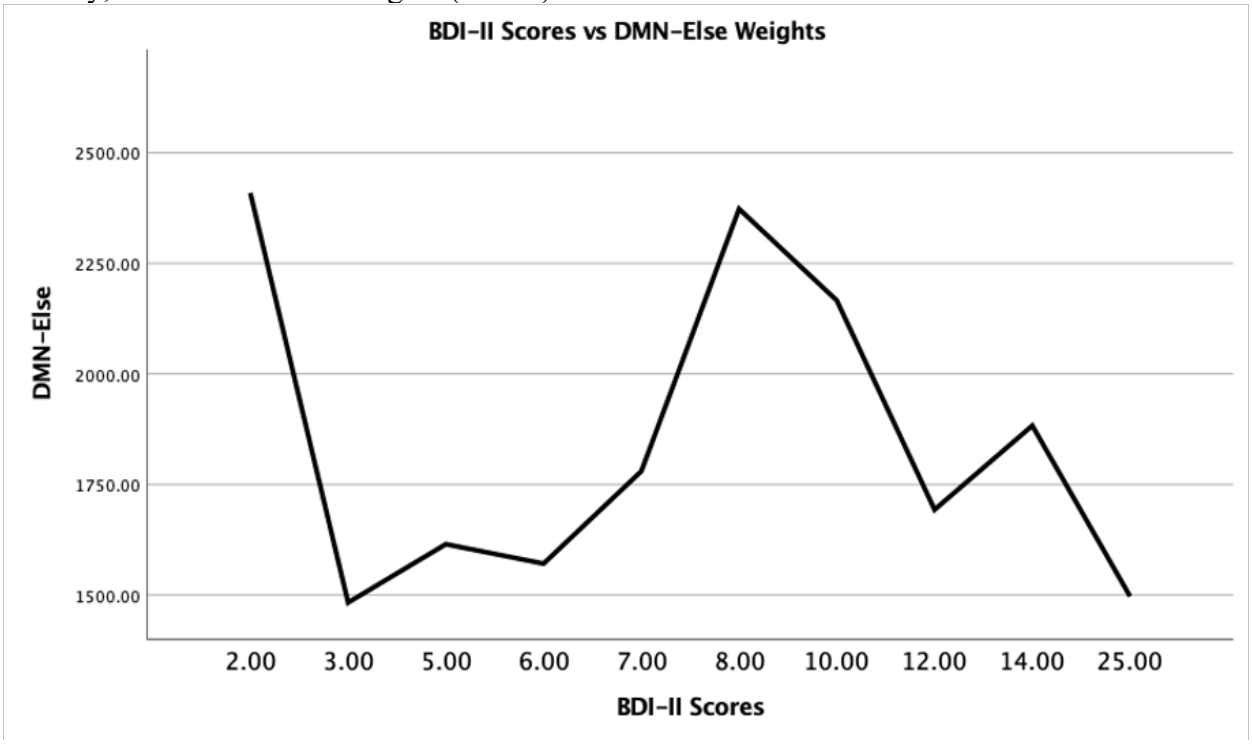

Figure 4: Linear model of relationship between BDI-II Scores, measurement of depression severity, and DMN-Else weights (values).

Strength Connectivity Between Networks

Within the DMN-DMN network, the p-value showed to be 0.286 while that value for the DMN-Else network was 0.355. Both values are not significant and therefore have no effect on what was observed.

Discussion

In this study, we found no evidence of depression after TBI associating with the individual networks that were examined, including the Left Amygdala-Right Amygdala, Amygdala-Else, Amygdala-DMN, DMN-DMN, and DMN-Else. No linear correlation was found between severity of depression and connectivity values within the networks where we were able to find data on (DMN-DMN, DMN-Else), indicating that there is no direct relationship between the severity of depression and amount of DMN connectivity within the amygdala region. Therefore, network connectivity, whether increased or decreased, in the amygdala and the DMN might not be altered by severity of depression.

The question stands on how no connections were found in the networks that included the Amygdala (Amygdala-Amygdala, Amygdala-DMN, Amygdala-Else). There is a sense that the amygdala must be connected to itself, so for the data to show no connection between the amygdala and itself must indicate an error in the methodologies. Further studies may involve the use of different methodologies to examine the pattern of connection with increasing severity in depression after TBI.

There are also clear inaccuracies regarding the strength of connectivity between networks. What can be found unusual is that the strength of the DMN-DMN is not significant. However, the network connected to itself is most likely to have a very strong connection, so the presented p-values are unlikely to be relied on.

Limitations of this study include sample size. We only had a sample size of 13, which is a significantly small population. Additionally, three of the 13 participants had mild-moderate depression while only one had moderate-severe depression. Given this, there is a lack of variability to determine the hypothesized causes and effects of depression on brain connectivity in TBI patients. Also, there is the limitation of the bias in BDI-II measures. Since the BDI-II test is self-administered, there is a great chance of bias in question-answering. Therefore, there is a lack of reliability on the scores for each participant.

In conclusion, there is a significant number of changes that can be made to this study regarding the inconsistencies and inaccuracies presented within the results. However, depression comorbid with TBI may not indicate any causation on how the amygdala connectivity is affected.

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