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Examining the Role of Amygdala Connectivity in Depression After TBI

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Abstract

Traumatic brain injury (TBI) is a condition that can occur as a result of forceful trauma to the head, which can be due to factors such as a car accident, falls, and sports injuries. While it is vital to know how a traumatic brain injury can occur, it is extremely important to know the effects of it on an individual's functioning and emotions. As a result, this study aims to determine whether amygdala connectivity is a predictor of depression in participants with a traumatic brain injury. I hypothesized that the greater the amygdala connectivity among patients with TBI, the higher the depression scores they would exhibit. In order to determine to what extent amygdala connectivity is correlated to depression among TBI patients, this study leveraged existing resting-state functional MRI scans of 44 subjects with varying severity of TBI. The within-network connectivity from these scans were analyzed and correlated with the scores from the geriatric depression scale among participants with TBI. My hypothesis was partially supported. Although the effect for the overall TBI group was not statistically significant, the effect within the severe TBI group was and produced a medium effect size. Additionally, although the effect for the mild TBI group was only marginally significant, it was of a medium effect size and likely not statistically significant due to the small sample size. Given that more severe TBI disrupts the neural circuits of the amygdala, this may be associated with a greater potential for depressive episodes.

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Chapter 1

Introduction

Traumatic brain injury (TBI) is a condition that has grown throughout the population over the years due to the rise of an increasing number of head injuries and head trauma, such as through sports concussions and car accidents. TBI can be defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon et al., 2010). When discussing alterations in brain function, it is important to discuss that there are many ways and mechanisms for what can happen. When TBI happens, in order to examine brain changes, there can be a possible loss in memory, altered level of consciousness, vision and emotion changes, balance and speech changes, etc. (Menon et al., 2010). Each of these brain changes are processed in different sections of the brain, such as the frontal, temporal, parietal, and occipital lobes, which means that TBI can affect multiple parts of the brain at once. Furthermore, TBI can take on multiple forms of severity, such as mild, moderate, and severe. There are different criteria for each of these levels of severity, based on their GCS scores. According to a recent review article, "A Glascow Coma Scale, or GCS, is a scale used to objectively describe the extent of impaired consciousness in all types of acute medical and trauma patients. The scale assesses patients according to three aspects of responsiveness: eye-opening, motor, and verbal responses" (Jain & Iverson, 2018). Since the GCS is on a point scale of 3 to 15, different score values correspond to different levels of severity. In the GCS, a mild TBI has a GCS score of 13–15, a moderate TBI has a GCS score of 9–12, and a severe TBI has a GCS score ≤ 8, (Vervoordt et al., 2021). Therefore, the lower the number, the more severe the brain injury, and the person's level of function is greatly impaired.

Therefore, it is important to understand the effects of TBI on different parts of the brain, which can lead to alterations of a person's everyday functioning. One of these areas is the amygdala, which is a structure in the limbic system that controls and processes emotion (Davis & Shi, 2000). When the amygdala has altered volume or connectivity due to damage to the limbic system, it can lead to emotional dysregulation and a lack of control over an individual's emotions. This can lead to many mental health conditions such as anxiety disorders, mood disorders, and personality disorders. One of the major mood disorders that can occur from altered amygdala connectivity is depression. In a study that discusses the effect of TBI as related to amygdala connectivity and depression, "group analysis revealed enhanced bilateral amygdala connectivity for the TBI-plus-depressive symptoms group" (Han et al., 2015). Essentially, when an individual is experiencing depressive symptoms after TBI, there is an association with an increase in amygdala connectivity due to altered brain chemistry after the trauma. Furthermore, in order to measure amygdala function and connectivity, it is important to utilize functional MRI imaging, which measures blood flow in the brain. According to the study that had taken and analyzed resting state functional MRI data after TBI, "increased resting state functional connectivity between the hippocampus and amygdala was associated positively with BDI-II scores" (Luo et al., 2023). The Beck Depression Inventory (BDI) is a scale that is used to measure the extent of depressive symptoms that a person experiences. Amygdala connectivity has been linked to an increase in depressive symptoms among participants with TBI (Han et al., 2015).

Furthermore, it is important to relate amygdala connectivity and depression, as amygdala connectivity changes can lead to mood disorders. Depression is a condition where a person's feelings and thoughts are disrupted, which can lead to symptoms such as sadness, frustration, and

worry (Bernard, 2018). Furthermore, it can be understood that brain volume and depression scores can be correlated to describe the extent of depression in individuals with TBI. According to a recent study that analyzed depression scores and amygdalar volume after TBI, “depression scores were positively correlated with left amygdalar gray matter volume” (Medeiros et al., 2022). Thus, an increase in amygdalar volume was associated with an increase in depression scores. Therefore, an alteration to the amygdala plays a key role in determining the relationship between depression and TBI.

With these considerations in mind, this study will examine resting-state fMRI data. According to a research study, resting-state fMRI data is defined as a brain imaging technique that examines “the relationship between the neuronal activation patterns of anatomically separated brain regions, reflecting the level of functional communication between regions” (Van Den Heuvel & Pol, 2010). These data points are taken when a person is at a state of rest, where they are not completing any task. From there, the resting states of voxels in the brain, which are three-dimensional spatial representations of a certain brain region, are compared with each other in order to determine if there are correlations between two brain regions or within one brain region (Van Den Heuvel & Pol, 2010). An example of a between-network resting state connection is correlating regions between the hippocampus and amygdala. The strength of the connectivity values can then be measured to see if there is a relationship, with higher within-network or between-network connectivity values illustrating a stronger correlation. In this study, within-network connectivity values will be used in order to measure the strength of amygdalar functional connectivity.

Using existing data, this study will utilize the Geriatric Depression Scale in order to determine the extent of depressive symptoms. The Geriatric Depression Scale involves a series

of 30 yes or no questions that examine aspects of an individual's quality of life and level of emotional functioning in society (Montorio & Izal, 1996). There are varying levels of severity that the GDS categorizes, such as mild, moderate, severe, and no signs of depression. A higher number on the GDS illustrates a more severe state of depression for a certain participant.

Overall, while studies have been conducted on the relationship between the amygdala and depression among participants in TBI, there is less research done on the specifics of leveraging resting-state fMRI data in order to examine this relationship among TBI participants. Therefore, this present study will utilize within-network connectivity values of amygdalar resting-state fMRI data and correlate that with GDS scores within the TBI participants to determine the relationship between amygdala connectivity and depression. I hypothesize that among participants with TBI, as within-network amygdalar connectivity increases, the depression scores on the GDS also increase.

Chapter 2

Methodology

Participants

In this study, the included sample consisted of 44 subjects that had experienced TBI, all between the ages 54-78 (M = 62.45). The participants were selected from the Hershey Medical Center, Moss Rehabilitation Research Institute, and Pennsylvania State University. The TBI group participants needed to have some severity of a Traumatic Brain Injury for least one year before the study was conducted. The data collected are from participants that have experienced a Traumatic Brain Injury, ranging from mild up to severe according to the GCS. In this scale, a moderate TBI has a GCS score of 9–12, a severe TBI has a GCS score ≤ 8, and a mild TBI has a GCS score of 13–15 (Vervoordt et al., 2021). After these participants are evaluated on the Glasgow Coma Scale, fMRI imaging is taken of their brains. For the purpose of this study, while multiple scans were performed on their brains, such as structural scans, the current study will only be analyzing the results of their resting-state fMRI data. Furthermore, participants were given a series of questionnaires and psychological tests to complete while they participated, including the Geriatric Depression Scale, which is used in this study.

Measures

Geriatric Depression Scale

The GDS is a series of 30 yes or no questions that examine aspects of an individual's quality of life and level of emotional functioning in society (Montorio & Izal, 1996). There are varying levels of severity that the GDS categorizes, such as mild, moderate, severe, and no signs of depression. A higher number on the GDS illustrates a more severe state of depression for a certain participant.

Resting-state fMRI (rsfMRI)

A brain imaging technique that examines "the relationship between the neuronal activation patterns of anatomically separated brain regions, reflecting the level of functional communication between regions" (Van Den Heuvel & Pol, 2010). These scans are taken when a person is at rest, which means they are not completing any tasks at the time the scans were taken. rsfMRI then allows the opportunity to examine the within-network connectivity values of different brain regions, which is a term that compares the strength of the connection between nodes within a network (Keyvanfard et al., 2023).

The participants completed 2, 10 minute resting-state scans. Participants were told to keep their eyes open and on the white cross in the center of the screen, ensuring that they do not fall asleep during this time. The phase-encoding direction of the resting-state scans were Anterior-Posterior, and the resting-state runs had included the values of TR = 2,000 ms, TE = 30 ms, and flip angle = 90. (Esteban et al., 2019; Mullin et al., in press 2025).

Procedure

Once the fMRI and GDS data was collected with each of the participants, the data was preprocessed using the fMRI preprocessing. Results from this manuscript come from fMRIPrep 23.1.3 (Esteban et al., 2019). Weighted functional connectivity matrices were created for each subject. These matrices describe the relationship between the brain regions using Pearson correlation coefficients. Within-network connectivity was calculated using scripts from the Brain Connectivity Toolbox by Rubinov and Sporns (2010).

The Brainnetome atlas was used to obtain within-network connectivity values for the amygdala. The amygdala is under the subcortical nuclei in the Brainnetome atlas, with the four regions being 211-214, with 211 being the medial left amygdala, 212 being the medial right

amygdala, 213 being the lateral left amygdala, and 214 being the lateral right amygdala (*Brainnetome Atlas*. Atlas., 2016). Using R-studio version 2024.09.1, the pre-processed within-network connectivity values were inputted, as well as the GDS data for each participant. From there, a linear regression model was used to determine the statistical significance and correlation value for each of the different types of severity. In this case, the first regression model ran was the comparison between GDS and within-network connectivity among all subjects in total. Then, the comparison between GDS and within-network connectivity of each of the three types of TBI severities were also run with a regression model in order to determine the respective values.

Chapter 3

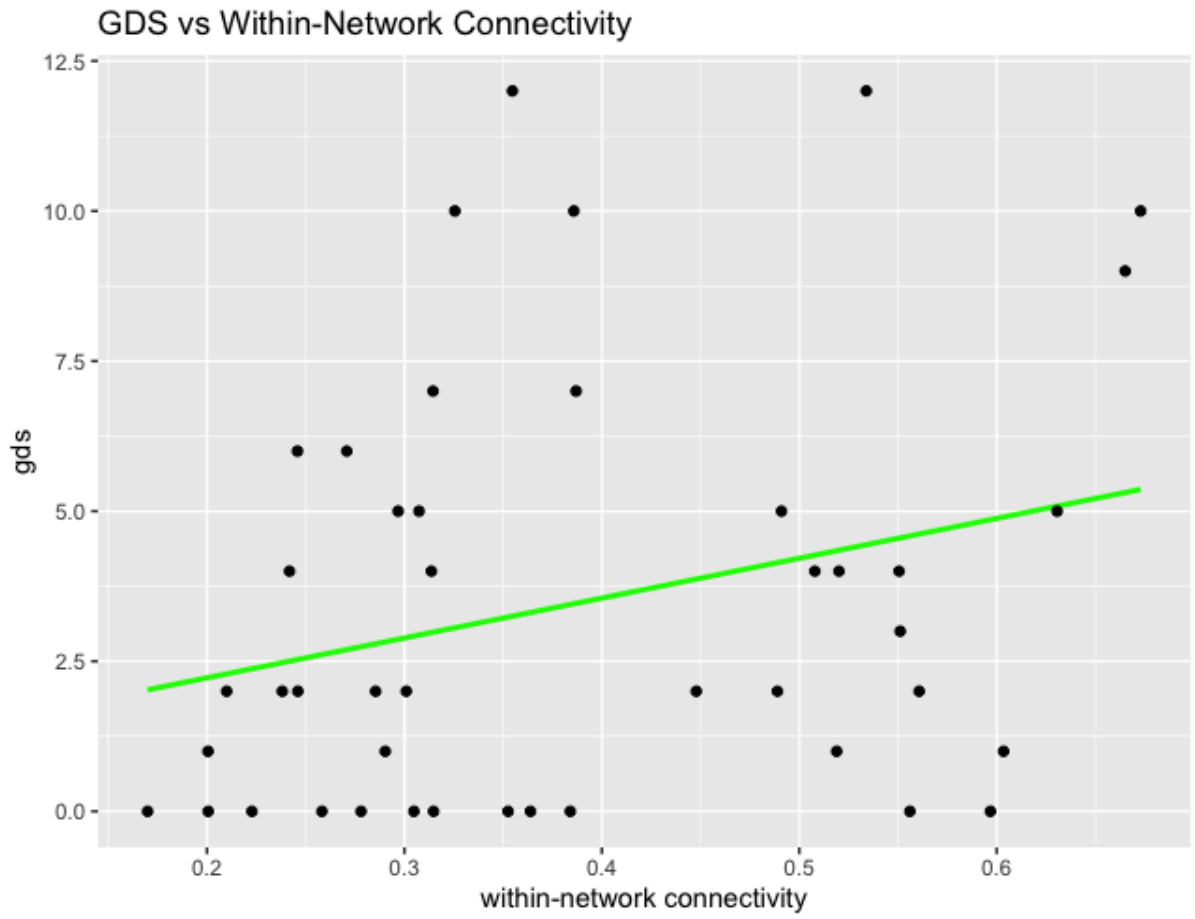
Results

The sample population of 44 subjects was comprised of 13 subjects with mild TBI, 12 subjects with moderate TBI, and 19 subjects with severe TBI.

TBI Subjects Overall

In the 44 subjects total, the correlation and p-values were as follows: $r(42) = 0.270$, $p = 0.077$. Although this correlation indicated that greater within-network amygdala connectivity was associated with higher depression among members across all TBI groups, the effect was only marginally significant with what would be considered a small effect size. Furthermore, for every one point increase in GDS, within-network connectivity goes up by 0.011.

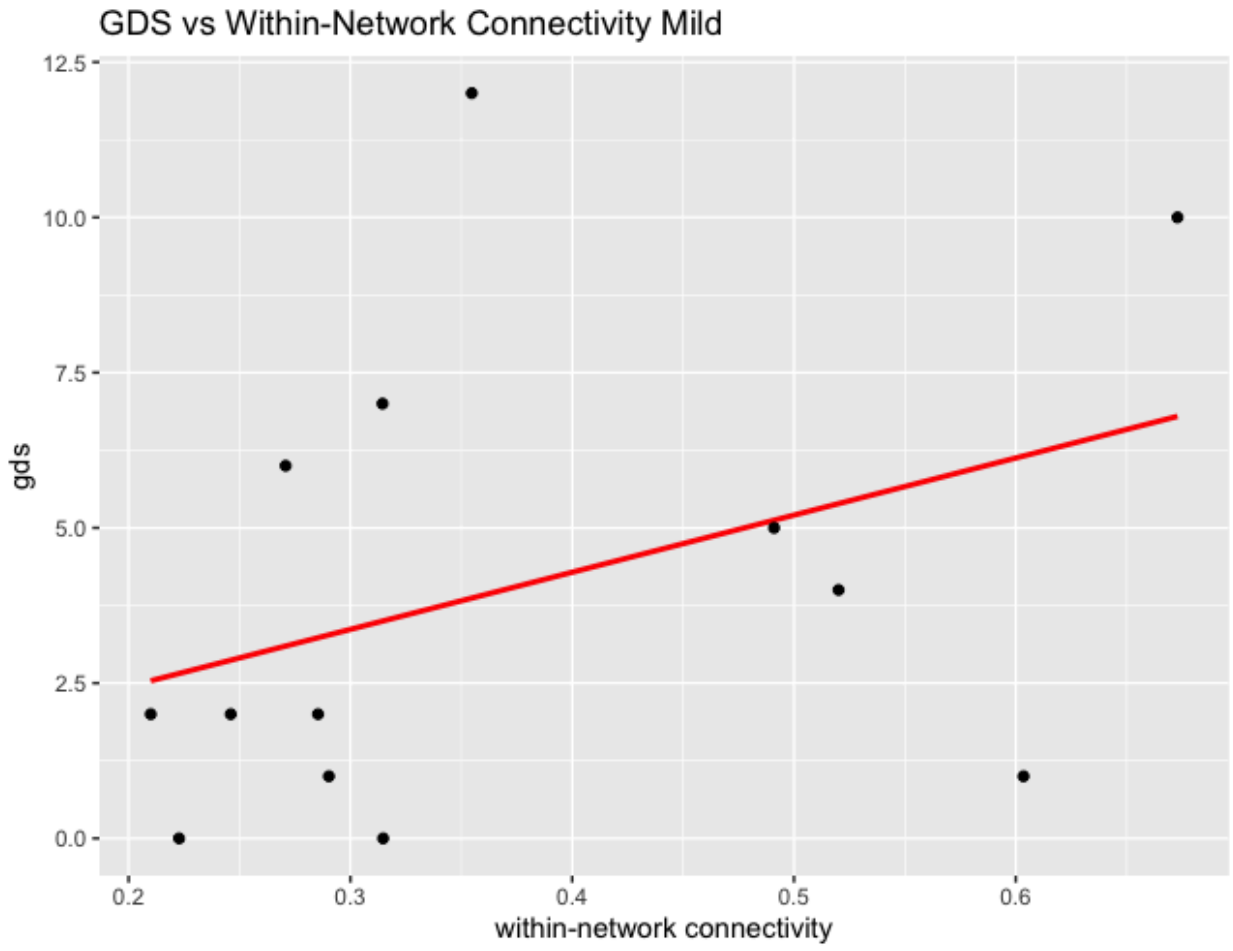
Figure 1. GDS vs. Within-Network Connectivity



TBI Subjects Mild

In the 13 subjects total, the correlation and p-values were as follows: $r(11) = 0.364$, $p = 0.221$. This indicated that the correlation between GDS scores and within-network amygdala connectivity among members of this mild TBI group was not statistically significant, although this was mainly due to the small subject size and limited statistical power. The effect size would be considered "medium" according to Cohen's criteria, suggesting that increased connectivity and increased depression were meaningfully associated in this group (Diener, 2010). Furthermore, for every one point increase in GDS, within-network connectivity goes up by 0.014.

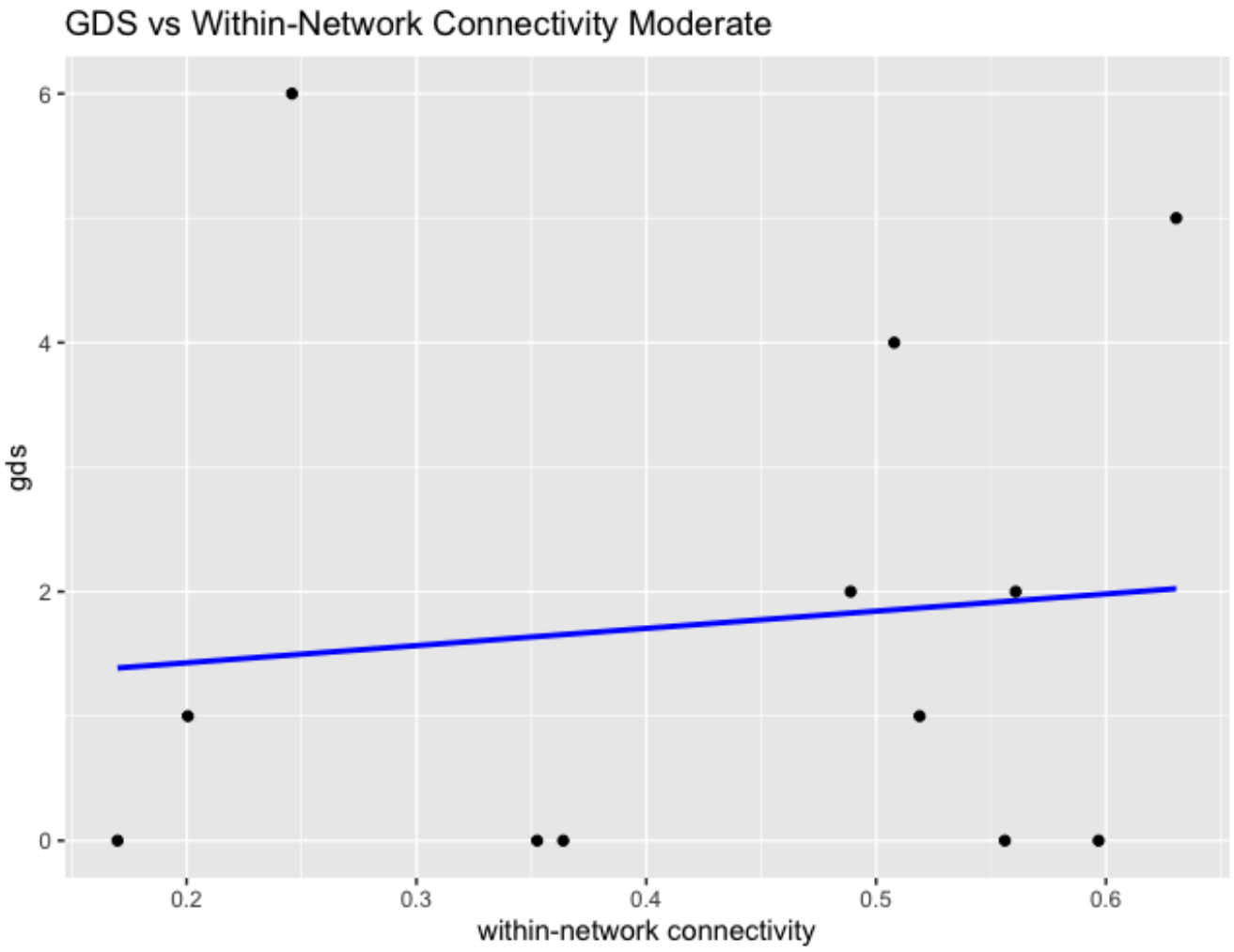
Figure 2. GDS vs. Within-Network Connectivity Mild



TBI Subjects Moderate

In the 12 subjects total, the correlation and p-values were as follows: $r(10) = 0.104$, $p = 0.748$. This indicated that the correlation between GDS scores and within-network amygdala connectivity among members across this moderate TBI group was not statistically significant. Furthermore, for every one point increase in GDS, within-network connectivity goes up by 0.009.

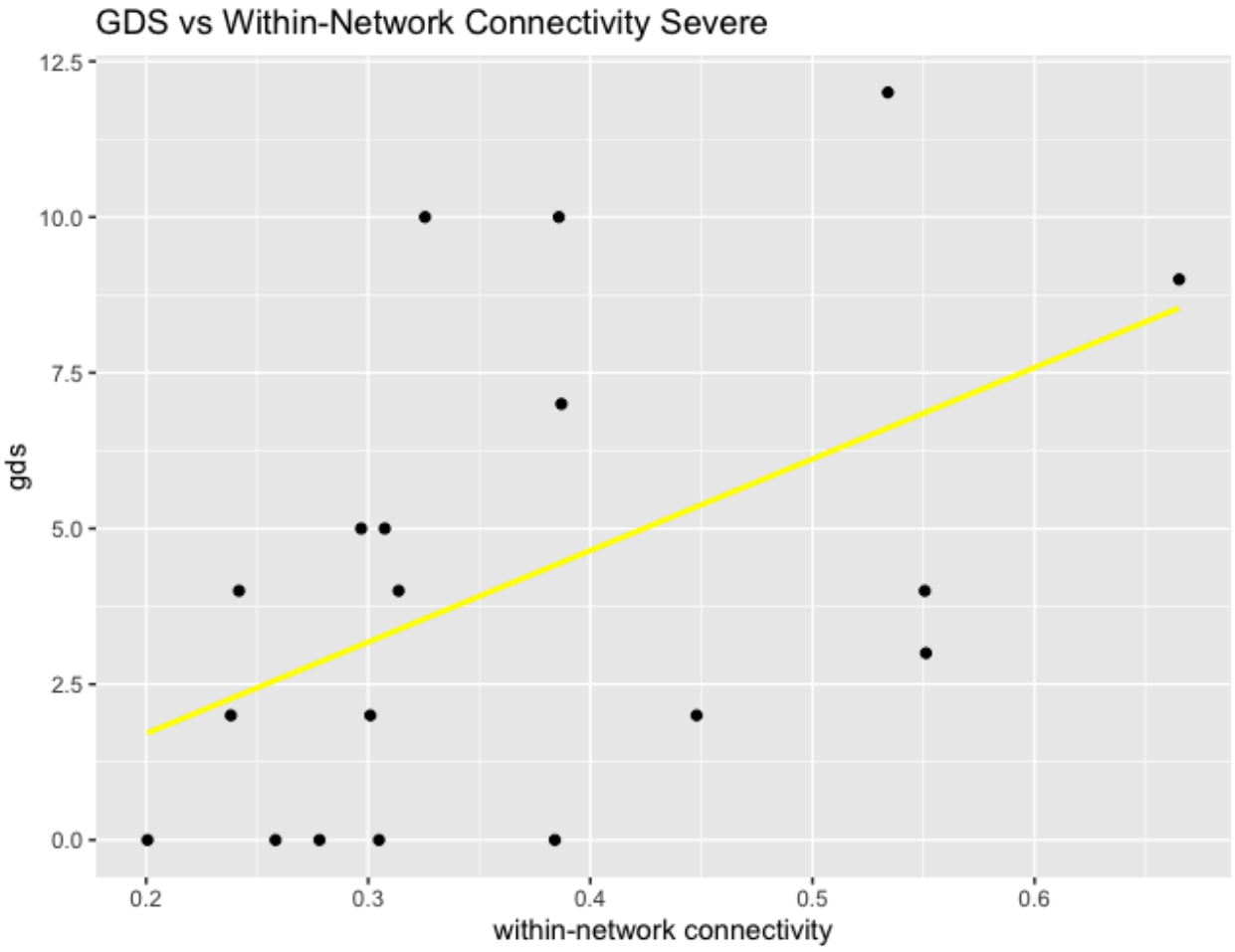
Figure 3. GDS vs. Within-Network Connectivity Moderate



TBI Subjects Severe

In the 19 subjects total, the correlation and p-values were as follows: $r(17) = 0.489$, $p = 0.034$. This indicated that the correlation between GDS scores and within-network amygdala connectivity among members of this severe TBI group was statistically significant, with a "medium" effect size (Diener, 2010). Furthermore, for every one point increase in GDS, within-network connectivity value goes up by 0.016.

Figure 4. GDS vs. Within-Network Connectivity Severe



Chapter 4

Discussion

The purpose of this study was to determine whether there was an association between amygdala connectivity and depression among participants with TBI. I hypothesized that an increase in within-network connectivity of the amygdala is related with an increase in the GDS scores of participants across all TBI severity groups. This hypothesis was partially supported. Consistent with hypotheses, participants with severe TBI exhibited a statistically significant relationship between within-network amygdala connectivity and GDS scores, with a medium effect size. Overall, the correlation between within-network connectivity and GDS was a moderate, positive correlation of 0.489. This confirms the findings that an increase in within-network connectivity of the amygdala is associated with an increase in GDS score, but only after severe TBI. Although the effect in the mild TBI group was only marginally significant, this was mainly due to low statistical power; the effect size was in the medium range according to Cohen's criteria (Diener, 2010).

Amygdala Hyperconnectivity

This study revealed that amygdala connectivity increased when TBI participants reported increased depressive symptoms. In order to understand the mechanism between amygdala hyperconnectivity and depression, it is important to reference previous studies on amygdala hyperconnectivity. A study conducted by Peluso et al. (2009) examines the relationship between amygdala hyperconnectivity and depressive symptoms among participants, explaining that "patients with unipolar depression tend to over-activate the left amygdala in response to fearful or sad faces." Since looking at negative emotion faces leads to a more potential to increase depressive symptoms among already depressed participants, this means that an increase in

depressive symptoms are resulting in the amygdala working overdrive in terms of emotions. This can be related to this present study, as it was found that GDS scores have a tendency to increase when within-network amygdala connectivity increases, especially among mild and severe TBI participants.

Similar Literature

While this present study had examined amygdala connectivity with depression after TBI, a similar study had looked into a different mechanism than the one tested in this study, by Garcia & Hillary; this study utilized the default mode network and strength of the amygdala connectivity, whereas this present study had examined within-network connectivity in terms of the amygdala only. Furthermore, in terms of depression scale, this present study had utilized the Geriatric Depression Scale, while the similar study had utilized the Beck Depression Inventory, which are two different scales (Garcia & Hillary). Overall, this study found that there was zero strength connectivity between the left and right amygdala, zero strength connectivity between the amygdala and the DMN, and zero strength connectivity between the amygdala and other parts of the brain (Garcia & Hillary). Furthermore, these authors found no statistically significant relationships between depression scores and network connectivity among participants with TBI. This partially conflicted with the results of the present study, as in their study, the researchers found that people with severe TBI showed no statistically significant relationship between depression scores and network connectivity. However, in this present study, there was a significant result with within-network connectivity and GDS among people with a severe TBI, and a marginally significant medium effect size for those with mild TBI. In their study, Garcia and Hillary acknowledged that there could have been inaccuracies with the sample size and the

depression scale measure that they had used. This could be a possible reason why there were different results between their study and the present study.

While the mild and moderate groups in the present study had shown no significant results, the question was why? A potential explanation to this can be linked to a past study that examined depressive symptoms among participants with a TBI. According to this study, "mild TBIs were associated with significantly more cases of depression (64%) than the mixed (mild/moderate/severe: 36%) and severe (39%) TBI samples" (Osborn et al., 2014). Since an increase in depression illustrates altered connectivity in the brain related to emotional processing, this suggests that the amygdala is altered during a mild TBI. Therefore, the amygdala connectivity being altered could mean hyperactivity of the amygdala that results from this TBI, thus what should have happened with the expected results of this present study.

Limitations

There were three major limitations that could be applied to further studies in order to improve methodology. The first limitation was the smaller sample size and age range of participants. Since the sample size was just 44 participants, and they were all 54 and older, there could have been a chance that representing the study population with more younger participants would have led to statistically significant results. In further research, the participants can come from ages 18 and older, where participants would be recruited to each of the three TBI severity categories of mild, moderate, and severe. As illustrated by the mild TBI findings where there was an effect size that was medium but only marginally statistically significant, larger sample sizes in future work may be more likely to yield statistically significant results.

The second limitation of this study was the use of the Geriatric Depression Scale. While the Geriatric Depression Scale was a good representation of the extent of the participants'

depression severity, other depression scales can be used in future studies. The depression scales that can be used in further research include the Beck Depression Inventory and the Neurobehavioral Functioning Inventory Depression Scale (Seel & Kreutzer, 2003). These depression scales could lead to more consistent results in terms of amygdala connectivity and depression scores among participants.

The third limitation of this study was the lack of testing other networks, such as the Default Mode Network. Testing other types of connectivity instead of using just the brainnetome axis and fMRI prep leads to the potential for more consistent results. Furthermore, using another data network alongside within-network connectivity of the amygdala may lead to examining relationships between other brain regions and depression scores. For example, using a different type of connectivity may see that the frontal lobe connectivity is related to depression scores among TBI participants.

Chapter 5

Conclusion

In conclusion, TBI is a condition that can be extremely harmful to the brain. One of those examples is this present study on depressive symptoms and the amygdala. This study hypothesized that an increase in within-network connectivity in the amygdala was associated with an increase in GDS scores among participants with a TBI. It was found that there was only a significant positive correlation among the severe TBI group and not the mild and moderate TBI groups, illustrating that the greater severity of TBI alters the amygdala connectivity at a much higher rate, which is associated with greater depressive symptoms. With this said, as noted, the effect size for the mild group was in the medium range, so the lack of statistical significance among this group was likely due to its small sample size.

This research is important as individuals are suffering from depression everyday, and there sometimes may be no known cause. Some individuals are unaware that a TBI that impacted them years ago could be contributing to their symptoms. Therefore, this research serves as a guide for individuals that could be experiencing depression after TBI in order for them to learn how their amygdala could be functioning during this time. Overall, this study can inspire future research that aims to understand if depression can be partially explained by varying patterns in resting-state brain connectivity.

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Table 1

Participant Demographics

	TBI Group (*N*=44)
Characteristic	**Mean**
Age	62.45
Education (Years)	14.05
Time Post Injury (Hours)	3018.02
PTA (Days)	17.20
GCS	8.59
% Mild	29.55% (*N*=13)
% Moderate	27.27% (*N*=12)
% Severe	43.18% (*N*=19)
Sex	31 Male, 13 Female
Ethnicity	1 Hispanic
Race	28 White/Caucasian, 16 Black/African-American