Analysis of Structural Network Topology in Depression using Graph Theory

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Abstract

Neuroimaging studies have suggested a difference in structural brain connectivity in depression. Recently, structural brain connectivity and psychopathology have been studied using graph theory analysis, which provides metrics on properties of brain organization. While there have been some studies applying this analytic technique to study depression, these have largely been done using categorical rather than dimensional approaches to psychopathology. This study applied both a traditional categorical approach and a dimensional approach to examine the relation between commonly used graph theory measures and depression.

The dimensional analysis included 439 subjects and the categorical approach included 357 subjects with depressive symptoms and 82 subjects without any diagnoses. Anatomical co-variance matrices were constructed using 9 morphometric features and matrices were analyzed to produce the following metrics: normalized clustering coefficient, normalized path length, small-world parameter, normalized global efficiency, and normalized local efficiency. The categorical approach utilized an ANCOVA and the dimensional approach utilized multiple regressions. The categorical analysis did not suggest a significant difference between the "depressed" and "healthy" group with regards to any of the graph theory metrics. In the dimensional analysis a significant positive relation was identified between depressive symptom counts and both normalized local efficiency and normalized clustering coefficient. This shows some concordance with previous studies, and suggests that global features of white matter microstructure may be relevant for depression when examined dimensionally. Future studies using other types of neuroimaging data and applying graph theory techniques may yield additional insight into which graph theory metrics are most relevant for depression.

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric diseases today and is becoming increasingly prevalent (Zhang et al., 2011). In order to meet DSM-V criteria for MDD, one must have either depressed mood or loss of interest or pleasure for a period of more than two weeks, as well as additional symptoms such as fatigue, worthlessness, irritability, suicidality, or change in sleep, weight, or concentration. Studies examining the etiology of depression have revealed alterations in brain anatomy, such as decreased volume of brain structures and differences in structural connectivity (Rubinov & Sporns., 2009). Increasingly, studies are beginning to look at the implications of brain structural network topology differences in those with depression.

Graph theory analysis in analyzing structural connectivity

Graph theory analysis techniques have recently been implicated as a way to look at brain structural network topology, or the pattern of interconnectivity of brain regions. Graph theory is a set of mathematical analytic procedures that have been applied to neuroimaging data in order to analyze the topological organization of the brain (Long et al., 2014). Graph theory provides a unifying method by which to describe a diverse array of brain networks, regardless of scale (Fornito et al., 2016). This is mainly due to the modeling of the brain using nodes and edges. Nodes are the fundamental elements of brain networks in graph theory, and they can correspond to individual neurons, neuron clusters, or macroscopic brain regions (Fornito et al., 2016). Nodes

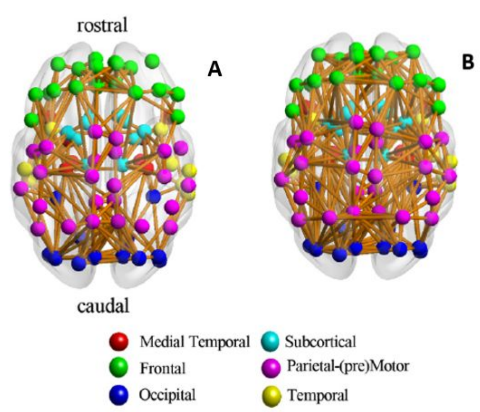

Figure 1. Comparison of structural brain connectivity in a healthy control (A) versus an individual with depression (B). Image B shows the increased structural connectivity in an individual with depression. (Long et al., 2014)

represent regions of the brain that have anatomical or functional connections (Rubinov & Sporns, 2009). Edges are connections between different nodes and can be quantified in several ways, including via white matter connectivity, functional connectivity, and covariance of morphometric features (Long et al., 2011). A model of nodes and their connecting edges is displayed in Figure 1. Nodes and edges together are elemental components that create a map of brain networks, which can be broadly classified as scale-free, random, or small-world networks (Humphries & Gurney, 2008). Scale-free networks are characterized by nodes that are relatively independently clustered and are absent of hierarchical organization. Nodes in scale-free networks do not have homogeneous architecture in that some nodes may have very few connections and other nodes may have many connections (Sporns et al., 2004). In contrast, nodes of random networks have approximately the same number of connections, creating a more homogeneous architecture. Connections between different nodes in a random network have equal probability (Sporns et al., 2004). Small-world networks serve as an intermediate between scale-free networks and random networks, as they combine areas of ordered lattice-like connections with areas of randomness. Namely, small world networks consist of nodes with short distances between them, but are part of a larger network (Sporns et al., 2004). Differences in the three network types are depicted in Figure 2. These types of networks can further be studied using various graph theory metrics (Fornito et al., 2016).

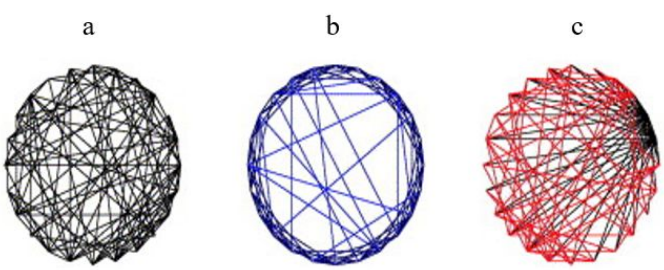

Figure 2. A comparison of random networks (a), small-world networks (b), and scale-free networks (c)

Graph theory metrics in depression

One graph theory metric that has been implicated to be relevant in depression is clustering coefficient. The clustering coefficient represents the fraction of nodes connected to each other that are also connected to a separate common node (Kargaonkar et al, 2014). Path length is another relevant metric that is defined as the sum of edge lengths along a given path (Bai et al., 2014). Both clustering coefficient and path length are modeled in Figure 3. As shown in the image, path length has more of an emphasis on the connections that connect various nodes in different areas, and it is a measure that encompasses more of the brain. On the other hand, clustering coefficient places greater emphasis on nodes that are closer, thereby encompassing less of the brain (Rubinov et al., 2009). Both of these measures are often used to describe connections in small-world networks, as small-world networks are usually characterized by large clustering coefficients and small path lengths (Bai et al., 2014).

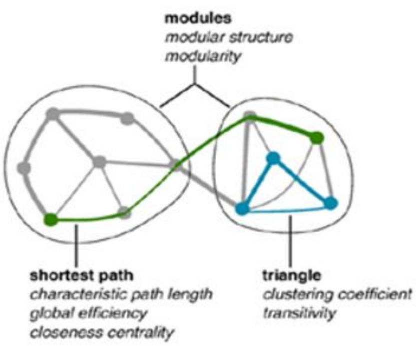

Figure 3. Diagram of path length, global efficiency, and clustering coefficient (Rubinov et al., 2009)

Because small-world networks are one of only three types of network classifications, it is a relatively broad category. In order to further classify and quantify networks within the small-network classification, a graph theory metric known as small-worldness is used (Humphries & Gurney, 2008). Therefore, small-worldness can be used to classify the degree to which a network can be considered “small-world”, and whether it is more similar to a random network or a scale-free network.

Another graph theory metric implicated in depression is global efficiency. Global efficiency, also shown in Figure 3, is formally defined as the harmonic mean of the inverse path length, but essentially serves as a measure of parallel information transfer in a network (Bai et al, 2014). A metric known as local efficiency serves to measure the efficiency of communication between nodes even after removal of a nearby node (Bai et al, 2014). Both global efficiency and local efficiency are referred together as network efficiency, which is defined as the relative ease at which pairs of nodes can communicate with each other (Fornito et al., 2016).

The aforementioned graph theory metrics have previously been found to have values that differ between healthy controls and individuals with a diagnosis of depression. Both clustering coefficient and path length were found to be significantly reduced in MDD participants in comparison to healthy controls (Long et al, 2014). Small-worldness has been found to be significantly smaller in those with MDD (Singh et al., 2013). Global efficiency and local efficiency have been found to be increased in those with MDD (Kargaonkar et al, 2014; Bai et al., 2014). Therefore, overall network efficiency is expected to be greater in those with MDD (Zhang et al, 2014). The differing degrees of structural connectivity between depressed individuals and healthy controls are depicted in Figure 3.

While studies have shown clustering coefficient, path length, small worldness, global efficiency, and local efficiency to be significantly different between those with and without a diagnosis of depression, the direction of the relationship between depression and the values of the graph theory metrics have been inconsistent across studies (Bohr et al., 2013; Lord et al., 2012; Meng et al., 2014; Zhang et al., 2011; Long et al., 2014). While four of the previously cited studies analyze functional connectivity through the use of fMRI data, the study by Long et al. (2014) studies structural connectivity differences through the use of diffusion tensor imaging (DTI) data. The Long et al. study also analyzes whole brain network organization, versus local organization at particular anatomical sites of interest. The results obtained from the Long et al. (2014) study also concur with results obtained in many other studies, suggesting that the results were highly reproducible (Singh et al., 2013; Bai et al., 2014; Kargaonkar et al., 2014; Zhang et al., 2014). Participants in the Long et al. study who were designated as “depressed” were considered severely depressed as they had to score highly on the Hamilton Rating Scale for Depression (HRSD) to be included. Healthy controls were selected based on the lack of all psychopathology determined from the results of the Structured Clinical Interview for the DSM-IV and based on a lack of serious family history of neurological or psychiatric illness. Because of the large difference between the very healthy controls and severely depressed group, it is possible that the results of the study are exaggerated.

A number of metrics can be generated by applying graph theory to quantify the structural connectivity of the brain, and because of the large number of possibilities and the relative novelty of graph theory analysis in neuroscience, there is no clear standard for which metric to select when studying a certain psychopathology. Therefore, graph theory metrics are often arbitrarily selected in a given study, and these same metrics, if found to produce significant results, are used in later studies (Rubinov & Sporns, 2009). Often times, these metrics are selected due to their relative simplicity in terms of calculation and modeling.

Categorical versus Dimensional Analysis

Categorical classification is most often used to study psychopathology. However, recently, there has been a push to study psychopathology using a more dimensional approach due to the limitations associated with a categorical approach. The main issue with categorical analysis is the considerable comorbidity across disorders and heterogeneity within disorders (Krueger et al., 2005). Psychopathology, in general, is expressed in more of a dimensional manner than a categorical manner, as variation in psychopathology is characterized by several dimensions of thought, affect, and behavior. Therefore, these multiple dimensions can be refined in order to maximize the homogeneity within a disorder and minimize the co-occurrence of different disorders (Krueger et al., 2005). Because of the inherent dimensional nature of the expression of psychopathology, a dimensional approach provides a better way to study psychopathology.

The Present Study

This study explores how graph theory can be applied to identify patterns in structural network topology in adults with depressive symptoms, using both a categorical and dimensional approach. Thus, this tests the utility of taking a dimensional approach to examine the relationship between network topology and psychopathology. The graph theory measures of interest are path length, clustering coefficient, small-worldness, global efficiency, and local efficiency (Long et al., 2014).

For the categorical approach, the graph theory metrics of interest were compared between individuals who didn’t meet criteria for any diagnoses and individuals who met criteria for MDD. The dimensional approach was operationalized by using depressive symptom counts to represent the course of depression.

For the categorical portion of the study, similar connectivity patterns to previous studies were expected. Specifically, those in the depressed group were expected to have a reduced clustering coefficient, path length, and small-worldness, and increased global and local efficiency (Long et al., 2014; Singh et al., 2013; Kargaonkar et al., 2014; Bai et al., 2014; Zhang et al., 2014). These same relationships were also expected to be applied to the dimensional aspect of the study in the following manner. As the number of symptom counts increased, the clustering coefficient, path length, and small-worldness were expected to decrease and the global and local efficiencies were expected to increase. Therefore, depressive symptom counts were expected to display a negative relationship with clustering coefficient, path length, and small-worldness, and a positive relationship with global and local efficiencies.

The dimensional aspect of the study helps provide insight into how brain connectivity changes may occur throughout the course of depression. However, since most existing studies use a case-control approach, there has not been sufficient data to suggest whether graph theory measures will show a significant dimensional relationship with MDD symptoms, and so, one of the goals of this study is to investigate whether these relationships exist.

Methods

Participants

The study was conducted using data that had already been collected under a NIMH Research Domain Criteria (RDoC) grant (R01MH098098), which consisted of a sample of 499 young adults from the second wave of the Tennessee Twin Study. Participants were selected based on psychopathology risk and were asked to provide a genetic sample and complete a diffusion tensor imaging scan, functional magnetic resonance imaging (fMRI) scan, 3 functional neuroimaging tasks, a structured clinical interview, self-report measures, and a drug screen. The sample for the current study consisted of 439 subjects ranging from ages 23 to 31 that were selected based on whether they had useable T1 volumetric data. For the categorical study,

Table 1
Demographic information of population

Demographic Variable	Counts	Percentage
Sex		
Male	207	47.2%
Female	232	52.8%
Race		
White	316	72.0%
Non-White	123	28.0%
Handedness		
Left	46	10.5%
Right	393	89.5%

Demographic Variable	Mean	Standard Deviation
Age	26.05	1.779

exclusion criteria for the healthy controls was based on the presence of other psychopathology diagnoses in those without a diagnosis of depression. However, for those with a diagnosis of depression, the presence of additional psychopathology was not used as an exclusion criteria in order to maximize the sample size of the "depressed" group. Because of this exclusion criteria, only 251 of these participants were included in categorical study. In this sample, 31 subjects had a depression diagnosis with 4 subjects having only a depression diagnosis and 27 subjects having other diagnoses in addition to depression (3.74 ($s = 1.861$) mean number of other diagnoses). 220 subjects from this sample did not have any diagnoses and served as the "healthy controls". All 439 subjects were included in the dimensional study.

Measures

In order to define nodes, the T1 image was segmented using the Destrieux atlas from FreeSurfer version 5.1.0. The following morphometric features were extracted from each region:

number of vertices, gray matter volume, surface area, mean cortical thickness, standard deviation cortical thickness, mean curvature, Gaussian curvature, curvature index, and folding index (Fischl, 2012). To produce an individual anatomical covariance matrix for each subject, the 9 morphometric features listed previously were correlated across pairs of regions. The matrices were then thresholded by excluding negative correlations and preserving significant correlations ($p < 0.05$) to create the matrix (Gong et al., 2012).

Graph theory analysis was conducted on the matrices using the Matlab Brain Connectivity Toolbox (Rubinov & Sporns, 2009). This produced the metrics of interest (path length, clustering coefficient, global efficiency, and local efficiency). In order to normalize these metrics, 100 random matrices were generated for each subject, preserving the degree, weight, and strength distribution of their matrix. Each graph theory metric of interest was calculated for each random network and then averaged to produce a single metric per subject. Then each subject's graph theory metric was divided by the graph theory metric derived from the random networks to produce the normalized measure. Small-worldness was calculated by dividing the normalized clustering coefficient by the normalized path length. The final metrics that were included in analyses were as followed: normalized clustering coefficient, normalized path length, small-worldness, normalized global efficiency, and normalized local efficiency.

Participants were administered the Young Adult Diagnostic Interview for Children (YA-DISC), (Hart et al., 1995). This is a structured clinical interview that was administered without any skip-outs. Thus it can produce both symptom counts and presence versus absence of diagnoses.

Data Analysis

The study was split up into 2 main approaches: a case-control approach and a dimensional approach. The case-control study used a between-subjects design as participants were divided based on diagnosis of depression: a control group consisting of those without any diagnoses of psychopathology and an experimental group consisting of those who met criteria for depression (some of these subjects met criteria for other diagnoses as well). Mean values of each graph theory metric values were compared between these different groups in order to find a significant difference. This was done using an ANCOVA that controlled for the following covariates: age, sex, ethnicity, scanner, and handedness.

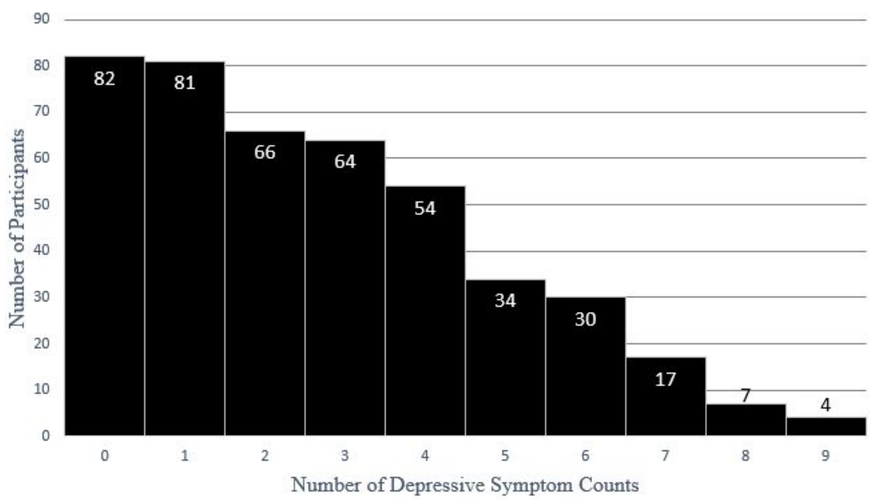

Figure 4. Distribution of depressive symptom counts across the sample

As part of the dimensional analysis, subjects were categorized based on the number of depressive symptoms they displayed, ranging from 0 to 9. The frequency of depressive symptom counts in the sample is depicted in Figure 4. Each subject’s depressive symptom count was treated as an independent variable and each subject’s value for the different graph theory metrics served as the dependent variable. The dimensional analysis was conducted using Mplus 8.1 (Muthén & Muthén, 2018). This utilized multiple regressions that accounted for clustering of twin pairs and sampling methodology, and also took into account the same covariates as in the categorical analysis. A familywise error correction was also conducted as part of the dimensional analysis in order to account for running multiple regressions.

Results

Categorical Analysis

The categorical analysis was conducted by comparing values for the various graph theory measures between those with and without a diagnosis of depression. Of the 5 graph theory metrics that were calculated, none were found to be significantly difference (*ps* > 0.10) between the group with a depression diagnosis and the group without a depression diagnosis. When accounting for covariates in the ANCOVA analysis, normalized clustering coefficient, normalized path length, normalized local efficiency, and small-worldness were found to have a significant relationship with age ($p < 0.05$). The mean values of the graph theory metrics for "depressed" and "not depressed" groups are outlined in Table 2, and the results of the ANCOVA are outlined in Table 3.

Table 2
Mean values, standard deviation, and standard error of various graph theory measures for participants with and without a diagnosis of depression

Graph Theory Metric	Depression Diagnosis	Mean	Standard Deviation
Normalized Path Length	No	1.586	0.038
	Yes	1.582	0.040
Normalized Clustering Coefficient	No	5.270	0.804
	Yes	5.659	1.130
Normalized Local Efficiency	No	3.693	1.055
	Yes	4.124	1.611
Normalized Global Efficiency	No	0.672	0.028
	Yes	0.664	0.034
Small Worldness	No	2.469	0.241
	Yes	2.516	0.305

Table 3
Results from ANCOVA analyzing the differences in mean graph theory metric values between those with and without a diagnosis of depression, controlling for covariates age, sex, race, handedness, and scanner

Graph Theory Metric	F-value	Significance
Normalized Path Length	0.492	0.484
Normalized Clustering Coefficient	0.864	0.354
Small Worldness	0.944	0.332
Normalized Global Efficiency	0.000	0.984
Normalized Local Efficiency	1.814	0.179

Dimensional Analysis

The dimensional analysis was conducted by running a multiple regression of the values of the various graph theory measures on depressive symptom counts (0 to 9). Of the 5 graph theory metrics that were calculated, normalized clustering coefficient and normalized local efficiency were found to have a significant relationship with depressive symptom count.

Table 4
Multiple regression of graph theory metrics on depression symptom counts controlling for demographic covariates of no interest

Graph Theory Metrics	Coefficient	Standard Error	P-value
Normalized Clustering Coefficient	0.119	0.052	0.021*
Normalized Global Efficiency	-0.051	0.068	0.455
Normalized Local Efficiency	0.105	0.052	0.042*
Normalized Path Length	-0.055	0.054	0.308
Small Worldness	0.043	0.050	0.387

*Indicates a significant relationship

Normalized clustering coefficient was found to have a significant positive relationship with depressive symptom count ($p = 0.021$), meaning that as depressive symptom count increases, normalized clustering coefficient increases. Normalized local efficiency was also found to have a significant positive relationship with depressive symptom count ($p = 0.042$), meaning that as depressive symptom count increases, normalized local efficiency increases. These values did not survive familywise error correction. The results from the multiple regression are outlined in Table 4. Figures 5 and 6 depict the plot of normalized local efficiency and normalized clustering coefficient values against depressive symptom counts in order to visually depict the relationship between the variables.

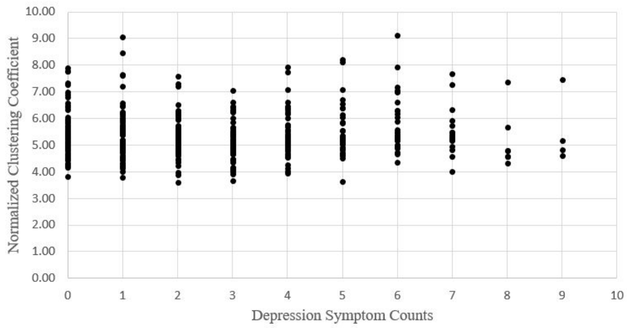

Figure 5. Scatterplot of normalized clustering coefficient and depressive symptom counts

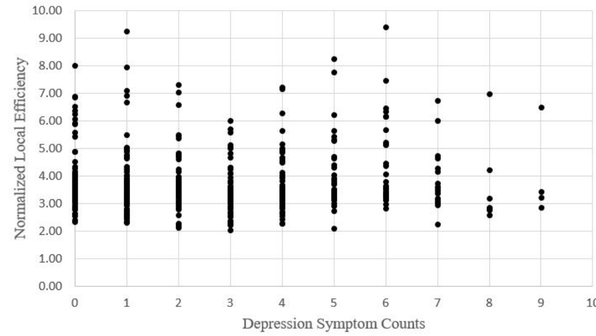

Figure 6. Scatterplot of normalized local efficiency and depressive symptom counts

Discussion

Categorical Analysis Results

The lack of significant results in the categorical approach suggests that there are no significant differences in the measured graph theory metrics between individuals in the study with a diagnosis of depression and individuals in the study without a diagnosis of depression. This thereby suggests that there are no significant structural connectivity differences between the two groups. A lack of difference is possibly due to the composition of the sample used in the study. This is a community sample with a wide range of psychopathology, and thus, those individuals who didn't meet criteria for depression may still have had a number of subthreshold symptoms of depression or other psychopathology. This is different from the typical case-control design which uses hyper-normals (Long et al., 2014). In addition, the majority of individuals in the depression group also met criteria for other diagnoses. This contrasts typical studies that often select samples with limited comorbidity (Long et al., 2014). The use of hyper-normals for the control group and those without comorbidity for the experimental group suggests that results from previous findings on graph theory metrics in depression may not apply to more representative samples, which may experience some degree of comorbidity of psychopathology.

Dimensional Analysis Results

The dimensional approach suggested that an increase in depressive symptom counts is significantly related to an increase in normalized clustering coefficient and an increase in normalized local efficiency. While increased local efficiency is expected to be seen in those with depression when comparing depressed patients to a healthy control, clustering coefficient is expected to lower when comparing depressed patients to healthy controls (Long et al., 2014). However, since increased local efficiency allows for increased efficiency in communication between nodes even after the removal of a nearby node, it would be reasonable to expect that an increased clustering coefficient would help contribute to an increased local efficiency. Also, since the results from Long et al. (2014) were obtained using a categorical approach, the same results may not hold true for a dimensional analysis. If this is true, this means that while clustering coefficient is lower for those with depression in comparison to those without depressive symptoms, when compared across the range of people with varying depressive symptom counts, the clustering coefficient increases over the course of depression. In addition, previous findings were largely from DWI and resting state, it may be the case that morphometric properties show a different relation with depressive symptoms (Long et al., 2014; Bai et al., 2014).

Limitations

Some limitations of the study result from the use of T1 morphometric data. While this type of data is relatively simple to process and provides indications of connectivity between brain regions, these connections are based on correlations in morphometric features. Therefore, the connectivity is not direct, so graph theory analysis may not be able to accurately depict structural connectivity. Conversely, connections from DTI data are based on direct anatomical structural connections, and so, graph theory metrics are better applied to give more accurate results regarding structural connectivity.

There were also some limitations with regards to the sample. The sample was limited to young adults, and therefore, the results have limited applicability to the general population encompassing broader age ranges. In addition, the relationship seen between age and normalized clustering coefficient, normalized path length, normalized local efficiency, and small-worldness in the categorical ANCOVA analysis was probably due to the limited age range present in the sample. Since the age range is narrow, there is less variability in age which makes statistical analysis more difficult to interpret. For the categorical approach, the subjects that served as a "healthy control" to the group with a depression diagnosis were not pure healthy controls due to the fact that subjects in this group may have had symptoms of depression, but just not enough to qualify them for a diagnosis of depression. While this standard for a "healthy control" is a more accurate representation of what a healthy control in the general population looks like, most previous studies have used healthy controls that do not have any psychopathology diagnoses or symptoms of depression at all (a hyper-control). This creates a challenge when comparing the results of this study to previous studies. In addition, a majority of subjects in the "depressed" group (27 out of 31 subjects) had diagnoses for psychopathology other than depression. These other diagnoses could have affected the subject's structural brain connectivity from the connectivity seen in subjects that only have a diagnosis of depression. Participants' brain connectivity could also be affected by the fact that the YA-DISC was administered a year before the MRI scan was conducted, meaning that if participants were exhibiting symptoms or had a diagnosis of depression a year ago, they may no longer have those same symptoms or may be in remission from their diagnosis. A brain in remission may exhibit different structural connectivity patterns than one with a current diagnosis of depression.

Another limitation comes with the network construction, which was created globally across the brain. Since depression is primarily linked to specific anatomical structures, namely those in the limbic system, a localized approach using sub-networks in anatomical regions of interest might provide more significant graph theory metric values (de Kwaasteniet et al., 2013; Geng et al., 2016). However, a global construction was used over a localized approach because of the importance of finding broader relationships within the brain that may be implicated in a dimensional approach. In addition, most of the previously cited studies took a global network construction approach as well.

Conclusions and Future Directions

While the categorical analysis did not suggest a significant difference in structural brain connectivity between those with and without a diagnosis of depression, the lack of a true healthy control and the lack of truly independent samples (due to the presence of twin pairs) likely caused this lack in difference. However, because the study by Long et al. (2014) included a depression group with people with very severe depression and a healthy control group of people with no symptoms for psychopathology at all, it is possible that the extreme difference between the groups produced a difference in structural connectivity. These extreme groups are not as representative of the population either, as fewer people have such extreme diagnoses.

The dimensional analysis suggested an increase in normalized clustering coefficient and normalized local efficiency over the course of depression (represented by increasing symptom counts). Increasing clustering coefficient was not expected, but since the expected results were based on a study that used a categorical approach, clustering coefficient has interesting implications in not only serving as a distinguishing factor between people with and without a diagnosis of depression, but also serving a distinguishing factor between people in different stages in their course of depression.

Because a majority of the current studies using graph theory to study connectivity of various psychopathology use a categorical approach, it will be helpful to apply a dimensional approach to analysis in the future. This dimensional approach should be applied to analyze different types of neuroimaging data as well, including DTI and resting state data. Because of the limited knowledge in the field now, not much can be done to more broadly apply the findings. However, if more studies as done, there may be better-supported findings with implications for the diagnosis and tracking of the progress of depression and other psychopathology, in addition to the development of more effective treatment methods.

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