The general factor of psychopathology and brain network topology

By

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To my parents who promoted curiosity and helped cultivate my interest in psychology

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

Introduction

The general factor of psychopathology

Traditionally, research on psychopathology has focused on specific disorders and employed case-control designs. This approach has proven problematic given the high degree of comorbidity across disorders and the dimensional rather than categorical manner in which psychopathology is expressed (Caspi & Moffitt, 2018; Insel et al., 2010; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017). One solution is to characterize psychopathology in terms of latent factors based on the empirically defined organization of symptoms, with second-order factors capturing the transdiagnostic structure of symptoms.

Initially, studies used a two-factor model in which there is an externalizing and externalizing factor. However, these two factors are positively correlated, indicating that these dimensions still show a degree of overlap (Angold & Costello, 2009). To address this, bifactor models have been used as a tool to quantitatively characterize the dimensional structure of psychopathology (Lahey et al., 2015). This model (Figure 1) include a nonspecific general bifactor on which all prevalent psychiatric disorders load, as well as a specific internalizing and specific externalizing factor. With the introduction of the general factor the internalizing and externalizing factors are orthogonal. The key advantage of this model is that it allows one to disentangle the substantial common variance that is shared across disorders or dimensions (and which has been argued to reflect substantial sharing of etiology across different types of psychopathology), from the variance that is specific to internalizing and externalizing disorders or symptoms. The bifactor model produces a better fit statistic than the correlated factors model

(Lahey, Zald, et al., 2017). Caspi and colleagues used data from the Dunedin study to identify a similar model, which includes a general, “p-factor”, that is defined by shared variance among all disorders (Caspi et al., 2014). When considered at the level of individuals, persons with a broad range of symptoms that cut across second-order dimensions of psychopathology will have a high general factor score, which distinguishes them from persons whose symptoms are limited to just one second-order dimension, such as specific externalizing or specific internalizing symptoms.

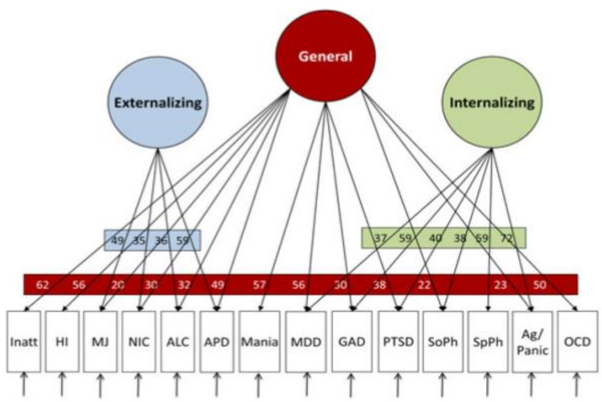

Figure 1. Bifactor model of psychopathology (Inatt = inattention, HI = hyperactivity/impulsivity, MJ = marijuana use, NIC = nicotine us, ALC = alcohol use, APD = antisocial personality disorder, MDD = major depressive disorder, GAD = generalized anxiety disorder, PTSD = posttraumatic stress disorder, SoPh = social phobia, SpPh = specific phobia, Ag/Panic = agoraphobia/panic, OCD = obsessive compulsive personality disorder) (Lahey, Zald, et al., 2017).

One might wonder what exactly this general factor is capturing. It has been hypothesized to capture a range of processes such as disordered thinking, poor emotion regulation abilities, tendency to respond to stress with negative affect, or cognitive dysfunction. Each of these features is shared across disorders (Caspi & Moffitt, 2018). Given preliminary evidence that schizophrenia, mania, and obsessive compulsive disorder load heavily onto the general factor, features of these disorders may also represent the severe end of the continuum and be important for understanding the general factor (Caspi et al., 2014; Lahey, Krueger, et al., 2017).

Correlates of the general factor

The extent to which the bifactor model of psychopathology proves useful rests on its ability to reveal meaningful features and correlates of psychopathology. In support of this, the general factor predicts both current and future adaptive functioning and demonstrates stability across development (Greene & Eaton, 2017; Lahey et al., 2012; Tackett et al., 2013). A number of studies have begun to identify personality and behavioral correlates of this construct. It has been linked to deficits in executive function skills such as response inhibition and working memory (Castellanos-Ryan et al., 2016; Huang-Pollock, Shapiro, Galloway-Long, & Weigard, 2017; Martel et al., 2017). Further, a number of personality correlates have been identified including negative emotionality, impulsivity, and hopelessness (Castellanos-Ryan et al., 2016; Tackett et al., 2013) .

Fewer data exist regarding the neural correlates of the general factor. Structural correlates identified thus far include surface area and volume of multiple brain regions such as the orbitofrontal cortex, prefrontal cortex, ventro-lateral prefrontal cortex, occipital lobe, and cerebellum (Romer et al., 2018; Snyder, Hankin, Sandman, Head, & Davis, 2017). It has also been linked to white matter microstructure properties of the corpus callosum and the pons (Hinton et al., 2019; Romer et al., 2018). Functional correlates are also beginning to be identified. For example, delayed development in the default mode network has been linked to the general factor (Sato et al., 2016). Further, the general factor is associated with decreased perfusion within multiple brain regions including the dorsal anterior cingulate (Kaczkurkin et al., 2017). Finally, it has been linked to hypoactivation in the anterior cingulate cortex during working memory task (Shanmugan et al., 2016).

While such studies provide preliminary evidence of neural correlates for the general factor, more studies are needed to better characterize its neurobiological etiology. Such data would be particularly informative because it is difficult to interpret most existing case-control studies that cannot discriminate between neural correlates that reflect broad shared etiological features or narrower dimensional features of psychopathology. Identifying the neural correlates of shared features of psychopathology will help provide insight into their etiology and may thus yield novel therapeutic targets.

While the bifactor model shows promise, it is important to note some caveats. Though the superior fit statistic of the bifactor model is compelling evidence for its validity, there are some potential pitfalls with this conclusion, since the higher fit statistic may actually reflect an artifact of overfitting or be a product of measurement error (Bonifay, Lane, & Reise, 2017; Widiger & Oltmanns, 2017). Another criticism is that the factor loadings of first-order symptom dimensions on second-order latent factors vary across studies, which makes it difficult to meaningfully interpret these factors (Watts, Poore, & Waldman, 2019). Thus, in examining correlates of the bifactor model it is sensible to conduct the same analyses using the correlated factors model to determine which produces more meaningful results. Such an approach will provide additional information on the utility of the bifactor model for identifying correlates of psychopathology.

Brain network topology

Studies on the neural correlates of psychopathology have often focused on individual regions or a small collection of connected brain regions. However, findings at these levels may be indicative of patterns at the broader level of brain network organization (Bullmore & Sporns, 2009; Pol & Bullmore, 2013). It may be that while symptom and disorder level correlates are constrained to narrow circuits, the general factor of psychopathology is associated with broader properties of brain organization (Zald & Lahey, 2017). One way of looking at these properties is through the application of graph theory techniques to examine network topology (Bullmore & Sporns, 2009).

The premise of graph theory approaches is that the brain can be conceptualized as a non-random network (Bullmore & Sporns, 2009). The structure of this network is based on the connections between brain regions. From a network perspective, optimal brain structure likely consists of a large number of short connections within functionally distinct subnetworks and a smaller number of long connections between these subnetworks (Rubinov & Sporns, 2010; Tononi, Sporns, & Edelman, 1994). Graph theory analytic techniques can be applied to quantify the ways in which individuals may conform to or deviate from this optimal network structure.

Network construction

The first step to produce graph theory metrics is network construction. For this approach, brain regions are conceptualized as nodes, and the connections between them as edges (Bullmore & Sporns, 2009). These nodes and edges together form a connectivity matrix (Figure 2). The nature of the nodes can vary based on the parcellation scheme that is selected for dividing the brain into different regions (Van Wijk, Stam, & Daffertshofer, 2010). The edges can also be defined using multiple approaches, which broadly can be divided into the two categories of structural and functional network topology. These methodologies are used to quantify the extent to which a connection may exist between regions. For example, activity may be correlated between pairs of regions, and the correlation coefficient is used to quantify the strength of connection, which is referred to as the weight.

Matrices are often thresholded to remove spurious edges. Matrices can then either be binarized, with edges that have a weight greater than 0 set to 1, or the weights can be preserved (Figure 2). Using weighted matrices has the advantage that it does not treat all weights as equivalent, and thereby provides more nuanced information about connectivity. Once a matrix is generated it can be analyzed using graph theory tools to produce information about the configuration of the nodes and edges. This allows for quantification of properties of brain network organization.

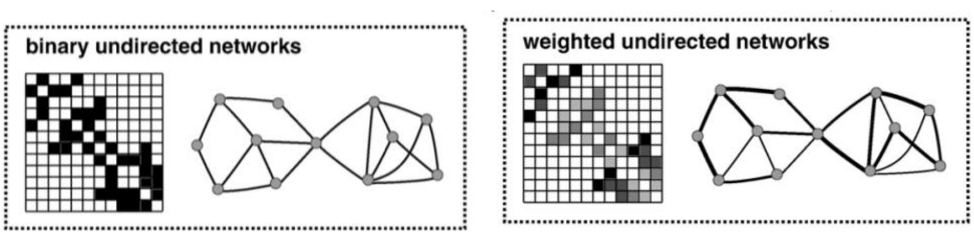

Figure 2. Connectivity matrices are the checkered boxes. Each row and column represents a brain region (node) and the boxes represent connections (edges). E.g. the box that is row 1 column 2 represents the connection between nodes 1 and 2. A white box indicates no connection, and a black or grey box represents a connection. In the left image, the matrix is binarized so that a presence of an edge is set to 1, and the absence is set to 0. In the right image, the matrix is weighted, so that the absence of an edge is 0, and the shading represents the strength of the weight with darker shading representing a stronger connection (Rubinov & Sporns, 2010).

Structural network topology

Structural network topology provides insights into the structure of brain networks, and can be measured via several types of data. One popular way to construct networks is using diffusion weighted imaging (DWI) data. In order to construct a matrix, tractography is applied to identify white matter connections between brain regions. These tracts can be identified either by deterministic or probabilistic tratography. The weight in determinist tractography can be fiber number, average length of tracts, or fractional anisotropy (a measure of white matter microstructure). The weight in probabilistic tractography is the probability that the two regions are connected. A key advantage of using DWI to construct matrices is that the interpretation is relatively straightforward in that it is indexing axonal connections between brain regions.

While using DWI to produce structural network topology matrices has a number of strengths, this approach does have some notable methodological limitations. These include challenges detecting long range connections such as interhemispheric tracts, the tendency towards false positives, and susceptibility to motion (Donahue et al., 2016; Maier-Hein et al., 2016; Maier-Hein et al., 2017; Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). An alternative to using DWI to study structural network topology is to use morphometric features derived from T1 scans. The predominate approach has been to produce group-level structural covariance matrices by correlating a single morphometric feature (e.g. volume or thickness) across subjects. These matrices can then be used to compare network topology measures between groups. The inability to extract subject-level metrics limits the utility of this approach. In particular, this precludes the ability to examine neural correlates of individual difference variables as well as to conduct dimensional analyses. A recent approach that addresses these limitations is to use multiple morphometric features (e.g. volume, thickness, curvature, etc.) to generate subject-level structural covariance matrices.

While subject-level anatomical covariance matrices are likely informative for studying structural network topological, the interpretation of metrics derived from these matrices is less intuitive than those generated via DWI matrices. Initial studies have begun to characterize what anatomical covariance matrices can tell us about network structure. First of all, these matrices show organizational properties that converge with DWI and functional matrices (Alexander-Bloch, Raznahan, Bullmore, & Giedd, 2013; Evans, 2013; Li et al., 2017; Seidlitz et al., 2018). There is also significant overlap with matrices derived from DWI data, and when an anatomical covariance matrix was compared with tract-tracing in a macaque, a significant portion of the edges reflected axonal connections (Figure 3) (Gong et al., 2012; Seidlitz et al., 2018). Additionally, regions that are connected by edges in anatomical covariance matrices have similar cytoarchitectural features (Seidlitz et al., 2018). Regions linked by edges have also been found to share similar maturational patterns and are somewhat predictive of functional networks (Alexander-Bloch et al., 2013). Finally, there is also preliminary evidence these linked regions have shared co-expression of genes (Seidlitz et al., 2018). Overall these findings suggest that anatomical covariance matrices provide information about underlying connections that converge with DWI matrices, but also confer some unique information. It is important to note that there has been some variability in the features selected to produce these structural covariance matrices. While these matrices appear to be relatively robust to the number of features, at present it is still an open question as to what the influence is of selecting certain features over others (Seidlitz et al., 2018).

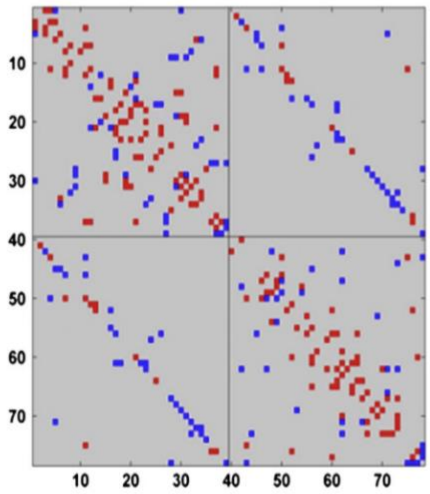

Figure 3. Convergence and divergence between a DWI matrix and a thickness covariance matrix. Dots in red are edges that are shared in DWI and thickness matrices, and blue dots show edges that are unique to the thickness covariance matrix (Gong, He, Chen, & Evans, 2012)

Functional network topology

By using functional magnetic resonance imaging (fMRI) data matrices can be constructed to look at functional network topology. This can be indexed via either resting-state or a task. In resting-state scans, time-series are extracted from each brain region of interest and then correlated between pairs of regions. In tasks one common approach is to take activation across a given trial type and correlate that between pairs of regions to produce matrices for each trial type; this allows for quantification of network features across different trial types which can then be assessed in relation to disorders. Using task-based data provides a window into how network structure may reconfigure to support shifting task demands.

Network organization

Graph theory analytics can be applied to generate a wide range of measures. In order to contextualize these measures, it is useful to detail some general principles of brain network organization. The brain represents a balance of low wiring costs and quick transfer of information, and network organization can be viewed in the context of these competing demands (Figure 4) (Bullmore & Sporns, 2012).

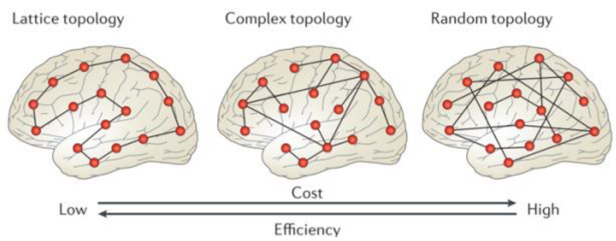

Figure 4. Models of network topology (Bullmore & Sporns, 2012).

There are several different organizational schemes that resolve these competing demands in different ways. In a lattice topology, there are only short-range connections, which minimizes the wiring cost but decreases efficiency of transfer of information. By contrast, random topology has a number of long range connections, and thus maximizes efficiency in transfer of information but increases wiring costs. Network topology in the brain likely reflects something between these two extremes by having complex topology.

In order to support complex topology, the brain is characterized by a few organizational principles. First of all, the brain has small world properties. This indicates that brains have highly connected nodes (like lattice topology) as well as short connection distances between nodes (like random topology). Another principle is that the brain is divided into modules (Figure 5). These modules contain highly interconnected nodes with more connections within than between modules (Bullmore & Sporns, 2009; Supekar, Menon, Rubin, Musen, & Greicius, 2008). These modules allow the brain to support specialized processing. Finally, the brain is characterized by the presence of hub nodes. These hub nodes are especially integral to transfer of information within the network because they are highly interconnected and form the backbone of the network (Rubinov & Sporns, 2010). These fall into two broad categories: connector hubs, which facilitate communication between modules, and provincial hubs, which facilitate communication within modules (Figure 5). Graph theory metrics allow for categorizing features of network topology, and often index the extent to which the brain may deviate from optimal organization.

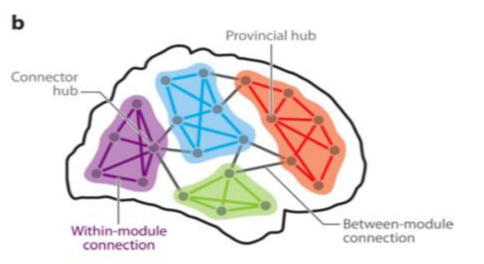

Figure 5. Depiction of hub nodes and modular structure of brain (Sporns & Betzel, 2016).

Psychopathology and brain network topology

Metrics implicated across disorders

Studies have begun to apply network analyses to examine the neural correlates psychopatholgy, and thus have begun to provide insights into relevant metrics. However, these studies have primarily been at the disorder and symptom level, and to our knowledge no studies to date have looked at the relation between the general factor of psychopathology and network topology measures. Thus, the extent to which findings at the symptom or disorder level are specific to these domains versus related to higher order factors remains unclear. At the higher order level, some neural correlates may be nonspecifically related to risk for any form of psychopathology through the general factor (Lahey, Krueger, et al., 2017). Such correlates are likely captured by graph theory metrics that have been implicated across a range of disorders, and thereby may be less specifically linked to a given disorder and instead reflect shared features of psychopathology (Table 1).

Table 1. Graph theory metrics posited to be relevant for psychopathology

Metric	Description
Degree	Average number of edges connected to each node
Mean clustering coefficient	Average number of connections between neighboring regions
Characteristic path length	Typical minimum number of edges connecting pairs of regions
Small world parameter	Mean clustering coefficient/characteristic path length
Modularity	Non-overlapping subgroups within a network

There are a number of graph theory metrics that have been implicated in psychopathology. One such metric is degree. Degree describes the average number of edges that each region is connected to. In Figure 6, node C would have the lowest degree (1) and node F has the highest degree (5). Changes in degree have been identified in across a range of regions in disorders such as alcohol dependence, depression, and social anxiety (Sjoerds et al., 2017; Yang et al., 2017; Zheng et al., 2015). Changes in degree may be indicative of differences in hub node properties. Degree is an important metric because it is a building block feature of networks that influences a range of other network measures (Rubinov & Sporns, 2010).

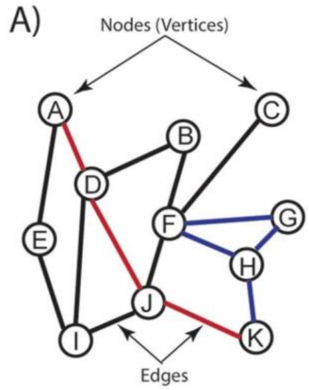

Figure 6. Depiction of a nodes and edges and their properties (Mears & Pollard, 2016).

Metrics capturing small world features have been among the most frequently examined in psychopathology. These characteristics include characteristic path length, average clustering coefficient, and the small-world parameter. Characteristic path length is the typical minimum number of edges one has to pass through to connect any two regions. In Figure 6, the path length between A and K is depicted in red and would be 3. This is a measure of integration and examines how efficiently information is transferred through the network. Clustering coefficient examines network segregation, and is calculated based on the average number of connections between adjacent brain regions. In Figure 6, the clustering coefficient of H would be 1/3 since only one of the three possible connections between its neighbors exists (F-G exists but not F-K or G-K). Average clustering coefficient across the network is a measure of local connectivity, and it can index how resilient a network is, since a more densely connected network can better survive insult. Optimal brain network structure is likely characterized by a high clustering coefficient and a low characteristic path length.

One way to index the extent to which a network adheres to a balance in integration and segregation is via the small-world parameter, which quantifies the ratio of mean clustering coefficient to characteristic path (both normalized by random networks that preserve the basic features of the network but has a random topology). For networks exhibiting small-world properties, the small-world parameter is generally greater than 1, since the clustering coefficient should be higher than that of a random network (normalized clustering coefficient > 1) and the characteristic path length is generally roughly equivalent to that of a random network (normalized path length ≈ 1). Perturbations in the small-world parameter suggest a tendency towards a less coherent and more random brain structure. Deviations from small-world architecture may produce less efficient processing, which may lead to deviations from optimal network functioning to support processes such as cognitive and emotional processing (Latora & Marchiori, 2001; J. Zhang et al., 2011). Deficits in small-world properties have been consistently identified in schizophrenia as well as in obsessive compulsive disorder, attention deficit and hyperactivity disorder, and antisocial personality disorder (Bassett et al., 2008; Jiang et al., 2017; Wang et al., 2009; J. Zhang et al., 2011; Zhang, Yang, Li, Yue, & Zang, 2011).

Modularity is another property of network topology that is likely relevant for psychopathology. This metric describes the extent to which the brain can be divided into non-overlapping modules, with more connections within than between modules. A modular structure allows for efficient processing within subnetworks, and there is often a hierarchical structure to these modules (Ferrarini et al., 2009). Changes in modularity have been implicated across a range of disorders including schizophrenia, antisocial personality disorder, and posttraumatic stress disorder (Alexander-Bloch et al., 2010; Jiang et al., 2017; Sartin-Tarm, Cisler, & Ross, 2018). Higher modularity may reflect more densely connected modules which are less sensitive to insult (Shekhtman, Shai, & Havlin, 2015).

In examining structural network topology in relation to psychopathology, it is important to consider other factors that might impact both topology and psychopathology. Childhood poverty is associated with increased rates of psychopathology, and there is preliminary evidence that structural network topology is also be impacted by poverty (Bor et al., 1997; Costello, Compton, Keeler, & Angold, 2003; Kim et al., 2019; Slopen, Fitzmaurice, Williams, & Gilman, 2010). There is also evidence that both network topology and psychopathology demonstrate sex differences (Chen, Liu, Gross, & Beaulieu, 2013; Elton et al., 2014; Gong et al., 2009; Ingalhalikar et al., 2014; Kessler et al., 2005). Thus, it may be the case that that relations between psychopathology and structural network topology are impacted by poverty status as well as by sex.

It is also important to note that studies on psychopathology and network topology have varied in their use of functional and structural neuroimaging data. While structural network topology is relatively stable, properties of functional network topology can reconfigure dynamically based on the context. Certain types of pathology may be linked predominately to one type of topology or to both, and each may provide different insights into etiology. Psychopathology is likely characterized by perturbations in both underlying structural network topology and in the ability of functional network topology to reconfigure dynamically to support changing environmental demands. Thus, it is likely that the general factor may show correlates of both types of topology.

Functional network topology

Functional topology can be considered in both the context of rest and in response to a task. The majority of graph theory studies on psychopathology have focused on resting-state data. However, looking at graph theory metrics during tasks may be especially meaningful for understanding the general factor, for psychopathology is often characterized by difficulties adapting to changing environmental demands (Caspi et al., 2014). Indeed, studies on graph theory metrics in healthy participants during tasks have shown that the extent to which networks reconfigure during tasks is predictive of performance (Fornito, Harrison, Zalesky, & Simons, 2012; Gratton, Laumann, Gordon, Adeyemo, & Petersen, 2016; Yue et al., 2017).

A handful of studies have linked graph theory metrics during a fMRI task to psychopathology. One such study linked increased modularity during a threat processing task to posttraumatic stress disorder (Cisler, Privratsky, Smitherman, Herringa, & Kilts, 2018). Another study using a cognitive control task found differences in global efficiency (a measure that is inversely related to path length) in individuals with schizophrenia as compared with healthy controls (Ray et al., 2017). Such studies suggest provide preliminary evidence that task-based functional topology may be relevant for psychopathology.

In examining task-based correlates that might be relevant to the general factor, a natural candidate would be a process that is disrupted across disorders. Aberrant reward processing is one such transdiagnostic construct that has been identified across a range of disorders (Whitton, Treadway, & Pizzagalli, 2015; Zald & Treadway, 2017). The nature of the perturbation varies, with some disorders showing a heightened response and others showing a blunted response. Given the transdiagnostic nature of reward processing, graph theory metrics during a reward task may be linked to the general factor. In particular, functional network topology may change in response to conditions with and without reward, and the magnitude and directionality of this change may be related to the general factor.

To our knowledge, only one study has looked at graph theory metrics during a reward anticipation task in individuals with psychopathology (Manelis et al., 2016). This study had both win and loss trials and compared individuals with depression, bipolar disorder, and healthy controls. They found that individuals with bipolar disorder had higher density (number of existing connections/possible number of connections) within a reward network than either individuals with depression or healthy controls during win anticipation. These findings provide initial evidence that functional network topology during a reward task may be relevant for psychopathology.

Present studies

The aim of this dissertation is to examine how structural and functional network topology may be linked to the general factor of psychopathology. In order to address this question, it is optimal to have a sample with a wide range of psychopathology which yields a sufficient latent factor score range. The Tennessee Twin Study (TTS) provides such a sample. The first wave of the TTS was conducted in 2001 (2000+ twin pairs) and consisted of a representative sample of all live twin births in the state of Tennessee from 1984 to 1995 (Lahey et al., 2008). During the first wave, the twin pairs were adolescents (ages 12-17). For the second wave, twin pairs were selected with oversampling for internalizing and externalizing psychopathology risk based on data from clinical interviews during wave 1. As such, this is a community sample with a wider range of psychopathology than is typically present in a standard case-control design. During the second wave of the study, participants completed a clinical interview as well as structural and functional neuroimaging scans. As such, this sample allows for the examination of network topology and the general factor of psychopathology.

This dissertation consists of three studies. Study one and two both focus on structural topology, with study one using DWI and study two using morphometric properties (volume, thickness, etc.). We have chosen to use these two modalities because they provide both overlapping as well distinct information about structural network topology (Evans, 2013; Gong et al., 2012). Study three focuses on functional network topology during a reward task. Across all studies, we examine if properties of network topology are related to the general factor of psychopathology. In addition, we test if relations exist at the level of higher-order specific internalizing or specific externalizing psychopathology. Examining relations across these different latent factors will provide additional confidence in the specificity of any identified significant relations between the general factor of psychopathology and graph theory metrics. Finally, we examine if relations exist with latent factors from a correlated factors model in which there is an internalizing and an externalizing factor that are allowed to correlate. This will allow us to test competing models of psychopathology. Given the dearth of studies on this topic to date, we did not formulate hypotheses, and instead examined relations with graph theory metrics commonly implicated across a range of disorders (degree, clustering coefficient, path length, small-world parameter, and modularity) and used false discovery rate corrections to account for the number of tests.

CHAPTER II

Study 1: Diffusion Weighted Imaging

Introduction

Study one looked at the relation between structural network topology as measured via diffusion weighted imaging (DWI) and the general factor of psychopathology. DWI matrices provide information about axonal connections between brain regions. We examined graph theory metrics (degree, clustering coefficient, path length, small-world parameter, and modularity) in relation to the bifactor model (general, specific internalizing, and specific externalizing) and the correlated factors model (internalizing and externalizing).

Materials and methods

Participants

All studies were conducted using data that was collected under a NIMH Research Domain Criteria (RDoC) grant (R01MH098098). Participants were selected from the Wave 1 of the Tennessee Twin Study (TTS) (Lahey et al., 2008) for the Wave 2 evaluation 10-15 years (median = 12 years) later.

Wave 1 sample

The wave 1 sample is representative of 6-17 year-old twins in Tennessee's five metropolitan statistical areas (MSAs) in 2000-2001. The Tennessee Department of Health identified all twin pairs born in Tennessee in the eligible age range; 2431 twin pairs were eliminated because they lived outside an MSA. A random sample was selected from the remaining families, stratified by age and geographic subareas, proportional to the number of families. Of 4012 selected households, 3592 (89.5%) were located and screened, with 2646 of screened families being eligible (co-residence with the caretaker at least half time during the past 6 months and twins and caretakers spoke English). Interviews were completed with 2,063 adult caretakers (90.8% biological mothers), with a 70% response rate. When caretakers were interviewed, 98% of both twins were interviewed. After excluding pairs in which either twin had been given a diagnosis of autism, psychosis, or seizure disorder, the sample consisted of 3,990 twins in 1,995 complete pairs. Caretakers classified 71% of the twins as non-Hispanic white, 24% African American, 2% as Hispanic, and 3% as other groups.

Wave 2 sample

Twin pairs for Wave 2 assessments were recruited in four replicates in reverse order of their age in wave 1 (16-17, 14-15, 12-13, and 10-11 years) to minimize the age distribution in wave 2. Twin pairs were eligible if the last known address of both twins was within 300 miles of Vanderbilt University (95.2% of twins). Wave 2 replicates were selected by oversampling on wave 1 psychopathology scores based on the greater rating of each symptom from the parent or youth. High-risk pairs were selected with certainty if either twin had symptom ratings on the total number of internalizing, attention-deficit/hyperactivity disorder, or the combination of oppositional defiant disorder and conduct disorder symptoms in the top 10% of that age range. In addition, 19-23% of the remainder of each replicate was randomly selected with two constraints: (1) monozygotic pairs were oversampled by randomly excluding 40% of the randomly selected dizygotic pairs, and (2) the number selected from the remainder of the sample varied slightly to equate replicate sizes (100-105 pairs).

Three pairs of twins could not be located and 37 pairs refused screening. Eighteen selected pairs of twins across replicates were declared out of scope due to previous participation in a pilot study, mental or physical incapacity, residence outside the U.S., imprisonment, or death. Individuals were pre-screened and excluded if they had multiple concussions with loss of consciousness or other head injuries, neurological diseases other than headaches, contraindications for MRI scanning, a diagnosis of schizophrenia, or a major developmental disorder. Vanderbilt University's Institutional Review Board (IRB) approved the study, and the study was conducted in accordance with the guidelines of the IRB including participants providing written informed consent. A total of 114 screened individual twins were ineligible for neuroimaging for feasibility (e.g., body weight) and safety reasons, but were eligible for assessment of psychopathology. Interviews regarding psychopathology were completed for 72% of the screened sample during 2013-2016, including 499 subjects (248 complete twin pairs (49.6% monozygotic; 66.9% high risk) and 3 individuals without their twin). Consistent with oversampling participants based on Wave 1 psychopathology, 50.3% met criteria for at least one Wave 2 mental disorder (46.2% of females; 54.8% of males) in the past year and 26.8% met criteria for ≥ 2 diagnoses. For study one we focused on participants who completed a DWI scan in addition to a clinical interview. This initial sample included 430 young adults.

Measures

During wave 2 of the study individuals completed a clinical interview, self-report measures, behavioral tasks, and neuroimaging scans.

Clinical interview

A trained interviewer administered the computer-assisted implementation of the Young Adult Diagnostic Interview for Children (YA-DISC) to all participants in wave 2 of this study (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The YA-DISC has the primary advantage that it has few skip-outs, and thus queries symptoms even when the participant cannot reach criteria for a diagnosis, which is critical when measuring dimensional psychopathology. This differs from most structured diagnostic interviews that insert multiple skip-outs to save time. The YA-DISC has been primarily developed for 18-24 year olds (Hart, Lahey, Loeber, Applegate, & Frick, 1995; Shaffer et al., 1996), whereas the present sample included subjects from 23-31. However, questions are worded in a manner that appears equally appropriate for individuals throughout their early adulthood. The present analyses are based on dimensional scores based on YA-DISC assessed symptoms of generalized anxiety disorder (GAD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), agoraphobia, obsessive-compulsive disorder (OCD), manic episodes, panic attacks, social phobia, specific phobia, antisocial personality disorder, attention deficit and hyperactivity disorder (ADHD), as well as nicotine, alcohol, marijuana, and other drug use disorders during the last 12 months.

Neuroimaging data

For diffusion weighted images the scan length was 5 min 2 s. We used a multi-slice Stejskal-Tanner spin echo sequence with an echo planar imaging readout (TE/TR=52/7750 ms, SENSE=2.2, FOV: 240x240 mm, 2.5 mm isotropic, 50 slices, 2.5 mm slice thickness). This was acquired with one image without diffusion weighting (“b_0”) and 32 diffusion-weighted images ($b=1000$ s/mm^2).

Data analyses

Neuroimaging data

Preprocessing and quality assurance

Quality checking of the DWI data for all subjects including movement and bias in measures was performed by consulting an automated quality assurance PDF (Lauzon et al., 2013). Studies have found that motion has a significant impact on metrics produced from DWI data, and thus it is important to be conservative and exclude outliers (Yendiki et al., 2014). Based on inspection of these data, we have excluded 20 subjects. Subjects were excluded based on limited coverage of the cortex or outliers for quality assurance metrics. After excluding these subjects, the sample size was 410.

Preprocessing was conducted using the Pipeline for Analyzing braiN Diffusion imAges (PANDA) (Cui et al., 2013). This pipeline allows for processing multiple subjects in parallel and implements widely used software packages such as the FMRIB Software Library (FSL) (Smith et al., 2004). DWI data were preprocessed including generation of brain masks, corrections for eddy-current distortions, and production of FA images. FA images were transformed to MNI space. We utilized the default parameters within the PANDA pipeline. Quality check PDFs were generated for these steps and were visually inspected. Based on visual inspection of PDFs we excluded one additional subject for whom brain segmentation failed. This yielded a final sample of 409 subjects.

Network construction

Network construction was also completed using PANDA. The first portion of network construction is defining nodes, which is done by segmenting the brain using a grey matter atlas. In order to do this, the FA image was registered to the T1 image and then both were registered to the ICBM152 template. Previous studies have often used the Automated Anatomical Labeling Atlas (AAL) or the Harvard-Oxford atlas (HOA), but these are problematic because nodes vary in size, which may skew the results (Fornito, Zalesky, & Bullmore, 2010; Kennedy et al., 1998; Tzourio-Mazoyer et al., 2002). Thus, we employed a finer-grained parcellation of the HOA atlas. The original parcellation contains 110 regions. This was parcellated into 471 regions according to the algorithm of Fornito and colleagues (Fornito et al., 2010). Because we had inconsistent coverage of the cerebellum across subjects, we excluded regions in the cerebellum, thereby resulting in 397 regions (Figure 7).

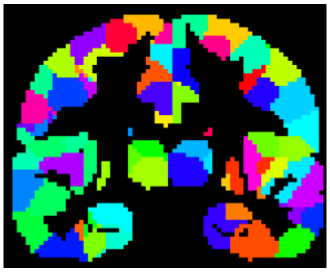

Figure 7. Parcellation of brain into 397 nodes.

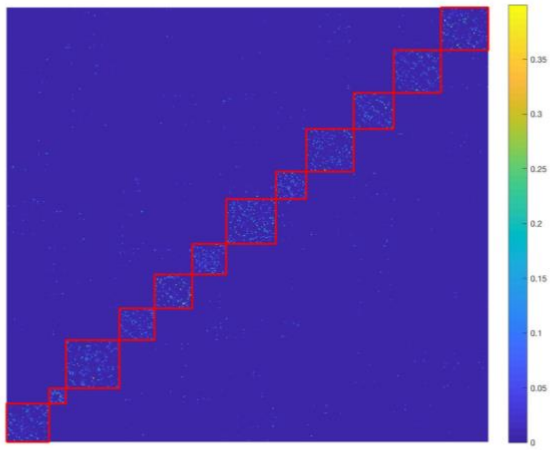

Figure 8. DWI weighted matrix organized based on community structure. Each row and column represents a brain region, and where the meet represents their edge. Red boxes represent modules. Color bar depicts probability of connection (edge weight).

The second portion of network construction is defining the edges, which are the connections between pairs of regions. A matrix was constructed via probabilistic tracking using FSL (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007; Behrens et al., 2003) (Figure 8). This was completed in two steps. First bedpostX was implemented to derive a probability distribution at each voxel. Next for each voxel 5000 samples were taken using probtrackx. The number of fibers connecting two regions divided by the total number of fibers leads to the edge weight. For pairs of regions each were used as the seed and termination mask and then the probability was averaged across the two. We did not threshold the matrices based on recent work indicating that the benefits of thresholding do not outweigh the costs (Civier, Smith, Yeh, Connelly, & Calamante, 2019).

Network analysis

Analyses of matrices were conducted using the MATLAB Brain Connectivity Toolbox (BCT; Rubinov and Sporns, 2010). We first calculated degree across each node and then took the average (degrees_und.m). In addition, we calculated average density across the network (density_und.m).

We next calculated small-world parameters. Average clustering coefficient (clustering_coef_wu.m; C) was calculated for each subject. For characteristic path length, we first generated a weighted connection-length matrix (weight_conversion.m) and then used that to generate a distance matrix (distance_wei.m). Finally, we used this distance to calculate characteristic path length (charpath.m; L). In order to normalize these metrics, we calculated average clustering coefficient and characteristic path length across 1,000 random networks per subject. These random networks have the same number of nodes and edges and preserved the degree distribution of the original network (Figure 9). We then divided each subject's value by the one derived from the random network to produce normalized path length ($\lambda = L_{subject}/L_{random}$) and normalized clustering coefficient ($\gamma = Cs_{ubject}/C_{random}$). The small world parameter (σ) was calculated as a ratio of these two metrics (γ/λ). For small world networks, $\lambda \approx 1$, $\gamma > 1$, and $\sigma > 1$.

We used Louvain community detection algorithm to calculate modularity (Q; community_louvain.m). Given that the modularity algorithm does not yield the same result each time, we ran it 1,000 times and averaged modularity (Q) across these runs. We then normalized this by a modularity calculated across a random network. In order to examine community structure across the sample, we also derived an agreement matrix for each subject across the 1,000 runs (agreement.m). We then generated a consensus partition for each subject using 1,000 runs and a threshold of .20 (consensus_und.m). Using the consensus partitions from each subject we calculated a group-level agreement matrix and then used this to produce a group-level consensus partition. We generated this consensus partition in order to verify that we could produce modules that demonstrate reasonable concordance with prior studies.

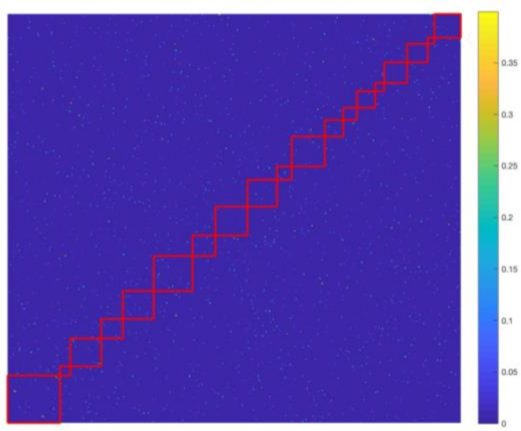

Figure 9. DWI random matrix organized by community structure.

Statistical analyses

Bifactor model

All factor analyses and structural equation modeling were performed using Mplus 8.1 (Muthén & Muthén, 2018). Theses analyses accounted for stratification and clustering with twin pairs and used joint weights that both (a) accounted for the inverse of the probability of selection into wave 2 based on the selection strategy, and (b) adjusted for any biases due to nonresponse or missing data after quality control relative to the participant’s age in wave 2, sex, family income, maternal education, and wave 1 measures of psychopathology, dispositions, and working memory using lasso logistic regression. These joint weights allow valid parameter estimates when weighted back to the full wave 1 TTS sample (Korn & Graubard, 1999). Robust maximum likelihood (MLR) estimation was used to account for non-normality in first-order symptom dimensions and adjust standard errors to reflect the clustering of twins within twin pairs.

In the first step of these analyses, general, specific internalizing, and specific externalizing factors were estimated using a bifactor measurement model. This model was estimated with fixed nonstandardized factor loadings for symptom dimension on externalizing, internalizing, and general factors based on a previously published study but using slightly updated weights (Lahey, Zald, et al., 2017). In this prior study, a bifactor model was fitted using a latent factor analysis with the full wave 2 TTS dataset (n=499) to produce the best fitting model. First-order symptom scores were allowed to load on a general factor. First order symptom counts of antisocial personality disorder and maladaptive nicotine, alcohol, and marijuana misuse all loaded significantly onto the specific externalizing factor and MDD, GAD, PTSD, agoraphobia/panic, social phobia, and specific phobia loaded significantly onto the specific internalizing factor. Because common variance is accounted for by the general factor, the specific internalizing and specific externalizing factors were set to be orthogonal. This differs from more traditional correlated factor models in which internalizing and externalizing factor loadings do not distinguish between common and specific sources of variance, and are therefore correlated. Standardized factor loadings in the bifactor measurement model of second-order factors used in these analyses are shown in Figure 10.

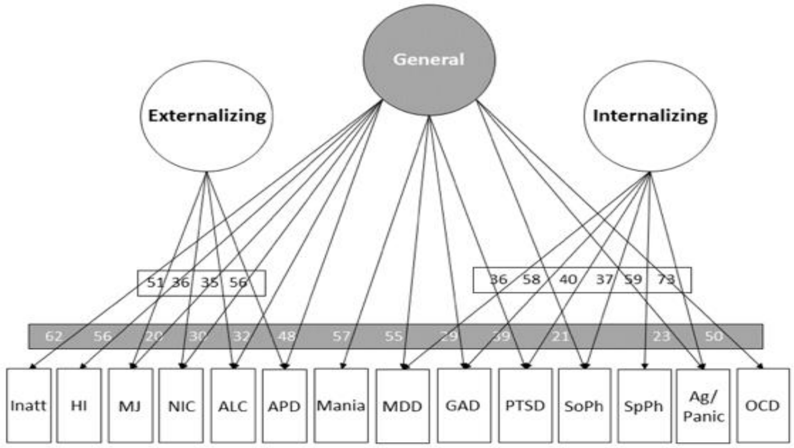

Figure 10. Bifactor model with standardized loadings (Hinton et al., 2019). Only significant loadings are listed (Inatt = inattention, HI = hyperactivity/impulsivity, MJ = marijuana use, NIC = nicotine us, ALC = alcohol use, APD = antisocial personality disorder, MDD = major depressive disorder, GAD = generalized anxiety disorder, PTSD = posttraumatic stress disorder, SoPh = social phobia, SpPh = specific phobia, Ag/Panic = agoraphobia/panic, OCD = obsessive compulsive personality disorder).

In the second step, to look at relations between graph theory metrics and latent factors of psychopathology, we conducted multiple regressions within structural equation models. Latent factor scores were entered as independent variables, and graph theory measures as dependent variables in separate models. In each model, the other latent factors were entered as covariates (e.g. for general factor the specific internalizing and specific externalizing served as covariates). We included the following covariates of no interest: age, sex, ethnicity, scanner and handedness. In order to minimize bias, these analyses applied weights to account for potential differences in the rates of subjects lacking useable neuroimaging data, and also accounted for clustering due to the non-independence of twin pairs and stratification based on the age of subjects during the original wave 1 data collection. Significance thresholds were set at $p < 0.05$ using false discovery rate (FDR) across all tests (15; 5 graph theory metrics x 3 latent factors).

Correlated factor model

Analyses with the correlated factors model was conducted in a similar way to the bifactor model. In the correlated factors model the first order symptom counts of inattention, hyperactivity-impulsivity, antisocial personality disorder, mania, and maladaptive nicotine, alcohol, and marijuana misuse all load on the externalizing and MDD, GAD, PTSD, agoraphobia, panic attacks, social phobia, specific phobia, and mania load on the internalizing factor. In this model, the internalizing and externalizing factors are allowed to correlate. As with the bifactor model, the factor weights were derived using the full wave 2 sample. Standardized factor loadings in the correlated measurement model of second-order factors used in these analyses are shown in Figure 11. Multiple regressions were conducted in the same way as for the bifactor model. Significance thresholds were set at $p < 0.05$ using FDR across all tests (10; 5 graph theory metrics x 2 latent factors).

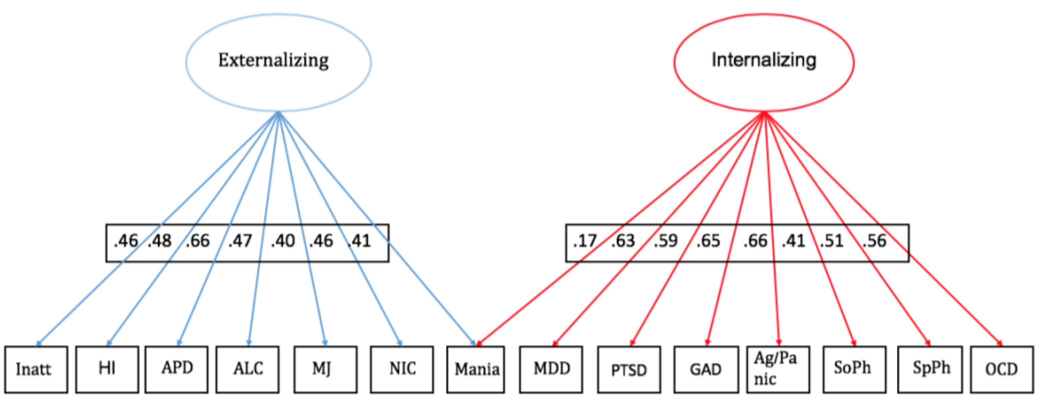

Figure 11. Correlated factors model with standardized loadings.

Sensitivity analyses

We conducted a series of planned sensitivity analyses to verify the robustness of significant relations observed in the bifactor or correlated factors model. As in the primary analyses, multiple regressions included covariates of no interest, used sampling weights, and accounted for clustering and stratification. In the first sensitivity analysis, we tested if relations remained significant with inclusion of the additional demographic covariates of family income and mother's education from wave 1. We also tested if relations remained significant with the inclusion of density as a covariate. Density is a ratio of the total number of edges to the total possible number of edges. Variable density across subjects can contribute to the emergence of significant differences in metrics, and thus it is important to covary for density to determine if this is driving significant relations (Hallquist & Hillary, 2019).

There are known sex differences in psychopathology (Caspi et al., 2014; Kessler et al., 2005). In the present sample, there were significant sex differences for all latent factors other than internalizing from the correlated factors model (Table 2). Given these findings as well as known sex differences in neuroimaging measures we conducted sensitivity analyses in which we tested significant relations observed in the full sample separately in males and females (Caspi et al., 2014; Hsu et al., 2008). We also tested for the presence of interactions with sex for each relation that was significant in at least one sex. In order to test for interactions, we ran a model in which regression coefficients were allowed to vary by sex for the significant latent factor and a model in which they were constrained to be equal in the two sexes. We then ran the Satorra-Bentler chi-square difference test to compare models, using the original formula and implementing the strictly positive version for any negative values (Satorra, 2000; Satorra & Bentler, 2010). For sensitivity analyses, the significance threshold was set to $p < 0.05$ for each test.

Table 2. Differences between latent factor scores in males and females [a]. Values in bold are significant after FDR correction.

Metric	Males mean (SD) n = 196	Females mean (SD) n = 213	T score	P value
General	0.17 (0.98)	-0.08 (0.74)	2.91	**.004**
Specific Internalizing	-0.12 (0.80)	0.24 (0.98)	-4.00	**.000**
Specific Externalizing	0.34 (0.89)	-0.13 (0.67)	5.96	**.000**
Internalizing	0.02 (1.00)	0.13 (0.98)	-1.20	.227
Externalizing	0.33 (1.05)	-0.11 (0.74)	4.92	**.000**

[a] These are factor score estimates since error is added when factors are extracted from Mplus

Results

Demographics

Demographics for the study 1 sample are presented in Table 3.

Table 3. Participant demographics for study 1.

Variable	**Mean (Standard Deviation)**
Age (Years)	26.04 (1.78)
Family income [a]	18.78 (4.97)
Mother's education (Years)	13.62 (2.71)
Variable	**N (Percentage)**
Sex	
Male	196 (47.90)
Female	213 (52.10)
Ethnicity	
White	295 (72.10)
African American	101 (24.70)
Other	13 (3.17)
Handedness	
Right	371 (90.49)
Left	39 (9.51)
Scanner [b]	
3TA	214 (52.30)
3TB	195 (47.70)

[a] Family income from wave 1 reported in brackets ranging from 0 (no income) to 24 ($100,000 and over). 18 = $35,000 - $44,999

[b] Imaging data were acquired on two identical 3T Intera-Achiava Phillips MRI scanners

Consensus partition

Consensus partition revealed 8 modules (Figure 12). This showed some overlap with prior studies, though those studies often find 5-6 modules (Chen et al., 2013; Hagmann et al., 2008; Tymofiyeva et al., 2013). This may be in part because those studies used a fewer number of nodes.

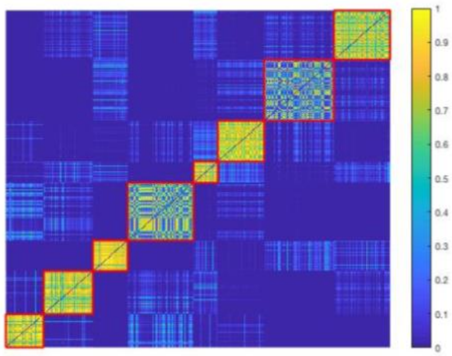

Figure 12. Consensus partition across subjects for DWI matrices.

Bifactor model

Primary analyses

There were no significant relations even at a trend level between latent factors from the bifactor model and graph theory metrics (Table 4).

Table 4. Multiple regressions of graph theory metrics derived from DWI tractography on latent general and specific internalizing and specific externalizing factors based on the fixed-loadings bifactor model, controlling demographic covariates of no interest [a] (all models n = 409).

	General		Internalizing		Externalizing	
Metric [b]	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value
Degree	-0.05 (0.08)	0.542	0.02 (0.07)	0.759	0.03 (0.09)	0.747
Clustering coefficient	-0.09 (0.08)	0.273	0.07 (0.08)	0.359	0.01 (0.08)	0.869
Characteristic path length	0.02 (0.07)	0.775	0.03 (0.07)	0.696	0.08 (0.09)	0.357
Small-world parameter	-0.02 (0.09)	0.807	0.00 (0.08)	0.989	-0.02 (0.09)	0.862
Modularity	-0.04 (0.07)	0.593	0.05 (0.07)	0.460	-0.01 (0.09)	0.936

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree were normalized to a random network

Exploratory analyses

Given that we did not find any significant relations in our primary analyses using the bifactor model, we conducted exploratory analyses. Prior studies have demonstrated the impact of poverty on both psychopathology and structural network topology (Bor et al., 1997; Costello et al., 2003; Kim et al., 2019; Slopen et al., 2010). A recent study looked at the relation between network topology as measured by DWI data and an income-to needs ratio (INR), which is the family income divided by the poverty line income for the given year and household size (Kim et al., 2019). The INR was significantly related to global efficiency (which is inversely related to characteristic path length). We thus tested if the relations between latent factors of psychopathology and graph theory metrics differed based on poverty status.

During wave 1 of the TTS, data was collected on family income and household size. The family income was reported based on ranges (e.g. $35,000 – $44,999). We thus calculated a categorical variable that denoted being above or below the poverty line during wave 1 using the poverty guidelines from 2000. While studies indicate that some additional information can be gained from a dimensional measure of poverty, the most robust predictor of outcomes is if individuals fall above or below the poverty line (Yoshikawa, Aber, & Beardslee, 2012).

In our sample, 63 subjects were below the poverty line (29 twin pairs and 5 individuals without a twin pair) and 346 subjects were above it. Demographics for the group below the poverty line are presented in Table 5. Before examining relations between graph theory metrics and latent factors in individuals above and below the poverty line, we first tested to see if graph theory metrics were significantly different between these two groups using a two samples t-test. Degree, clustering coefficient, path length, and the small world parameter were all significantly different between these two groups after FDR correction (Table 6). Modularity showed a trend-level difference ($p < .10$). We further tested for differences in latent factors from the bifactor model between the two groups (Table 7). Specific internalizing was significant after FDR correction, but neither specific externalizing nor general were.

Table 5. Participant demographics for study 1 for group below the poverty line during wave 1.

Variable	**Mean (Standard Deviation)**
Age (Years)	25.92 (1.80)
Family income [a]	9.25 (4.96)
Mother's education (Years)	11.90 (1.61)
Variable	**N (Percentage)**
Sex	
Male	24 (38.09)
Female	39 (61.90)
Ethnicity	
White	27 (42.90)
African American	29 (46.03)
Other	7 (11.11)
Handedness	
Right	56 (88.90)
Left	7 (11.10)
Scanner [b]	
3TA	29 (46.00)
3TB	34 (54.00)

[a] Family income from wave 1 reported in brackets ranging from 0 (no income) to 24 ($100,000 and

over). 9 = $7,000 – $7,900
[b] Imaging data were acquired on two identical 3T Intera-Achiava Phillips MRI scanners

Table 6. Differences between graph theory metrics derived from DWI tractography above and below the poverty line. Tests that survived FDR correction are displayed in bold.

Metric	Below poverty line mean (SD) (n = 63)	Above poverty line mean (SD) (n = 346)	T score	P value
Degree	63.84 (7.27)	67.35 (9.99)	3.31	**.001**
Clustering Coefficient	11.11 (0.70)	11.31 (0.79)	2.10	**.038**
Path Length	0.66 (0.13)	0.58 (0.15)	-4.10	**.000**
Small world	17.57 (3.73)	21.14 (8.14)	5.56	**.000**
Modularity	1.61 (0.02)	1.61 (0.02)	1.95	.055

Table 7. Differences between latent factors of psychopathology above and below the poverty line [a]. Tests that survived FDR correction are displayed in bold.

Metric	Below poverty line mean (SD) (n = 63)	Above poverty line mean (SD) (n = 346)	T score	P value
General	0.23 (1.03)	0.01 (0.84)	-1.61	.112
Specific Internalizing	0.53 (1.18)	-0.02 (0.83)	-3.45	**.001**
Specific Externalizing	0.18 (0.89)	0.08 (0.81)	-0.84	.403

[a] These are factor score estimates since error is added when factors are removed from Mplus

We next examined relations between latent factors and graph theory metrics separately in individuals above and below the poverty line and tested the interactions (Table 8). Regressions were conducted with the covariates of sex, scanner, handedness, age, and ethnicity. As in the primary analyses we ran FDR corrections within families of tests (above the poverty line (15 tests), below the poverty line (15 tests), and interactions (5 tests)). No regressions survived FDR correction. However, we identified relations that were significant at an uncorrected $p < .05$ level for the general factor with modularity, the specific externalizing factor with characteristic path length and clustering coefficient, and the specific internalizing factor with clustering coefficient.

We identified relations that were significant at a $p < .01$ level between specific externalizing and the small world parameter. There were significant interactions based on poverty status that survived FDR correction for specific externalizing with clustering coefficient and the small world parameter.

Table 8. Poverty line stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology from the bifactor model controlling for covariates of no interest [a]. Relations depicted in bold are significant after FDR corrections across families of tests (above poverty line, below poverty line, and interactions).

		Above Poverty Line (n = 346)		Below Poverty Line (n = 63)		Interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Degree [b]	General	-0.07 (.08)	0.398	0.24 (0.19)	0.212	--
Degree	Internalizing	0.06 (.09)	0.505	-0.15 (0.10)	0.134	--
Degree	Externalizing	-0.04 (0.09)	0.665	0.10 (0.19)	0.617	--
Path Length	General	0.03 (0.08)	0.752	-0.08 (0.15)	0.623	--
Path Length	Internalizing	-0.04 (0.09)	0.642	0.19 (0.13)	0.165	--
Path Length	Externalizing	0.04 (0.09)	0.665	0.45 (0.20)	0.020*	2.76
Clustering Coefficient	General	-0.11 (0.08)	0.185	-0.07 (0.13)	0.621	--
Clustering Coefficient	Internalizing	0.10 (0.10)	0.361	0.26 (0.13)	0.041*	0.62
Clustering Coefficient	Externalizing	0.05 (0.09)	0.584	-0.37 (0.15)	0.013*	**7.25**
Small World	General	-0.03 (0.09)	0.711	0.13 (0.16)	0.412	--
Small World	Internalizing	0.08 (0.10)	0.425	-0.18 (0.14)	0.198	--
Small World	Externalizing	-0.03 (0.09)	0.769	-0.46 (0.17)	0.007**	**21.98**
Modularity	General	-0.05 (0.08)	0.549	0.29 (0.13)	0.028*	2.41
Modularity	Internalizing	0.02 (0.09)	0.788	-0.13 (0.12)	0.273	--
Modularity	Externalizing	-0.01 (0.10)	0.955	-0.06 (0.18)	0.738	--

[a] Covariates of no interest: Age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, sex, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network
[c] Interactions with poverty status were tested using the satorra-bentler chi-square difference test
* $p < .05$ uncorrected
** $p < .01$ uncorrected

Sex-stratified analyses

Given previously identified sex differences in relations between an income to needs ratio and network topology metrics, we did a follow-up analysis looking at sex differences (Kim et al., 2011). We first conducted a two samples t-test to test for sex difference in graph theory metrics between individuals above and below the poverty line (Table 9). There were no significant differences (*ps* > .10). We next ran regressions between latent factors of psychopathology from the bifactor model and graph theory metrics separately in males and females in the group below the poverty line (Table 10). For these analyses, we focused on the trend-level relations found in individuals below the poverty line. The relation between characteristic path length and specific externalizing was significant in females but not males. The relation between clustering coefficient and specific internalizing was significant in males but not in females. Small world and clustering coefficient showed a significant relation with specific externalizing in both males and females. Modularity did not show a significant relation with the general factor in either sex. The only significant interaction based on sex was for the relation between clustering coefficient and specific internalizing ($p < .05$).

Table 9. Differences between graph theory metrics derived from DWI tractography for males and females below the poverty line (n = 63).

Metric	Males mean (SD) (n = 24)	Females mean (SD) (n = 39)	T score	P value
Degree	63.55 (7.80)	64.02 (7.01)	-0.24	0.808
Clustering Coefficient	10.96 (0.77)	11.21 (0.63)	-1.34	0.186
Path Length	0.66 (0.11)	0.66 (0.14)	0.15	0.880
Small world	17.07 (3.29)	17.88 (3.97)	-0.88	0.383
Modularity	1.61 (0.02)	1.61 (0.02)	0.95	0.349

Table 10. Sex stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology from bifactor model controlling for covariates of no interest in individuals below the poverty line during wave 1 (n = 63) [a].

		Males (n = 24)		Females (n = 39)		Interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Path Length	Externalizing	0.27 (0.18)	0.125	0.63 (0.22)	0.004**	1.96
Clustering Coefficient	Internalizing	0.39 (0.13)	0.004**	0.05 (0.12)	0.681	6.71*
Clustering Coefficient	Externalizing	-0.34 (0.16)	0.031*	-0.55 (0.15)	0.000**	0.09
Small World	Externalizing	-0.38 (0.14)	0.006**	-0.66 (0.16)	0.000**	1.38
Modularity	General	0.30 (0.22)	0.168	0.02 (0.20)	0.924	--

* $p < .05$
** $p < .01$
[c] Interactions with sex were tested using the satorra-bentler chi-square difference test

Given sex differences identified in relations between males and females in the group below the poverty line, we conducted a sex-stratified analysis in the full sample. For this we focused on relations that were significant in the group below the poverty line. We first looked at sex differences between metrics in the full sample using a two samples t-test (Table 11). There were no significant differences (*ps* > .10). We then examined the relations between graph theory metrics and latent factors in males and females (Table 12). There were no relations that were significant even at a trend level (*ps* > .10).

Table 11. Differences between graph theory metrics derived from DWI tractography for males and females in the full sample (n = 409).

Metric	Males mean (SD) (n = 196)	Females mean (SD) (n = 213)	T score	P value
Degree	66.13 (10.39)	67.43 (8.99)	-1.34	0.180
Clustering Coefficient	11.25 (0.76)	11.32 (0.80)	-0.87	0.385
Path Length	0.60 (0.16)	0.59 (0.14)	0.79	0.428
Small world	20.22 (6.65)	20.94 (8.62)	-0.95	0.343
Modularity	1.61 (0.02)	1.61 (0.02)	0.50	0.620

Table 12. Sex stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology controlling for covariates of no interest in the full sample (n = 409).

		Males (n = 196)		Females (n = 213)	
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Path Length	Externalizing	-0.05 (0.10)	0.666	0.13 (.16)	0.430
Clustering Coefficient	Internalizing	0.08 (0.17)	0.641	0.05 (.08)	0.530
Clustering Coefficient	Externalizing	-0.06 (0.12)	0.594	0.04 (.14)	0.787
Small World	Externalizing	0.06 (0.10)	0.579	-0.09 (.15)	0.558
Modularity	General	-.005 (0.09)	0.575	-0.03 (.10)	0.780

Correlated factors model

Primary analyses

We also looked at relations between latent factors from the correlated factors model with graph theory metrics in the full sample. There were no significant relations even at a trend level (Table 13).

Table 13. Multiple regressions of graph theory metrics derived from DWI tractography on latent internalizing and externalizing factors based on the correlated factors model, controlling demographic covariates of no interest [a] (all models n = 409).

	Internalizing		Externalizing	
	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Degree [b]	0.01 (0.08)	0.864	-0.06 (0.09)	0.521
Clustering coefficient	0.03 (0.08)	0.747	-0.05 (0.10)	0.570
Characteristic Path Length	0.04 (0.07)	0.593	0.03 (0.09)	0.752
Small world parameter	-0.03 (0.07)	0.721	-0.01 (0.08)	0.883
Modularity	0.06 (0.08)	0.497	-0.06 (0.10)	0.527

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network

Exploratory analyses

Given that we did not observe significant relations in the primary analyses for the correlated factors model, we conducted the same exploratory analyses as we did for the bifactor model. First, we looked at differences between latent factors from the correlated factors model above and below the poverty line (Table 14). Internalizing was significantly different but externalizing was not. We then examined relations between latent factors of psychopathology and graph theory metrics separately in individuals above and below the poverty line, and tested the interactions (Table 15). There were no significant or trend-level relations in individuals above the poverty line. A number of relations survived FDR corrections in the group below the poverty line. Externalizing had a significant relation with degree, clustering coefficient, and modularity. Internalizing had a significant relation with clustering coefficient. There was a significant interaction effect after FDR correction based on poverty status for externalizing with degree and modularity. Correlation plots for metrics that showed significant or trend level relations with bifactor or correlated factors model are depicted in Figure 13.

Table 14. Differences between latent factors of psychopathology from the correlated factors model above and below the poverty line [a]. Tests that survived FDR correction are displayed in bold.

Metric	Below poverty line mean (SD) (n = 63)	Above poverty line mean (SD) (n = 346)	T score	P value
Internalizing	0.54 (1.25)	-0.01 (0.91)	-3.34	**.001**
Externalizing	0.31 (1.05)	0.06 (0.90)	-1.76	.082

[a] These are factor score estimates since error is added when factors are removed from Mplus

Table 15. Poverty line stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology for the correlated factors model controlling for covariates of no interest [a]. Relations depicted in bold are significant after FDR corrections across families of tests (above poverty line and below poverty line).

		Above Poverty Line (n = 346)		Below Poverty Line (n = 63)		Interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Degree [b]	Internalizing	0.06 (0.11)	0.594	-0.10 (0.12)	0.410	--
Degree	Externalizing	-0.10 (0.10)	0.295	0.32 (0.10)	**0.002**	4.33*
Path Length	Internalizing	-0.01 (0.10)	0.942	0.04 (.10)	0.696	--
Path Length	Externalizing	0.02 (0.10)	0.819	0.25 (.14)	0.072	--
Clustering Coefficient	Internalizing	0.03 (0.12)	0.797	0.30 (0.09)	**0.001**	2.36
Clustering Coefficient	Externalizing	-0.06 (0.13)	0.651	-0.43 (0.09)	**0.000**	2.82
Small World	Internalizing	0.04 (0.10)	0.697	-0.01 (0.11)	0.934	--
Small World	Externalizing	-0.04 (0.11)	0.719	-0.24 (0.14)	0.095	--
Modularity	Internalizing	0.04 (0.11)	0.713	-0.07 (0.10)	0.518	--
Modularity	Externalizing	-0.07 (0.12)	0.566	0.29 (0.12)	**0.018**	**14.99**

[a] Covariates of no interest: Age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, sex, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network
[c] Interactions with poverty status were tested using the satorra-bentler chi-square difference test
$*p < .05$

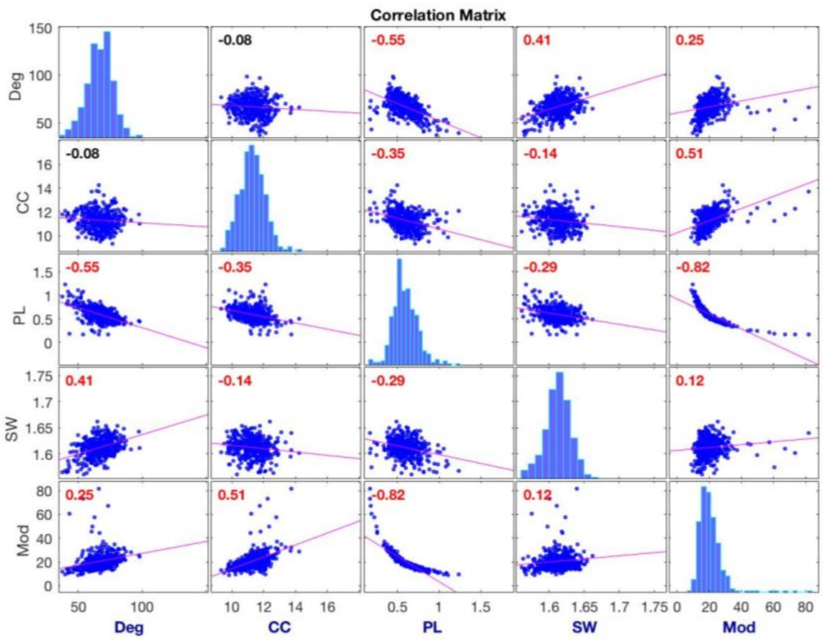

Figure 13. Correlation matrix between metrics that showed significant or trend level relations with bifactor or correlated factors model (Deg=degree, CC=clustering coefficient, PL = path length, SW = small world, Mod=modularity).

Sex-stratified analyses

As in the bifactor model, for significant relations in the group below the poverty line we looked at relations separately in males and females in the group below the poverty line (n = 63) and tested for interactions (Table 16). Degree with externalizing was not significant in either males or females. Clustering coefficient was significantly related to internalizing in both males and females. Clustering coefficient and modularity were significantly related to externalizing only in males. There was a significant interaction effect based on gender for internalizing with clustering coefficient as well as for externalizing with clustering coefficient and modularity.

Table 16. Sex stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology for correlated factor model controlling for covariates of no interest in full sample 1 (n = 409) [a].

		Males (n = 24)		Females (n = 39)		Interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Degree	Externalizing	0.69 (0.40)	0.082	-0.01 (0.17)	0.996	--
Clustering Coefficient	Internalizing	0.56 (0.25)	0.023*	0.26 (0.10)	0.007**	4.27*
Clustering Coefficient	Externalizing	-.087 (0.24)	0.000**	-0.11 (0.08)	0.201	5.43*
Modularity	Externalizing	0.78 (0.24)	0.021*	0.04 (0.18)	0.830	33.86**

* $p < .05$

** $p < .01$

[c] Interactions with sex were tested using the satorra-bentler chi-square difference test

Given the observed sex differences in the group below the poverty line, we completed a sex stratified analysis of relations that were significant in the group below the poverty line in the full sample (Table 17). There were no significant relations (*ps* > .10).

Table 17. Sex stratified analyses of graph theory metrics derived from DWI tractography on latent factors of psychopathology from correlated factors model controlling for covariates of no interest in the full sample (n = 409) [a].

		Males (n = 196)		Females (n = 213)	
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Degree	Externalizing	-0.02 (0.12)	0.864	-0.04 (0.12)	0.764
Clustering Coefficient	Internalizing	0.08 (0.17)	0.637	-0.02 (0.07)	0.817
Clustering Coefficient	Externalizing	-0.10 (0.15)	0.479	0.01 (0.14)	0.939
Modularity	Externalizing	0.07 (0.15)	0.625	-0.10 (0.11)	0.636

Discussion

In study 1, we looked at relations between graph theory metrics derived from DWI data and latent factors of psychopathology from the bifactor model and the correlated factors model. We did not identify any significant relations. We then conducted an exploratory analysis examining relations separately in individuals above and below the poverty line during wave 1 of the study. For the bifactor model we found trend-level relations between each latent factor and at least one graph theory metric in the group below the poverty line. In the correlated factors model we identified significant relations with both the externalizing and internalizing factor in individuals below the poverty line. There were no significant relations for the group above the poverty line within either model. In both models, there were a number of significant interactions for poverty status. These findings are novel since this is the first study to examine latent factors of psychopathology in relation to structural network topology. It is further the first to identify a poverty status interaction in the relation between these latent factors of psychopathology and network topology.

Primary analyses

The null findings for the primary analyses are in contrast to a number of prior studies that identified relations between a range of global graph theory metrics from DWI data and disorders such as ADHD, depression, substance use disorders, schizophrenia, and bipolar disorder (Bai et al., 2012; Beare et al., 2017; Çelik et al., 2019; Collin et al., 2016; Long et al., 2015; Wang et al., 2012; Zhang et al., 2015; Zhang et al., 2017). There are a number of potential explanations for the discrepancy between our findings and the existing literature. First, it is possible that relations between global graph theory metrics and psychopathology exist either at the first-order symptom or disorder level rather than the transdiagnostic level. Another possibility is that latent factors have correlates at the local rather than global level. This could include metrics derived across subnetworks or properties of hub nodes. In line with this possibility, a number of disorder-level studies using DWI data have identified such correlates (Korgaonkar, Fornito, Williams, & Grieve, 2014; Sacchet, Prasad, Foland-Ross, Thompson, & Gotlib, 2015; Sharp & Telzer, 2017; Tymofiyeva et al., 2017; van den Heuvel, Mandl, Stam, Kahn, & Pol, 2010). Further studies are needed to test these possibilities.

There are also a number of methodological factors that might contribute to the discrepancy. For one, the majority of prior studies used case-control designs with groups that are not representative of the general population, and we used a dimensional design in a community sample that is oversampled on risk for psychopathology. It is also important to consider methodological variability that exists within the literature for matrix construction. First of all, most studies identifying relations in case-control designs utilized the AAL or HOA atlas. These atlases feature 90 and 110 regions respectively, whereas we used a parcellation with 397 regions. Recent work has found that graph theory metrics vary based on the number of nodes, with the small world parameter demonstrating a 95% difference between 100 nodes and 4000 nodes

(Fornito et al., 2010; Zalesky et al., 2010). We also used probabilistic tractography, whereas some of the prior studies used deterministic tractography. There is some work showing that probabilistic tracking demonstrates higher reproducibility across scans (Bonilha et al., 2015). We also did not threshold matrices given recent work finding that the costs outweigh the benefits (Civier et al., 2019). Many prior studies utilized either a single threshold or calculated an area under the curve metric across multiple thresholds. Finally, there is inconsistent use of standardization to metrics from a random network, despite this likely being the best practice (Rubinov & Sporns, 2010). Methodological differences may explain, in part, the present findings and their inconsistency with the existing literature. Further work is needed to assess the extent to which relations between psychopathology and structural network topology metrics derived from DWI data are robust to methodological factors.

Poverty status exploratory analyses

Relations have previously been identified between childhood poverty and psychopathology as well as between childhood poverty and network topology from DWI data (Kim et al., 2019; Slopen et al., 2010). Thus, we conducted an exploratory analysis examining relations between latent factors of psychopathology and graph theory metrics separately in individuals above and below the poverty line during wave 1 of the TTS. We looked at relations in both the bifactor and correlated factors model. All graph theory metrics other than modularity showed a significant difference after FDR correction between these two groups, suggesting that childhood poverty may continue to impact network topology 12 years later. In individuals below the poverty line we found trend level relations for the bifactor model and significant relations for the correlated factors model.

Bifactor model

We identified trend-level relations between each latent factor from the bifactor model and at least one graph theory metric in the group below the poverty line. There were no significant relations at even a trend-level in the group above the poverty line. These findings are informative, since they suggest that global features of white matter network topology may be a correlate of latent factors of psychopathology, but only for individuals who were below the poverty line during childhood. This is in line with the logarithmic relation that has been identified between family income and network topology, indicating that the greatest impact is on those individuals exposed to poverty (Kim et al., 2019). However, it is noteworthy that the study by Kim and colleagues only identified a significant relation between income and global efficiency. This discrepancy could be in part because the present study utilized a categorical measure of income and the prior study used a dimensional measure. Socioeconomic disadvantage is associated with a range of stressors, and based on the present study it is difficult to determine which variables might be contributing to relations between graph theory metrics and latent factors in individuals below the poverty line (Marmot, 2003). It may be that there is some third variable that influences both network topology and psychopathology in individuals below the poverty line.

The specific externalizing factor showed the largest number of trend-level relations in individuals below the poverty line including a negative relation with the small world parameter and clustering coefficient as well as a positive relation with characteristic path length. The relation for small-world parameter had a significant interaction but the relation for characteristic path length did not. Poverty status has previously been linked to increased levels of externalizing psychopathology (McLoyd, 1998; Scaramella, Neppl, Ontai, & Conger, 2008; Slopen et al., 2010). There are a range of variables associated with poverty status that may be contributing to this such as higher levels of harsh parenting, additional exposure to stressors, and insufficient nutrition. These factors may lead to perturbations in network topology development, which in turn manifests in externalizing behaviors. Based on the present findings, the impact on network topology may be decreased local segregation and global integration. This likely translates to less efficient communication throughout the brain. The present findings are consistent with disruptions in small-world architecture have previously been identified in externalizing disorders such as ADHD and problematic substance use (Beare et al., 2017; Kim et al., 2011; Zhang et al., 2016).

While the majority of significant relations in individuals below the poverty line were with specific externalizing, specific internalizing and the general factor also demonstrated trend-level relations. Specific internalizing was positively related to the clustering coefficient. This is indicative of increased local connectivity resulting in more segregation within the brain. Additionally, the general factor was positively related to modularity in individuals below the poverty line. Increased modularity may mean that regulatory regions (e.g. prefrontal cortex) are separated from the regions they regulate (e.g. limbic regions), leading to the difficulties with emotion regulation that are observed across disorders (Davis et al., 2013). Neither of these relations had significant interactions.

We also completed a follow-up analysis of trend-level relations in individuals below the poverty line separately in males and females given prior findings on differential impact of childhood poverty on structural network topology in males and females (Kim et al., 2019). We identified sex differences with a significant interaction in some cases. This provides preliminary evidence that relations are generally stronger in females than males, but this was not true for all metrics. Our sample size for these sex-stratified analyses was small, and thus it is difficult to make strong conclusions. This does however highlight the importance of examining sex difference in studies on relations between psychopathology and structural network topology. These findings are consistent with prior work showing sex differences in structural network topology (Chen et al., 2013; Ingalhalikar et al., 2014). Prior work also has shown that these sex differences vary over the course of development, and as such longitudinal studies are needed to better understand the interplay among development, sex, psychopathology, network topology, and poverty.

Correlated factors model

Within the correlated factors model we identified significant relations that survived FDR correction in individuals below the poverty line. These relations existed for both the internalizing and externalizing factor. There were no significant relations above the poverty line. The externalizing factor had the largest number correlates including a positive relation with degree and modularity as well as a negative relation with clustering coefficient. There was a significant interaction for modularity and a trend-level interaction for degree. An increase in degree is indicative of more densely connected networks, and may be reflect perturbations in properties of hub nodes (Bullmore & Sporns, 2009). The increases in modularity may reflect more segregated processing with regulatory regions becoming isolated from the regions they regulate. A decrease in clustering coefficient may be indicative of decreased local segregation which makes the brain less resilient to insult.

The internalizing factor showed a significant positive relation with clustering coefficient though the interaction was not significant. Increased local segregation is associated with internalizing symptoms in individuals below the poverty line during childhood. It may be that this increased local communication contributes to the ruminative processes that characterize internalizing disorders. It is important to note that this positive relation with clustering coefficient was the opposite directionality from what was observed in externalizing. There are a few implications of this finding. For one, that there is some specificity in relations between latent factors and graph theory metrics. It also implies that there may be an optimal level for these graph theory metrics, with increases versus decreases manifesting in different symptomatology. Finally, as in the bifactor model, we identified sex differences in the relations between graph theory metrics and latent factors. This further highlights the importance of not treating sex as a nuisance variable.

Implications

In both the correlated and bifactor model, we found relations between psychopathology and graph theory metrics, but only in individuals below the poverty line in wave one. It is noteworthy that the relations only survived FDR correction in the correlated factors model. It is interesting that in both models, only internalizing was significantly different between individuals below and above the poverty line, but that externalizing showed the larger number of correlates. These models revealed different correlates and these results thus highlight the need to consider using both models when examining correlates of psychopathology. These results also indicate the importance of considering the impact of poverty when looking at relations between structural network topology and psychopathology.

Limitations

These exploratory analyses need to be considered in the context of several caveats. First of all, information on childhood poverty was collected during wave 1 and DWI data during wave 2, which were typically 12 years apart. We do not have information on poverty status during wave 2 of the study. We also do not have information on poverty status throughout childhood, which is important because there is evidence for plasticity of the brain and decreases in severity of psychopathology during childhood if poverty status changes (Blair & Raver, 2016; Costello et al., 2003). It also important to note that in the group below the poverty line there was a higher portion of individuals who identified as African American or other than in the group above the poverty line, and thus ethnic stratification and poverty status may be confounded within the present study. Additionally, we had a relatively small sample size of individuals below the poverty line (n=63), and our power was further reduced when taking into account twin pairs. Analyses on sex differences were even more under powered. Thus, the present results should be interpreted with caution. However, these findings do suggest that an important future direction would be to conduct longitudinal studies measuring income, psychopathology, and network topology throughout childhood. This could better disentangle the complex interactions that are likely at play among childhood poverty, psychopathology, structural network topology, and sex.

Limitations and future directions

Despite the strengths of this study including the use of a large sample size, there are a number of limitations. There are some limitations specific to using DWI data to construct matrices including the potential impact of motion, tendency to detect false positives, and difficulties identifying long-range tracts (Donahue et al., 2016; Maier-Hein et al., 2016; Maier-Hein et al., 2017; Yendiki et al., 2014). In addition, based on our scanning parameters we had limited coverage of the cerebellum, and thus metrics did not include topology within the cerebellum. Future studies should examine local measures of network topology in relation to latent factors of psychopathology as well as test how robust prior findings are to changes in methodology. Further, additional longitudinal studies are needed to clarify relations among latent factors psychopathology, structural network topology, childhood poverty, and sex.

There are also several limitations that apply across all three studies in this dissertation. For one, presence of twin pairs leads to a reduction in the power compared with what the sample size would suggest. Additionally, there are some critiques of the bifactor model. In particular that the superior fit statistic does not necessarily support this being the better model (Bonifay et al., 2017). Additionally, loadings of first-order symptom dimensions on second-order factors vary across studies, which may limit interpretability of these factors across studies (Watts et al., 2019). Another limitation is that we excluded individuals who reported psychotic disorders on screening, and therefore more extreme forms of psychopathology were not included in the present sample. Moreover, we did not probe for psychotic symptoms outside of mood congruent symptoms in the context of mood disorders questions. As such, we could not test for correlates of a second-order thought disorder factor, or include thought disorder dimensions in the extraction of the general factor. Studies employing a more comprehensive interview should examine if this putative thought disorder factor has unique network topology correlates. Finally, the FDR correction for the large number of tests we ran created a higher bar for identifying significant relations.

Conclusions

In the present study, we did not find relations between DWI derived metrics of structural network topology and latent factors of psychopathology. We did however find trend-level relations between latent factors from the bifactor model with graph theory metrics in individuals who were below the poverty line during wave 1 of the study. Additionally, we found significant relations between the correlated factors model and graph theory metrics in individuals below the poverty line.

CHAPTER III

Study 2: Anatomical covariance

Introduction

Anatomical covariance matrices have been applied to identify differences in structural network topology between healthy individuals and those with psychopathology across several disorders (Ajilore et al., 2014; Sun, Peverill, Swanson, McLaughlin, & Morey, 2018; Wang et al., 2016; Wheeler et al., 2015). These studies have typically used group-level matrices and a categorical approach. In study two, we use subject-level anatomical covariance matrices derived from 9 morphometric features from a T1 scan to look at relations between structural network topology measures and the general factor. We examined graph theory metrics (degree, clustering coefficient, path length, small-world parameter, and modularity) in relation to the bifactor model (general, specific internalizing, and specific externalizing) and the correlated factors model (internalizing and externalizing). To our knowledge this is the first study to examine individual-level covariance matrices in relation to latent factors of psychopathology.

Materials and methods

Participants

For study two we focused on wave 2 TTS participants who completed a T1 scan. The initial sample included 449 young adults.

Measures

Neuroimaging data

Imaging data were acquired on two identical 3T Intera-Achieva Phillips MRI scanners using a 32-channel head coil. T1-weighted images were acquired with a 3-D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (TE/TR/TI=4.6/9.0/644(shortest) ms; SENSE=2.0; echo train=131; scan time=4 min 32 s; FOV: 256x256x170 mm, 1 mm isotropic resolution).

Data analyses

Network construction

Cortical segmentations of T1 images were derived using the *recon-all* script from FreeSurfer version 5.1.0 which is freely available online (https://surfer.nmr.mgh.harvard.edu/). These procedures have been described in detail elsewhere (Fischl, 2012; Fischl et al., 2002). All segmentations were visually inspected and manual edits were made for all subjects according to the standardized protocols on the software's website. We excluded data from 12 subjects whose segmentations failed quality assurance checks after manual edits (excessive movement, processing errors, etc.), for a total of 437 subjects with useable data.

All matrix construction was done using in-house MATLAB scripts. The Destrieux atlas parcellation was used to produce nodes (148 total regions; Figure 14) (Fischl et al., 2004). For each region, we extracted 9 morphometric features (Table 18). Each feature was z-transformed given the variability in scale across features.

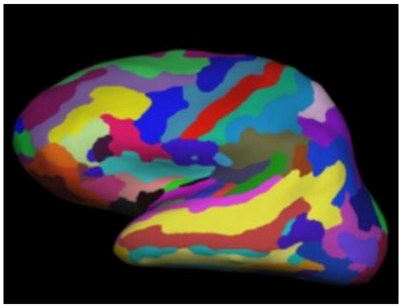

Figure 14. Destrieux atlas parcellation scheme (Fischl et al., 2004)

Table 18. Morphometric features used for matrix construction

Feature
Number of vertices
Gray matter volume
Surface area
Mean cortical thickness
Standard deviation cortical thickness
Mean curvature
Gaussian curvature
Curvature index
Folding index

In order to produce subject-level matrices, for each subject we correlated the 9 morphometric features between each pair of regions (Figure 15). We then thresholded the matrices. First we excluded negative correlations since there is mixed evidence for the interpretability of negative correlations within the context of morphometric matrices (Gong et al., 2012). We then only preserved weights with significant correlations ($p < .05$). We utilized weighted matrices in our analyses (Figure 16; weight is correlation coefficient).

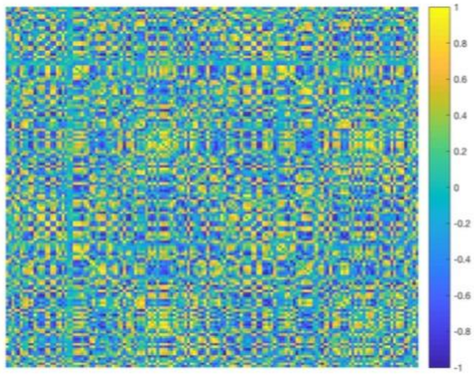

Figure 15. Unthresholded morphometric matrix from a sample subject

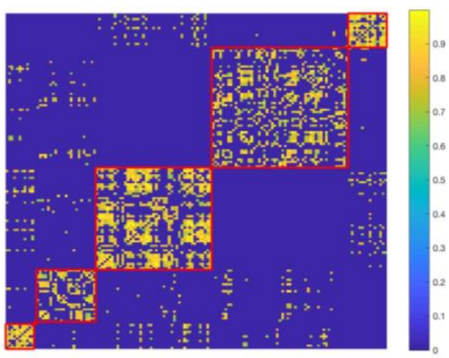

Figure 16. Sample thresholded matrix from a sample subject arranged by community structure

Network analysis

As in study 1, analyses of matrices were conducted using the MATLAB Brain Connectivity Toolbox (BCT; Rubinov and Sporns, 2010). As in study 1 metrics were standardized by random matrices (Figure 17).

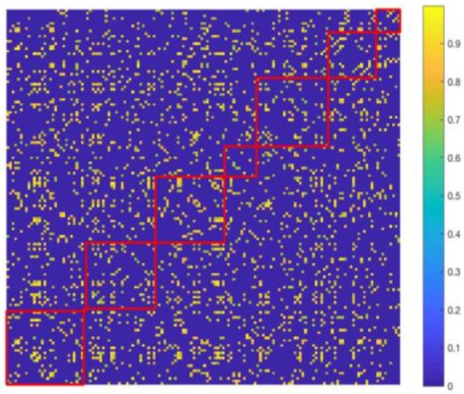

Figure 17. Sample DWI random matrix

Statistical analyses

As in study 1, we conducted multiple regressions with latent factors as independent variables and graph theory measures as dependent variables. These regressions accounted for clustering of twin pairs and included weights that were specific to T1 data. As in study 1 covariates of no interest included age, sex, ethnicity, and handedness. We also included the additional covariate of total intracranial volume. We used FDR corrections across 15 tests for the bifactor model (5 graph theory metrics x 3 latent factors). For the correlated factors model we did FDR corrections across 10 tests (5 graph theory metrics x 2 latent factors). We also conducted sensitivity analyses on any significant relations including sex stratified analyses and controlling for additional covariates (family income and mother's education as well as density). For sensitivity analyses, we used $p < .05$.

Results

Demographics

Demographics for participants in study 2 are detailed in Table 19.

Table 19. Participant demographics for study 2.

Variable	**Mean (Standard Deviation)**
Age (Years)	26.05 (1.78)
Family income [a]	18.84 (4.99)
Mother's education (Years)	13.59 (2.74)
Variable	**N (Percentage)**
Sex	
Male	207 (47.40)
Female	230 (52.60)
Ethnicity	
White	315 (72.10)
African American	107 (24.50)
Other	15 (3.40)
Handedness	
Right	392 (89.70)
Left	45 (10.30)
Scanner [b]	
3TA	225 (51.50)
3TB	212 (48.50)

[a] Family income from wave 1 reported in brackets ranging from 0 (no income) to 24 ($100,000 and over). 18 = $35,000 - $44,999

[b] Imaging data were acquired on two identical 3T Intera-Achiava Phillips MRI scanners

Consensus partition

Consensus partition yielded 4 modules, which shows concordance with previous findings in morphometric similarity matrices (Figure 18) (Seidlitz et al., 2018). These modules roughly map onto the four lobes of the brain collapsed across both hemispheres.

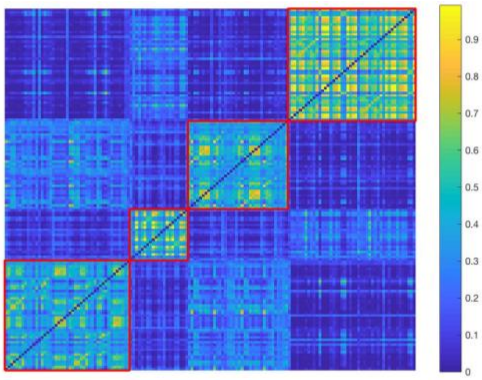

Figure 18. Consensus partition across subjects.

Bifactor model analyses

Primary analyses

Results of regressions are presented in Table 20. There were no relations that survived FDR corrections. Trend level relations that were significant at $p < .01$ were identified between the general factor and both characteristic path length and modularity. Trend level relations significant at $p < .05$ were identified between the general factor and degree as well as between the externalizing factor and characteristic path length. Correlation matrices for trend level relations are depicted in Figure 19. No significant or trend level relations were identified for the internalizing factor.

Table 20. Multiple regressions of graph theory metrics derived from morphometric features on latent general and specific internalizing and externalizing factors based on the fixed-loadings bifactor model, controlling demographic covariates of no interest [a] (all models n = 437). Regressions that were significant after FDR correction are displayed in bold [b].

	General		Internalizing		Externalizing	
Metric [b]	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value
Degree	-0.16 (0.06)	0.014*	0.05 (0.12)	0.663	0.02 (0.09)	0.798
Clustering coefficient	0.06 (0.06)	0.355	0.05 (0.06)	0.412	-0.03 (0.08)	0.713
Characteristic path length	-0.18 (0.06)	0.007**	0.03 (0.06)	0.629	0.15 (0.07)	0.047*
Small-world parameter	0.09 (0.06)	0.136	0.04 (0.06)	0.516	-0.06 (0.08)	0.473
Modularity	-0.18 (0.06)	0.004**	0.06 (0.06)	0.322	0.08 (0.09)	0.397

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, scanner, and total intracranial volume; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network
* $p < .05$ uncorrected
** $p < .01$ uncorrected

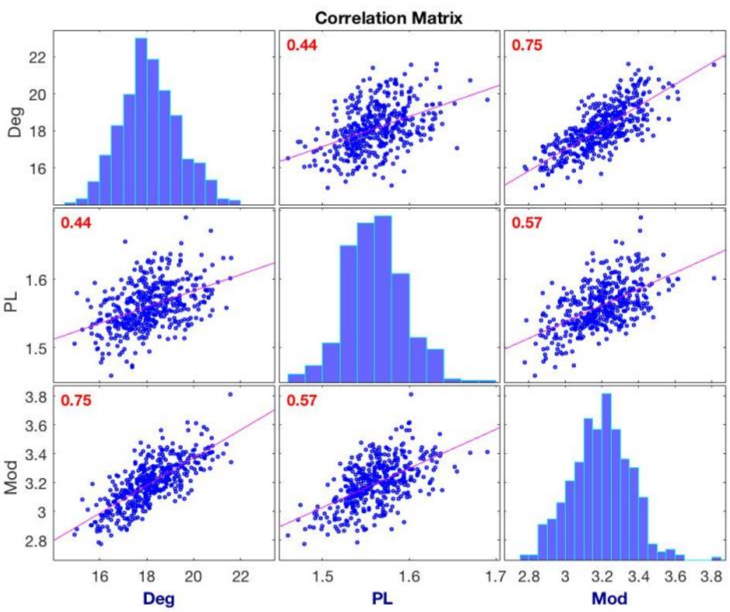

Figure 19. Correlation matrix for metrics showing trend level relations with latent factors (Deg = degree, PL = path length, Mod = modularity).

Sensitivity analyses

Additional sensitivity analyses were performed on trend level relations (general factor with degree, modularity, and path length as well as externalizing factor with path length) to verify robustness of these relations (Table 21). All relations remained significant at a $p < .05$ level after inclusion of the additional covariates of family income and mother's education. All relations remained significant at $p < .05$ after inclusion of density as a covariate.

Table 21. Sensitivity analyses to verify robustness of significant relations [a].

		Density		Family income and mother's education	
Outcome	Latent factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Degree [b]	General	-0.04 (0.02)	0.016*	-0.15 (0.06)	0.018*
Modularity	General	-0.10 (0.04)	0.029*	-0.18 (0.06)	0.004**
Path Length	General	-0.13 (0.06)	0.032*	-0.18 (0.07)	0.007**
Path Length	Externalizing	-0.14 (0.07)	0.047*	0.15 (0.07)	0.043*

[a] All analyses included the following covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, scanner, and total intracranial volume; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network
* $p < .05$
** $p < .01$

We also ran sex stratified analyses for all trend-level relations in the full sample. First, we ran a two-sample t-test to compare graph theory metrics between males and females (Table 22). There were no significant differences. We then looked at relations between graph theory metrics and latent factors separately in males and females (Table 23). The relations for degree, modularity, and path length with the general factor were only significant in females. Path length with the externalizing factor was not significant in either males or females. There was a significant interaction between sex and the general factor in their associations with graph theory metrics for degree ($p < .05$).

Table 22. Differences in graph theory metrics derived from morphometric similarity between males and females in the full sample (n = 437).

Metric	Males mean (SD) (n = 207)	Females mean (SD) (n = 230)	T score	P value
Degree	18.29 (1.18)	18.28 (1.30)	0.03	0.975
Clustering Coefficient	3.87 (0.31)	3.92 (0.35)	-1.62	0.105
Path Length	1.56 (0.04)	1.55 (0.04)	1.42	0.156
Small world	2.49 (0.23)	2.53 (0.26)	-1.81	0.071
Modularity	3.22 (0.16)	3.19 (0.16)	1.86	0.064

Table 23. Sex stratified analyses of significant relations in males and females controlling for covariates of no interest [a].

		Males (n = 207)		Females (n = 230)		Interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Degree [b]	General	0.00 (0.11)	0.977	-0.32 (0.09)	0.001**	5.10*
Modularity	General	-0.14 (0.11)	0.215	-0.29 (0.11)	0.006*	1.05
Path Length	General	-0.19 (0.11)	0.092	-0.23 (0.10)	0.024*	0.01
Path Length	Externalizing	0.18 (0.11)	0.105	0.06 (0.108)	0.555	--

[a] Covariates of no interest: Age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, scanner, and total intracranial volume; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network
* $p < .05$
** $p < .01$
[c] Interactions with sex were tested using the satorra-bentler chi-square difference test

Correlated factors analysis

Primary analyses

We ran regressions between externalizing and internalizing factors within the correlated factors model with graph theory metrics. No significant relations were identified even at a trend level (Table 24).

Table 24. Multiple regressions of graph theory metrics derived from morphometric features on latent internalizing and externalizing factors based on the correlated factors model, controlling demographic covariates of no interest [a] (all models n = 437). Regressions that were significant after FDR correction are displayed in bold.

	Internalizing		Externalizing	
	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Degree [b]	0.03 (0.13)	0.814	-0.15 (0.12)	0.193
Clustering coefficient	0.09 (0.09)	0.280	-0.02 (0.09)	0.829
Characteristic Path Length	-0.07 (0.07)	0.304	-0.04 (0.08)	0.604
Small world parameter	0.10 (0.08)	0.230	-0.01 (0.08)	0.921
Modularity	0.01 (0.08)	0.918	-0.13 (0.09)	0.163

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, scanner, and total intracranial volume; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree are normalized to a random network

Discussion

In study two, we examined relations between latent factors of psychopathology and graph theory metrics derived from subject-level anatomical covariance matrices constructed using 9 morphometric features from a T1 scan. We identified trend-level negative relations between the general factor and degree, characteristic path length, and modularity. We also identified a trend-level positive relation between the externalizing factor and characteristic path length. These relations remained robust to the inclusion of additional covariates including mother's education, family income, and matrix density. We did not find significant relations with the correlated factors model. These findings are novel in that studies of anatomical covariance in psychopathology have generally focused on group-level matrices using a single morphometric feature and employed case-control designs.

Bifactor model

General factor correlates

The general factor was negatively associated with degree at a nominally significant level ($p < .05$) when collapsed across sexes. In a sex-stratified analysis there was a significant interaction with a trend level relation in females ($p < .01$), and a non-significant relation in males ($p > .10$). A decrease in degree indicates that regions on average have fewer edges connected to them, and by extension fewer neighbors. A decrease in degree may also be indicative of perturbations in properties of hub nodes, since hubs are high degree nodes (Bullmore & Sporns, 2009). This is meaningful because hub nodes play a key role in the efficiency of transfer of information throughout the brain, and as such networks are vulnerable to insult to these nodes (Fornito, Zalesky, & Breakspear, 2015). Hub nodes are thought to be especially relevant in psychopathology (Mears & Pollard, 2016; Menon, 2011). Given that structural covariance matrices show some overlap with axonal connections, it may be that the decrease in degree indicates that hub regions are less densely connected and thus transfer information less efficiently (Seidlitz et al., 2018). A prior study found that in anatomical covariance networks the hubs were predominately in the motor and association areas (Seidlitz et al., 2018). Stronger connectivity in association areas has been shown to be important for supporting modular organization and efficient processing (Ardesch et al., 2019). This decrease in degree is especially noteworthy given that changes in degree influence a range of other network topology metrics (Rubinov & Sporns, 2010).

We also identified a trend-level negative relation between the general factor and characteristic path length ($p < .01$). A decrease in path length in the absence of changes in clustering coefficient is suggestive of being closer to random topology in which networks are more densely connected and thereby have higher wiring costs. Regions linked by edges in anatomical covariance matrices are thought to share developmental trajectories (Alexander-Bloch et al., 2013). Thus, denser connections may be indicative of decreased differentiation in brain areas during development, and in turn perhaps less specialization. One prior study using a group-level thickness covariance matrix identified increased path length in individuals with schizophrenia compared with healthy controls (Zhang et al., 2012). The difference in directionality could be due to a number of methodological differences such as using a single morphometric feature versus multiple and using a categorical design versus a dimensional one. While the present study did not include individuals with schizophrenia, prior work suggests these symptoms loads heavily onto the general factor (Caspi et al., 2014). Thus, further work in a sample with individuals with schizophrenia is needed to parse out how characteristic path length in anatomical covariance matrices may be related to the general factor.

Finally, we identified a negative trend-level relation between the general factor and modularity ($p < .01$). Decreased modularity is indicative of less segregation within the brain and more tendency towards subtle randomization (Latora & Marchiori, 2001). Regions that are connected by edges in anatomical covariance matrices have similar cytoarchitectural features. Thus, the general factor may be linked to less segregation of the brain by cytoarchitectural class, and thereby less specialization of function. Networks with decreased modularity are less able to survive insults and may not be able to as rapidly reconfigure to support changing environment demands, and this in turn may translate to cognitive deficits (Kashtan & Alon, 2005). This is consistent with difficulties that individuals with psychopathology may have adapting to changing environmental demands. In particular, the general factor has been linked to both cognitive deficits and the tendency to respond to stressors with negative affect (negative emotionality/neuroticism) (Caspi & Moffitt, 2018; Tackett et al., 2013).

We found that that the general factor was associated with decreased path length, degree, and modularity. It may be that in individuals with higher general factor have difficulties with local communication as evidenced by decreased modularity and degree but an improvement in global communication as supported by deceased characteristic path length. This suggests less adaptive topology with tendency towards more random topology. This is consistent with studies in a range of psychiatric disorders such as schizophrenia (Micheloyannis et al., 2006). Overall these findings suggest that global network topology properties may be relevant for the general factor. It further suggests that previous relations identified between individual disorders and network topology may be explained at least in part by the general factor.

Externalizing and internalizing correlates

We found a nominally significant positive relation between the specific externalizing factor and characteristic path length ($p < .05$). A higher characteristic path length has previously been identified in individuals with conduct disorder as compared to healthy controls using a group-level thickness covariance matrix and a case-control design (Jiang et al., 2016). This suggests that externalizing disorders may be associated with deficits in global integration, which impacts the way in which information is transmitted in the brain (Rubinov & Sporns, 2010). In particular, this may be indicative of difficulties with long-range connections in the brain. Externalizing psychopathology is marked by deficits in impulse control. Thus, the present findings may that reflect regulatory regions (e.g. prefrontal cortex), may have more difficulties communicating with the regions that they inhibit (e.g. limbic areas). This is supported by prior work showing that lower effortful control abilities were associated with increased characteristic path length within frontal regions (Fekete, Beacher, Cha, Rubin, & Mujica-Parodi, 2014). The directionality of the association here is opposite from the general factor, which highlights the importance of examining both non-specific and specific features of psychopathology in relation to structural network topology.

We did not identify any significant relations with the internalizing factor. It may be that while global network topology is relevant for the general factor, perturbations at level of specific nodes or subnetworks are more relevant for the internalizing and externalizing factor. Indeed, this makes intuitive sense, with the broader aspects of psychopathology being linked to global properties of network topology while more specific features being linked to properties of subnetworks. Further work is needed to test this hypothesis.

Sex stratified analyses

We completed follow-up analysis testing trend level relations separately in males and females. All relations between the general factor and graph theory metrics were significant in females but not in males. There was a significant interaction for degree. This suggest that males and females may have different relations between the general factor and network topology. One prior study found sex differences in properties of structural network topology, including increased modularity in males and sex differences in intra- and inter- hemispheric communication (Ingalhalikar et al., 2014). Studies on psychopathology and network topology often treat sex as a nuisance variable, and the present findings highlight the need to test relations separately in males and females. This is especially important given that degree, a building block metric, demonstrated a significant interaction. Additional longitudinal studies are needed to parse out the mechanisms for sex differences in relations between network topology and the general factor of psychopathology.

Correlated factors model

We did not identify significant relations at even the trend level in the correlated factors model. This is meaningful, because it indicates the potential utility of the bifactor model over the correlated factors model in identifying neural correlates of psychopathology. Given that the majority of relations with the bifactor model were identified with the general factor, it may be that such relations are washed out when the shared variance across disorders is not removed from the internalizing and externalizing factors. This particularly salient for characteristic path length, since the opposite directionality in general factor and specific externalizing may have canceled each other out in the correlated factors model thereby producing a non-significant result.

Limitations and future directions

This study had a number of notable strengths including the use of a large community sample with a wide range of psychopathology. However, there are also some limitations. This study shares limitations with study 1 in terms of use of twins, large number of comparisons, and use of global rather than subnetwork level metrics. There are also some limitations that are specific to this methodology. For one, we thresholded the matrices based on the significance of the correlations. There is some debate within the field about the optimal way to threshold matrices (Hallquist & Hillary, 2019). In addition, we excluded negative weights given the mixed evidence on their interpretability, but some studies do opt to include these weights (Gong et al., 2012). Finally, there is debate about the optimal way to parcellate the brain for network analyses, and parcellation scheme can impact the results (Van Wijk et al., 2010). While the Destrieux atlas has been commonly used in studies of anatomical covariance, other parcellation methods exist.

As such the present results may not be robust to use of a different thresholding approach, inclusion of positive weights, and use of a different parcellation themes. Further studies should examine how these different choices may impact relations observed in the context of psychopathology. Additionally, generating subject-level matrices requires using a fewer number of data points for correlations, which may reduce the stability. Given that this approach is newer there are fewer studies to contextualize the current findings. Finally, there are ongoing challenges in the interpretation of graph theory metrics derived from anatomical covariance matrices and what these metrics are indexing. Additional studies are needed to clarify the meaning of these metrics.

Conclusions

In the present study, we found trend level relations between the general factor of psychopathology and measures of structural network topology. This adds to a growing body of literature on the neural correlates of the general factor. It also adds to an emerging literature on the role of networks of anatomical covariance in psychopathology (Roos, Fouche, & Stein, 2017; Weber, Killgore, Olson, Rosso, & Rauch, 2014; Zhang et al., 2012). It further suggests that graph theory metrics derived from individual-level matrices of anatomical covariance may be promising for revealing neural correlates of psychopathology.

CHAPTER IV

Study 3: Functional magnetic resonance imaging reward task

Introduction

Study three is designed to look at the relation between the general factor and functional network topology during a reward task. We examined graph theory metrics (degree, clustering coefficient, path length, small-world parameter, and modularity) in relation to the bifactor model (general, specific internalizing, and specific externalizing) and the correlated factors model (internalizing and externalizing). We used a difference score between $5 and $0 trials in order to understand how changes in functional network topology in relation to reward may be related to the general factor.

Materials and methods

Participants

A total of 448 subjects completed the Monetary Incentive Delay (MID) task. Fourteen of these subjects were excluded due to data processing or task validity issues (missing scan logs, subjects falling asleep during the task, etc.). The remaining 434 subjects underwent preprocessing and quality assurance. Quality assurance was conducted using the Artifact Detection Toolbox (ART; nitrc.org/projects/artifact_detect) using global signal and motion thresholds of z>3 and 1mm. Subjects were excluded who had 20% or more of their TRs censored. We included subjects in our analyses who had either two or three useable runs. This sample consisted of 326 subjects with useable data for 2 or 3 runs.

Neuroimaging task

The Monetary Incentive Delay (MID) task is a commonly used cued reward task (Knutson, Westdorp, Kaiser, & Hommer, 2000). In this task individuals first view a fixation cross and then a cue indicating the amount of money they can win ($0, $1, or $5). Next, they see a fixation cross which is followed by a target which they must hit a button in response to. Finally, they view another fixation cross and then receive feedback on if they received a reward (Figure 20). Participants receive a portion of their earnings, and are informed of this prior to completing the task.

Figure 20. Sample MID trial (Benningfield et al., 2014).

The MID task has been shown to engage reward circuitry and allows researchers to parse out the neural correlates of reward anticipation versus reward attainment (Benningfield et al., 2014; Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson et al., 2000). In the present study, we focus on the reward anticipation phase of the task (pre-target delay). We chose to focus on this phase because we wanted to index motivational rather than consummatory responses. An additional reason to choose this phase is that the reward attainment phase has variable trial numbers across participants depending on task performance, and thus may yield less stable matrices across subjects. Subjects completed 3 runs of the task, and each trial type ($0, $1, $5) occurred 40 times across the task.

Data analyses

Neuroimaging data

Preprocessing

MRI data were preprocessed using the FMRIPREP-v1.0.0 pipeline [6] (see fmriprep.readthedocs.io/en/1.0.0/workflows.html for details) with slice time correction and MNI normalized outputs. Images were smoothed with a 4mm full width at half-maximum (FWHM) Gaussian kernel using SPM 12 (Friston et al., 1994).

First level analyses

First level analyses were conducted using SPM 12. The general linear model (GLM) included 6 motion and rotation regressions. A time series analysis was conducted using a beta series in which a separate beta is modeled for each condition across each run, resulting in a total of 40 betas for each condition ($0, $1, and $5 anticipation) (Rissman et al., 2004).

Network construction

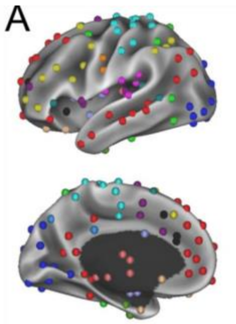

Figure 21. 300 ROI set (Seitzman et al., 2018).

We used the 300 Regions of Interest set (ROI; Figure 21) which divides the brain into 300 spherical ROIs (4mm and 5 mm) that are functionally defined and cover the whole brain including the cerebellum and subcortical regions (Seitzman et al., 2018). We excluded 1 subject who had poor coverage across a large number of ROIs, and only included ROIs that had coverage for all subjects (some subjects were missing voxels in the cerebellum). This yielded a total of 247 ROIs per subject.

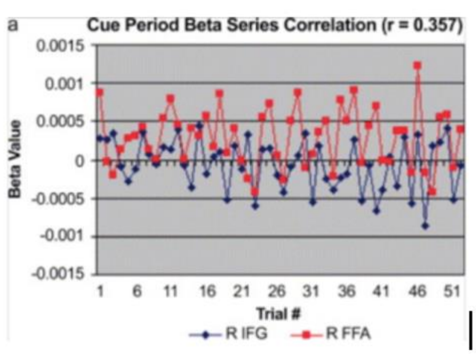

Fig 22. Depiction of beta series correlations between two regions (Rissman, Gazzaley, & D'esposito, 2004)

In our analyses, we focused on $0 and $5 trials in order to use the most robust contrast for no reward versus reward and minimize the number of tests we conducted. We extracted a beta series from each ROI for each trial type ($0 and $5). For each trial type, we then correlated beta series between pairs of regions (Figure 22) in order to construct a connectivity matrix. Thus, there was a matrix for each subject for each trial type (Figure 23). Correlation coefficients were then r to z transformed to normalized values. To threshold these matrices we excluded correlations that were not significant ($p < .05$; Figure 24).

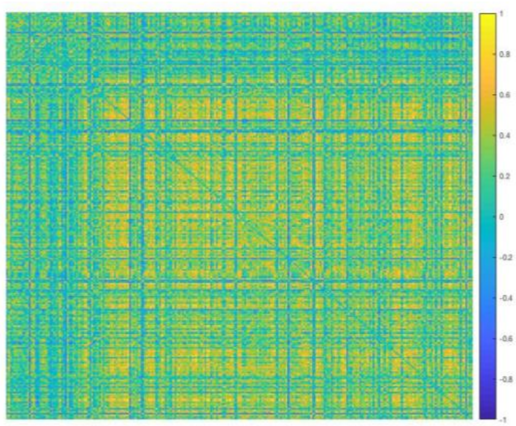

Figure 23. Untresholded matrix for one subject's $5 trials.

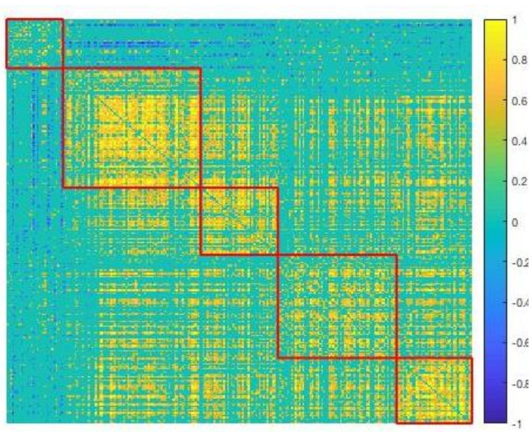

Figure 24. Thresholded matrix for $5 trials for same subject as figure 23.

Network analyses

Graph theory metrics were calculated for each cue type ($0 and $5), and we then calculated a difference score by subtracting the $0 metric from the $5 metric (positive score = higher in $5 and negative score = higher in $0). Since the fMRI data contained negative weights we used slightly different BCT functions that take the presence of these weights into account. For modularity, we used the same function (community_louvain.m) but treated negative weights asymmetrically. We chose this because negative and positive weights do not have the same role in functional networks and have different associations with modules (Rubinov & Sporns, 2011). For clustering coefficient, we used the Costantini and Perugini generalization of the Onnela formula to generate one clustering coefficient that takes into account negative and positive weights (clustering_coef_wu_sign.m) (Costantini & Perugini, 2014). For path length, we took the absolute value of negative weights and then calculated characteristic path length the way we did in study 1 and 2. As in the other studies we generated random matrices to normalize matrices. Random matrices contained both positive and negative weights (Figure 25).

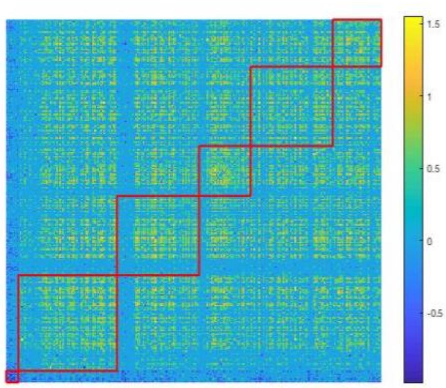

Figure 25. Sample random matrix for $5 trial.

Statistical analyses

Multiple regressions were conducted in the same way as in study 1 and 2. Our primary analyses were on the difference in graph theory metrics between $0 and $5 trials. We conducted multiple regressions with latent factors as independent variables and graph theory measures as dependent variables. These regressions accounted for clustering of twin pairs and included weights that were specific to the MID data. Covariates of no interest included age, sex, ethnicity, scanner, and handedness. For the bifactor model we completed FDR corrections across 15 tests (5 graph theory metrics x 3 latent factors). We conducted analyses with the correlated factors model and applied FDR corrections across 10 tests (5 graph theory metrics x 2 latent factors).

For sensitivity analyses, we first looked at any significant relations separately in $0 and $5 trials to better characterize associations. We also conducted the same sensitivity analyses for significant relations as in study 1 and 2 including sex stratified analyses and controlling for additional covariates (family income and mother's education as well as density). We also performed an additional sensitivity analysis in which we included a categorical covariate for 2 versus 3 runs to ensure findings were not being driven by the number of runs (3 runs = 243 subjects; 2 runs = 82 subjects). In all sensitivity analyses we used $p < .05$ as a significance threshold.

Results

Demographics

Demographics for the study 3 sample are presented in Table 25.

Table 25. Participant demographics for study 3.

Variable	Mean (Standard Deviation)
Age (Years)	26.03 (1.78)
Family income [a]	19.21 (4.57)
Mother's education (Years)	13.79 (2.75)
Variable	**N (Percentage)**
Sex	
Male	152 (46.80)
Female	173 (53.20)
Ethnicity	
White	244 (75.10)
African American	71 (21.80)
Other	10 (3.10)
Handedness	
Right	296 (91.10)
Left	29 (8.90)
Scanner [b]	
3TA	173 (53.20)
3TB	152 (46.80)

[a] Family income from wave 1 reported in brackets ranging from 0 (no income) to 24 ($100,000 and over). 19 = $45,000 - $54,999

[b] Imaging data were acquired on two identical 3T Intera-Achiava Phillips MRI scanners

Consensus partition

Consensus partitions for $0 and $5 trials both yielded 3 modules (Figure 26). These modules were generally consistent across trial types. The first module was composed of somatomotor, auditory, and cingulo opercular regions, the second primarily visual regions, and the third primarily default mode and fronto parietal regions. This shows some overlap with prior studies that used resting state data, though the present study yielded fewer modules. Studies using resting data often produce 5 modules which can be divided into somatosensory/motor and auditory, attention, visual, default-mode, limbic/paralimbic, and sub-cortical (He et al., 2009). However, there is some variability in number of modules identified using resting state data, with other studies finding 4 modules which are labeled as sensorimotor, default mode, visual processing, and mesocortical (Luo et al., 2015). It could be that there is more individual variability in modules during task states which thus produces fewer modules that overlap across subjects. Another possibility is that task states yield fewer modules.

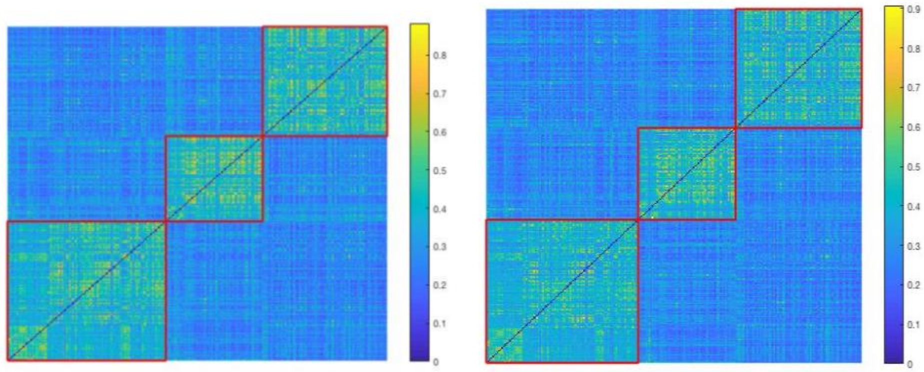

Figure 26. Consensus partition across subjects. \$0 trials left and \$5 trials right.

Bifactor model analyses

Primary analyses

We conducted regressions to look at relations between difference scores for graph theory metrics (\$5-\$0) and latent factors from the bifactor model. Results for these regressions are presented in Table 26. No relations survived FDR correction. There were trend level relations that were significant at an uncorrected threshold of $p < .05$ between specific externalizing and both clustering coefficient and the small world parameter as well as between specific internalizing and characteristic path length. There was a nominally significant relation ($p = .05$) between the general factor and characteristic path length.

Table 26. Multiple regressions of difference in graph theory metrics between \$0 and \$5 conditions in the MID task on latent general and specific internalizing and externalizing factors based on the fixed-loadings bifactor model, controlling demographic covariates of no interest [a] (all models n = 325). Regressions that were significant after FDR correction are displayed in bold [b].

	General		Internalizing		Externalizing	
Metric [b]	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value	Regression Coeff (SE)	P value
Degree	-0.00 (0.08)	0.958	0.08 (0.10)	0.425	-0.09 (0.09)	0.359
Clustering coefficient	-0.03 (0.08)	0.730	-0.02 (0.07)	0.804	0.16 (0.08)	0.041*
Characteristic path length	-0.16 (0.08)	0.053[t]	0.15 (0.07)	0.039*	-0.11 (0.07)	0.171
Small-world parameter	-0.01 (0.08)	0.862	-0.04 (0.08)	0.636	0.17 (0.08)	0.040*
Modularity	0.12 (0.09)	0.204	-0.08 (0.08)	0.358	0.15 (0.09)	0.101

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures, other than degree, were normalized to a random network
* Significant at $p < .05$ but don't survive FDR correction
[t] Significant at $p < .10$

Sensitivity analyses

We conducted a series of sensitivity analyses for all trend-level relations. For these analyses, we used a $p < .05$ cut-off. In general graph theory metrics were moderately correlated between \$0 and \$5 trials, with modularity showing the lowest correlation ($r = .52$) and clustering coefficient and degree showing the highest ($r = .70$). We thus looked at \$0 and \$5 trials for all graph theory metrics that showed trend level relations (Table 27). The general factor was related to path length during \$0 trials at a $p < .05$ level.

Table 27. Multiple regressions of difference in graph theory metric difference scores between $0 and $5 conditions in the MID task on latent internalizing and externalizing factors based on the fixed-loadings correlated factors model, controlling demographic covariates of no interest [a] (all models n = 325).

		$0 Trials		$5 Trials	
Outcome	Latent factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
CC [b]	Externalizing	-0.11 (0.12)	0.359	0.02 (0.10)	0.838
Path Length	Internalizing	-0.14 (0.07)	0.036	0.02 (0.05)	0.708
Path Length	General	0.14 (0.06)	0.023*	-0.03 (0.07)	0.680
Small-world	Externalizing	-0.10 (0.12)	0.407	0.03 (0.10)	0.760

[a] All analyses included the following covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures were normalized to a random network
* $p < .05$

We next tested if relations were robust to inclusion of additional covariates of density, family income and mother's income from wave one, and number of runs (Table 28). Relations were largely robust to these covariates. We then ran sex stratified analyses. First, we ran two-sample t-tests to compare graph theory metrics between males and females (Table 29). There were no significant differences (*p*s > .10). Then we ran regressions separately in males and females (Table 30). Relations were significant in females but not in males for all relations other than path length with specific internalizing, which was not significant in males or females. There was a significant interaction for characteristic path length.

Table 28. Sensitivity analyses for graph theory metrics from MID task and bifactor model to verify robustness of significant relations [a].

		Density		Family income and mother's education		Number of Runs	
Outcome	Latent factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
CC [b]	Externalizing	0.13 (0.08)	0.083	0.16 (0.08)	0.040*	0.16 (0.08)	0.039*
Path Length	Internalizing	0.15 (0.07)	0.037*	0.14 (0.07)	0.045*	0.16 (0.07)	0.030*
Path Length	General	-0.16 (0.08)	0.053*	-0.16 (0.08)	0.049*	-0.17 (0.08)	0.038*
Small-world	Externalizing	0.14 (0.08)	0.081	0.17 (0.08)	0.039*	0.16 (0.08)	0.038*

[a] All analyses included the following covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures were normalized to a random network
* $p < .05$

Table 29. Differences between graph theory metrics derived from the MID task for males and females in the full sample (n = 325).

Metric	Males mean (SD) (n = 152)	Females mean (SD) (n = 173)	T score	P value
Degree	-1.15 (37.97)	-2.24 (38.53)	0.26	0.798
Clustering Coefficient	-0.04 (0.66)	0.06 (0.87)	-1.16	0.248
Path Length	0.00 (0.05)	0.01 (0.04)	-0.97	0.334
Small world	-0.02 (0.52)	0.04 (0.69)	-0.91	0.363
Modularity	-0.06 (0.65)	0.00 (0.56)	-0.87	0.383

Table 30. Sex stratified analyses of significant relations for graph theory metrics from MID task and bifactor model controlling for covariates of no interest [a].

		Males (n = 152)		Females (n = 173)		Test of interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
CC [b]	Externalizing	0.13 (0.08)	0.107	0.25 (0.12)	0.042*	0.98
Path Length	Internalizing	0.13 (0.10)	0.197	0.16 (0.10)	0.103	--
Path Length	General	0.01 (0.10)	0.930	-0.26 (0.13)	0.046*	10.39**
Small World	Externalizing	0.16 (0.09)	0.067	0.26 (0.12)	0.038*	0.75

[a] Covariates of no interest: Age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).

[b] All measures were normalized to a random network
[c] Interactions with sex were tested using the satorra-bentler chi-square difference test
* $p < .05$
** $p < .01$

Correlated factors model

Primary analyses

We looked at relations between graph theory metrics and the correlated factors model (Table 31). There was a significant relation that survived FDR correction between the externalizing factor and characteristic path length. There was a trend-level relation that was significant at $p < .05$ between externalizing and modularity. Figure 27 depicts correlation plots between graph theory metrics that showed trend level or significant relations with either the bifactor model or the correlated factors model.

Table 31. Multiple regressions of difference in graph theory metrics difference scores between $0 and $5 conditions in the MID task on latent internalizing and externalizing factors based on the fixed-loadings correlated-factors model, controlling demographic covariates of no interest [a] (all models n = 325). Regressions that were significant after FDR correction are displayed in bold.

	Internalizing		Externalizing	
	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Degree [b]	0.11 (0.11)	0.325	-0.10 (0.09)	0.247
Clustering coefficient	-0.08 (0.06)	0.188	0.11 (0.08)	0.175
Characteristic Path Length	0.11 (0.08)	0.176	**-0.22 (0.08)**	**0.005**
Small world parameter	-0.10 (0.07)	0.142	0.13 (0.08)	0.113
Modularity	-0.09 (0.08)	0.251	0.23 (0.10)	0.018*

[a] Covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures other than degree were normalized to a random network
* Significant at $p < .05$ but don't survive FDR correction

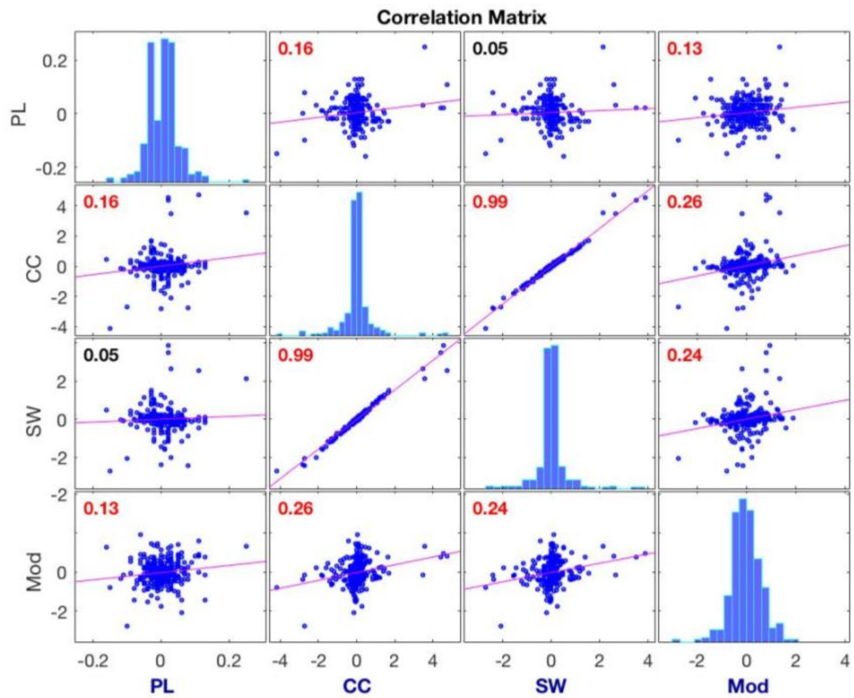

Figure 27: Correlation plots of differences scores for metrics that showed significant or trend level relations (PL = path length, CC = clustering coefficient, SW = small world parameter, and Mod = modularity).

Sensitivity analyses

We also conducted sensitivity analyses for the correlated factors model. We first looked at relations in \$0 and \$5 trials separately (Table 32). There was a relation significant at $p < .05$ for characteristic path length with externalizing for \$5 trials. We next looked at relations with additional covariates (Table 33). All relations remained significant with the inclusion of density, mother's education and family income, and number of runs. Finally, we looked at relations separately in males and females (Table 34). Relations were significant in females but not in males. There was a significant interaction for modularity.

Table 32. Multiple regressions of difference in graph theory metrics between $0 and $5 conditions in the MID task on latent general and specific internalizing and externalizing factors based on the fixed-loadings bifactor model, controlling demographic covariates of no interest [a] (all models n = 325). Regressions that were significant after FDR correction are displayed in bold [b] [a].

		$0 Trials		$5 Trials	
Outcome	Latent factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Path Length [b]	Externalizing	0.06 (0.09)	0.561	-0.16 (0.06)	0.011^{*}
Modularity	Externalizing	-0.10 (0.09)	0.252	0.13 (0.11)	0.241

[a] All analyses included the following covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures were normalized to a random network
* $p < .05$

Table 33. Sensitivity analyses to verify robustness of significant relations between MID task graph theory metrics and correlated factors model [a].

		Density		Family income and mother's education		Number of Runs	
Outcome	Latent factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value
Path Length	Externalizing	-0.22 (0.08)	0.005^{**}	-0.22 (0.08)	0.004^{**}	-0.22 (0.08)	0.004^{**}
Modularity	Externalizing	0.22 (0.10)	0.028^{*}	0.23 (0.10)	0.020^{*}	0.23 (0.10)	0.016^{*}

[a] All analyses included the following covariates of no interest: Age in wave 2, sex, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures were normalized to a random network
* $p < .05$
** $p < .01$

Table 34. Sex stratified analyses of significant relations for correlated factors model and MID graph theory metrics controlling for covariates of no interest [a].

		Males (n = 152)		Females (n = 173)		Test of interaction [c]
Outcome	Latent Factor	Regression Coefficient (SE)	P value	Regression Coefficient (SE)	P value	χ^2
Path Length	Externalizing	-0.20 (0.11)	0.073	-0.24 (0.11)	0.026^{*}	0.03
Modularity	Externalizing	0.19 (0.19)	0.319	0.30 (0.11)	0.007^{**}	14.31^{**}

[a] Covariates of no interest: Age in wave 2, parent-classified race-ethnicity (Non-Hispanic white versus others), handedness, and scanner; regression coefficients are fully standardized (M = 0, SD = 1).
[b] All measures were normalized to a random network
[c] Interactions with sex were tested using the satorra-bentler chi-square difference test
[*] $p < .05$
[**] $p < .01$

Discussion

Study three looked at the difference in graph theory metrics between a reward and no reward condition and how this was related to latent factors of psychopathology. In the bifactor model we identified trend level relations. In particular, there was a positive relation between the specific externalizing factor and both clustering coefficient and the small-world parameter, a negative relation between the general factor and characteristic path length, and a positive relation between the specific internalizing factor and characteristic path length. In the correlated factors model we identified a significant negative relation between the externalizing factor and characteristic path length as well as a trend level positive relation between the externalizing factor and modularity. To our knowledge this is the first study to examine graph theory metrics in a reward task in relation to latent factors of psychopathology.

Bifactor model correlates

We identified at least one trend-level relation between each latent factor from the bifactor model and a graph theory metric. We identified the largest number of correlates for the specific externalizing factor. For one we identified a positive relation with clustering coefficient, which suggests that individuals with greater externalizing symptomatology have higher clustering coefficients on \$5 than \$0 trials. This may be indicative of increases in local segregation during \$5 trials relative to \$0, with regions being more densely connected with their neighbors. The specific externalizing factor was also positively related to the small-world parameter, which indicates that individuals have higher small-world properties in high reward versus no reward conditions. Individuals with externalizing disorders demonstrate hyperactivation across a number of brain regions in response to reward (Buckholtz, Treadway, Cowan, Woodward, Benning, et al., 2010; Leyton & Vezina, 2013). The present findings suggest that this may also be accompanied by increases in segregated neural processing.

We also observed a positive relation between characteristic path length and the specific internalizing factor. Individuals with internalizing pathology have a higher path length on $5 trials compared with $0 trials. Though path lengths are more challenging to interpret in functional connectivity, increased path length tends to indicate less effective interactions among cortical regions (Bassett & Bullmore, 2006; Rubinov & Sporns, 2010). Therefore, during $5 trials individuals with higher levels of internalizing symptoms experience decreased global integration. In general individuals with internalizing symptoms show blunted responses to reward (Pizzagalli et al., 2009). This may also be accompanied by less efficient communication throughout the brain. Our findings of differential relations of internalizing and externalizing symptoms with graph theory metrics may parallel the previously observed divergent behavioral responses to reward (Zald & Treadway, 2017).

The general factor showed a trend level relation negative relation with characteristic path length. Individuals with higher levels of the general factor have a shorter path length on $5 trials as compared with $0 trials. Decreased path length coupled with preserved clustering coefficient is suggestive of a tendency towards more random topology with an increase in higher cost long-range connections (Latora & Marchiori, 2001; Sporns & Zwi, 2004). This is somewhat consistent with a prior finding of increased density during reward conditions that has previously been identified in individuals with bipolar disorder (Manelis et al., 2016).

We did a series of sensitivity analyses of trend-level relations. First, we looked at $0 and $5 trials separately. The only trend level relation was for $0 between characteristic path length and the general factor. This suggests that the relations observed here are primarily driven by differences between reward conditions rather than responses for a given trial type. We also included covariates of density, family income and education, and number of runs. Results were largely robust to inclusion of additional covariates.

Finally, we ran a sex stratified analysis. Regressions were generally significant in females and not in males. A prior study looking at resting-state topology in children identified sex differences within nodal properties, particularly within the default mode network and regions related to language and vision (Wu et al., 2013). In another study looking at resting state data using a sample of young adults, there was a sex-by hemisphere interaction for global topology as well as sex differences in nodal properties (Tian, Wang, Yan, & He, 2011). A previous study also found sex differences in relations between task-based functional network topology and psychopathology (Elton et al., 2014). Thus, it is evident that sex differences are important for functional network topology, and that sex shouldn't be viewed as simply a nuisance variable in these analyses. Additionally, sex differences may exist at the level of both local and global topology. Therefore, relations identified with global topology could be driven in part by topology of specific networks. Network topology may be a correlate of psychopathology in males and females, but the specific network that is impacted may differ. Further, sex differences and their relations with psychopathology may not be stable throughout life, but rather show a complex relationship with development. Additional longitudinal studies are needed to understand the mechanisms behind sex differences in relations between network topology and psychopathology.

Correlated factors model correlates

In the correlated factors model we identified significant relations between the externalizing factor and graph theory metrics. Overall this suggests that higher levels of externalizing symptoms are associated with different functional network topology between reward and no reward conditions. This is consistent with prior work showing that individuals with externalizing psychopathology are more sensitive to some aspects of reward (Buckholtz, Treadway, Cowan, Woodward, Li, et al., 2010; Leyton & Vezina, 2013).

There was a significant negative relation between characteristic path length and the externalizing factor. Individuals with higher levels of externalizing symptoms may have more difficulties appropriately reconfiguring their functional network topology to support changing task demands. In particular, these individuals tend to have a shorter path length on $5 trials compared with $0 trials. Reward may be a destabilizing context that leads to an increase in high-cost long-range connections (Latora & Marchiori, 2001; Sporns & Zwi, 2004). Increases in global integration without changes in clustering indicates a shift towards subtle randomization. Thus, reward leads to greater wiring costs and topology closer to that of a random network.

There was also a trend level positive relation between externalizing and modularity. Higher modularity on $5 trials as compared with $0 trials is associated with externalizing symptoms. This finding is consistent with prior work in resting state data linking increased modularity to impulsive behavior (Davis et al., 2013). It may be that in individuals with higher levels of externalizing symptoms, regulatory regions (e.g. cortical regions) become more separated from drive regions (subcortical regions) during high reward conditions. This provides additional support that for individuals with externalizing psychopathology reward represents a destabilizing context. Behaviorally this may translate to individuals with externalizing behaviors having trouble effectively using cognitive control in the presence of rewards (Casey, Jones, & Hare, 2008; Eisenberg et al., 2001).

When we followed up relations in $0 and $5 trials separately, the only significant relation was for externalizing with characteristic path length in $5 trials. Thus, the relation for path length and externalizing may be primarily driven by topology during reward trials. For modularity, what is most important is the difference between the conditions. Relations were robust to the inclusion of additional covariates, suggesting these weren't driving the results. In a sex stratified analysis, relations were significant in females but not males, and there was a significant interaction for modularity. This is interesting given that rates of externalizing disorders tend to be higher in males than females (Kessler et al., 2005). As with the bifactor results, this highlights the need to investigate sex differences when examining network topology in relation to latent factors of psychopathology.

Overall implications

We identified a significant relation in the correlated factors model whereas only trend-level relations in the bifactor model. This may be partially because for the correlated factors model we ran fewer tests, thus leading to a less stringent FDR correction. It does suggest that studies investigating latent factors should consider using the correlated factors model. This is particularly critical given that the correlates were not the same across the models. This is perhaps unsurprising given they are measuring overlapping yet distinct constructs. Overall these results support the potential utility of both the bifactor and correlated factors model for examining correlates of psychopathology.

Limitations and future directions

While this study had a number of strengths, a number of limitations must be noted. One limitation of this study is that we used stringent motion thresholds, thereby yielding the smallest sample size of any of the studies in this dissertation. Additionally, the study utilized an event-related design, which may yield less stable estimates than a block design. A total of 40 trials per condition is smaller than ideal, and metrics might be more stable with an increased number of trials. We also excluded 53 ROIs given limited coverage of the cerebellum, and thus the coverage of the cortex was not as complete. Further we did not censor TRs that were outliers because we did not want to create variability in number of trials per subjects. Overall, we did find some correlates at the global factor level. However, it may be that there are more correlates at the local level, and in particular at the reward network level. There are also challenges to interpreting change scores as well as to interpreting topology during task states rather than at rest. It can be difficult to isolate which variables are driving changes between states.

Additionally, work on network topology community structure has been dominated by the assumption that brain networks primarily have an assortative community structure. In this model, the brain consists of modules with more dense connections between than within modules. However, recent work has suggested that while resting-state topology is dominated by assortative community structure, during tasks there is a higher percentage of non-assortative community structures (Betzel, Bertolero, & Bassett, 2018). Thus, it may be that relations would be present for metrics of non-community structure, and thus future work should investigate this.

Finally, our analyses were focused on linear relations between graph theory metric difference scores and latent factors. It may be the case that these relations are more complex, and thus other studies should consider alternate models.

Conclusions

This was the first study to examine graph theory metrics during a reward task in relation to latent factors of psychopathology. We identified trend-level relations with all latent factors from the bifactor model and both a significant and trend-level relation with externalizing factor from the correlated factors analysis. This provides preliminary evidence of the utility of examining the extent to which functional network topology reconfigures to support changing tasks demands and how this is related to psychopathology.

CHAPTER V

General discussion

Summary

Studies on the neural correlates of psychopathology have largely been dominated by the use of case-control designs. There are known limitations of this approach including the high comorbidity between diagnoses (Caspi & Moffitt, 2018; Insel et al., 2010). One way to address this is to use a dimensional approach to psychopathology that includes an internalizing and externalizing latent factor. However, these two factors are correlated, indicating that they are likely measuring partially overlapping constructs. A recent approach to psychopathology addresses this problem by utilizing a bifactor model (Caspi et al., 2014; Lahey et al., 2012). This includes a general factor that accounts for overlap across all disorders, as well as a specific internalizing and externalizing factor that are not correlated. Studies have begun to identify structural and functional neural correlates of the general factor (Hinton et al., 2019; Kaczkurkin et al., 2017; Romer et al., 2018; Sato et al., 2016). While these results are promising, they have focused on collections of regions rather than global brain organizational structure. It may be that the general factor has correlates at this global level. By applying graph theory analytics to connectomes, it is possible to study network topology and examine the extent to which it may be related to the general factor or 2nd order factors of psychopathology (Bullmore & Sporns, 2009).

This dissertation examined relations between latent factors of psychopathology and measures of structural and functional network topology. Analyses included both the bifactor model as well as the correlated factors model to compare the utility of these models. Study 1 was focused on structural topology derived from diffusion weighted imaging (DWI) data, study 2 used morphometric features to study structural topology, and study 3 looked at functional topology in a functional magnetic resonance imaging (fMRI) reward task. Across the three studies we identified correlates of both the bifactor and correlated factors model (Table 35).

Table 35. Summary of relations between latent factors and graph theory metrics across studies. Relations in bold are significant with FDR correction, and other relations are significant at an uncorrected level of $p < .05$.

Latent factor	DWI	AC	fMRI
General	+ modularity	- degree - path length - modularity	- path length
Specific Internalizing	+ clustering coefficient	--	+ path length
Specific Externalizing	+ path length - clustering coefficient - small world	+ path length	+ clustering coefficient + small world
Internalizing	+ clustering coefficient	--	--
Externalizing	**+ degree** **- clustering coefficient** **+ modularity**	--	**- path length** + modularity

Bifactor model: general, specific internalizing, and specific externalizing; Correlated factors model: internalizing and externalizing
+ positive relation; - negative relation
DWI = diffusion weighted imaging; AC = anatomical covariance; fMRI = functional magnetic resonance imaging

Study 1 was focused on structural network topology as measured via DWI. I did not identify any FDR-corrected significant relations between the bifactor model or the correlated factors model and any graph theory metrics. In an exploratory analysis, I examined relations separately in individuals above and below the poverty line in wave 1 given prior work demonstrating the impact of poverty on both network topology and psychopathology (Costello et al., 2003; Kim et al., 2019). For the bifactor model, there were trend-level relations between graph theory metrics and all latent factors in individuals who were below the poverty line. This included a relation for the general factor with modularity, the specific internalizing factor with clustering coefficient, and the specific externalizing factor with characteristic path length, clustering coefficient, and the small-world parameter. For the correlated factors model, there was a significant relation between the externalizing factor and degree, clustering coefficient, and modularity as well as a significant relation between internalizing and clustering coefficient.

Study 2 examined structural network topology as measured by 9 morphometric features. There were trend-level relations between the general factor and degree, modularity, and characteristic path length as well as a trend-level relation between specific externalizing and characteristic path length. There were no significant relations for specific internalizing. There were also no relations at a significant or trend level for the correlated factors model.

Study 3 focused on functional network topology and examined differences in graph theory metrics between a no reward and reward condition. In the bifactor model, we identified trend level relations between specific externalizing and both clustering coefficient and small-world parameter, the general factor and characteristic path length, and specific internalizing and characteristic path length. In the correlated factors model we identified a significant relation between externalizing and characteristic path length as well as a trend level relation between externalizing and modularity.

Metrics were relatively uncorrelated across modalities, with only two metrics showing significant or trend-level correlations between DWI and morphometric features (Table 36). This suggests that each modality is providing relatively unique information. While variability in parcellation schemes and thresholding techniques across modalities does suggest using caution when interpreting these correlations, there are some important implications of these findings. For one, it raises questions about the extent to which anatomical covariance matrices are truly indexing axonal connections. Instead, this supports prior work demonstrating that it indexes shared developmental influences, trophic factors, cytoarchitecture, or genetic influences (Raznahan et al., 2011; Seidlitz et al., 2018). Additional studies are needed to clarify what anatomical covariance matrices are capturing. These findings also raise questions about the extent to which changes in functional covariance during tasks are constrained by structural topology, and how such changes are related to functional topology at rest. Given the minimal correlation across modalities, it may be that combining metrics from different modalities would improve prediction of psychopathology. Additional work is needed to test this hypothesis.

Table 36. Correlations between graph theory metrics across imaging modalities. Correlations in bold survived FDR correction with families of correlations (e.g. DWI & MSA, DWI & fMRI, fMRI & MSA).

	DWI & AC n = 400		DWI & fMRI n = 308		fMRI & AC n = 317	
	r	P value	r	P value	r	P value
Degree	-.06	.247	-.02	.741	.02	.740
Clustering Coefficient	.01	.869	.04	.502	-.02	.669
Path Length	.11	.022*	-.09	.130	-.01	.838
Small World	**.14**	**.006**	.02	.682	-.01	.824
Modularity	.01	.785	.01	.869	-.07	.224
Average	.07		.04		.03	

DWI = diffusion weighted imaging, AC = anatomical covariance, fMRI = functional magnetic resonance imaging

* $p < .05$ uncorrected

Significance and implications

The three studies in this dissertation are novel in that to our knowledge they are the first to examine network topology in relation to latent factors of psychopathology. Additionally, this dissertation examined multiple kinds of topology within the same sample, which is in contrast to most studies which focus on a single type of connectome.

Bifactor model

We identified trend-level correlates of the general factor across all three studies. In two out of three studies decreased path length was associated with the general factor. Decreased path length in the absence of changes in clustering coefficient is indicative of higher wiring costs with a tendency towards subtle randomization. Decreased modularity was also identified as a correlate of the general factor in two out of three studies. Decreases in modularity suggest less segregated processing and lead to networks that are less resilient to insult (Kashtan & Alon, 2005). This may be linked to the cognitive deficits that are characterize a range of psychopathology (Caspi & Moffitt, 2018). Morphometric similarity yielded the largest number of general factor correlates. Thus, lack of synchrony of developmental trajectories of brain regions may be particularly informative for the general factor.

We also observed correlates of both specific internalizing and externalizing. The majority of correlates were for externalizing, and thus global topology may be more relevant for externalizing symptomatology. At present, the mechanism for this remains unclear. Given that substance misuse symptoms load onto specific externalizing, it is possible that changes in topology are a consequence of rather than a vulnerability for psychopathology. Alternatively, disruptions in network topology may make individuals particularly vulnerable to impulse control difficulties. Finally, this may be driven by higher heterogeneity in the internalizing factor. In some studies, it splits into a fears and distress component, and in others it is a single factor (Lahey et al., 2012; Lahey, Zald, et al., 2017).

Differences in clustering coefficient and path length were both observed as a correlate of specific externalizing in two out of three studies. This suggests that the balance of integration and segregation be especially predictive of externalizing symptomatology. Perturbations in local and global communication may lead to difficulties in impulse control that characterize these disorders. Additional studies are needed to test this hypothesis. In particular studies could look at relations between impulse control measures and graph theory metrics.

Correlated factors model

Across studies, the only relations that survived FDR correction were within the correlated factors model. Therefore, the present results provide support for the utility of this model for examining neural correlates of dimensional psychopathology. As in the bifactor model, more correlates were identified for the externalizing factor than the internalizing factor. Changes in modularity were seen in two out of three studies though only reaching FDR significance in one study. Increased modularity implies more segregated processing within the brain. This finding is consistent with prior work showing that increases in modularity may lead to drive regions being separated from control regions which translates into difficulties with cognitive control (Davis et al., 2013). Increased degree, decreased clustering coefficient, and decreased path length emerged as relations that survived FDR correction. These findings are suggestive of decreased segregation and integration being associated with externalizing psychopathology. While we identified correlates in both DWI and functional topology, we did not identify any MSA correlates. Thus, the structure of white matter connections as well as functional topology in response to reward may be most relevant for the correlated factors model.

Overall implications

While we did identify several correlates of the general factor, these were all at a trend-level. Though this provides some evidence that global network topology is relevant for the general factor, it suggests that these may not be the most robust correlates. However, the present results do not rule out the possibility that network topology is important for the general factor. First of all, we selected graph theory metrics that have previously been identified using case-control design studies. It may be the case that graph theory metrics that we did not investigate are more relevant for the general factor. Another possibility is that functional network topology at rest is more predictive than functional topology during a task or structural topology. It could also be that perturbations exist at the level of local rather than global network topology. Further, the relative balance of global network topology properties within or across modalities could be more relevant than a single measure. This lack of significant correlates may also be due in part to limitations of the general factor. In particular, that there are many different pathways to reaching a high general factor score. Further, some individuals may be high on only the general factor, high on the general factor and one specific second-order factor, or high on all factors. It may be that these different profiles are associated with unique network topology correlates. Additional studies are needed to clarify the extent to which network topology plays a role in the etiology of the general factor.

This dissertation yielded more robust evidence for the role of global network topology in the correlated factors model than for the bifactor model. This could be driven in part by the larger number of tests for the bifactor model versus the correlates factors model (10 versus 15) which created a higher bar for significance in the bifactor model. It could also be that parsing out additional variance within the bifactor model for the general factor makes it more challenging to detect relations. Further work is needed to clarify what might be driving differences between the bifactor and correlated factors model. Few studies employ both the correlated factors and bifactor model when testing relations; the present findings suggest that examining both models is likely important as we continue to assess correlates of dimensional psychopathology and determine an optimal model.

An additional important finding in this dissertation is that relations between graph theory metrics from DWI topology and psychopathology varied based on poverty status. This suggest that developmental factors may be particularly important in influencing relations between structural network topology and psychopathology. In this dissertation we only examined the impact of poverty status for DWI topology given that a prior study found relations between DWI topology and childhood poverty (Kim et al., 2011). We did not examine the impact of poverty on relations in other studies because we felt this was beyond the scope of the primary goals of this dissertation, but childhood poverty may also be relevant for other forms of topology. These findings highlight the need to conduct longitudinal studies to understand the interplay between childhood factors, network topology development, and psychopathology. This is important work because it may help identify variables to serve as meaningful prevention targets.

In this dissertation, we also identified sex differences across all studies with at least one significant interaction in each modality (Table 37). There are known sex differences in psychopathology and sex differences have been identified in relation to neuroimaging data (Kessler et al., 2005). This indicates the importance of not considering sex as simply a nuisance variable when investigating neural correlates of psychopathology. Further work is needed to parse on the ways in which sex may impact relations between network topology and latent factors of psychopathology.

Table 37| Significant sex interactions across modalities

Latent factor	DWI topology	AC	fMRI
General	--	Degree	Path length
Specific Internalizing	Clustering coefficient	--	--
Specific Externalizing	--	--	--
Internalizing	Clustering coefficient	--	--
Externalizing	Clustering coefficient Modularity	--	Modularity

Bifactor model: general, specific internalizing, and specific externalizing; Correlated factors model: internalizing and externalizing
DWI = diffusion weighted imaging; AC = anatomical covariance; fMRI = functional magnetic resonance imaging

Limitations and future directions

This dissertation had a number of notable strengths including use of a large community sample with a range of psychopathology, implementing a dimensional approach to psychopathology, and inclusion of multiple imaging modalities. However, the findings need to be considered in light of a few limitations. When possible we tried to keep the methodology consistent across studies in order to be able to compare the results. However, there were a few differences because we also tried to make the best decisions for each type of data. The primary difference was the number of nodes and the nature of these nodes (study 1: 397 nodes from a fine-grained HOA atlas, study 2: 148 nodes from Destrieux atlas; study 3: 297 nodes from 300 ROI set). We tried to optimize the nodes for the given modality, but the number of nodes can impact graph theory metrics (Zalesky et al., 2010). Another difference between studies was the treatment of negative weights (study 1: excluded; study 2: no negative weights; study 3: included). We excluded negative weights from morphometric data because there is mixed information on their interpretability (Gong et al., 2012). Further work is needed to understand how differential treatment of negative weights may impact results.

Another limitation is that we focused on global rather than local properties of network organization. We focused on global properties given our hypothesis that the broad nature of the general factor might be impacted by broad properties of network organization. Given that we did identify some global correlates of the general factor but these did not survive FDR correction, examining local properties may yield important insights. Future studies should examine local metrics such as hub node properties. While this study examined both structural and functional network topology, examining resting-state data might provide important insights. Finally, we looked at structural and functional network topology separately, and thus it is unclear the way in which these may interact. Given that the metrics were relatively uncorrelated across modalities, it may be that they are more predictive of psychopathology when considered in combination. Additional studies can address this question using multi-layer matrices. A final limitation is the use of the general factor. Given that we saw more significance with the correlated factors model, the present findings may be consistent with critiques of the bifactor model such as overfitting and inconsistent factor loadings across studies (Bonifay et al., 2017; Watts et al., 2019). We also did not include more severe forms of psychopathology in the present study, and thus future studies should examine how this might impact relations with network topology.

Conclusions

In this dissertation, we identified both structural and functional topology correlates of the bifactor model and the correlated factors model. These results provided additional confidence in the value of utilizing a dimensional approach to psychopathology in order to better understand its neural correlates. It further supports the importance of looking at imaging modalities in combination, since psychopathology is likely impacted by a complex interaction of structural and functional perturbations. Using dimensional approaches to psychopathology may yield transdiagnostic neural correlates that can serve as novel therapeutic targets.

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