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Network models of aberrant brain connectivity for elucidation of the pathophysiology of schizophrenia

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ABBREVIATIONS

CNS	Central nervous system
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD	International Classification of Disease
DALY	Disability-adjusted life years
GABA	Gamma-aminobutyric acid
MRI	Magnetic resonance imaging
BOLD	Blood-oxygen-level-dependent
DWI	Diffusion weighted imaging
GWAS	Genome-wide association study
PRS	Polygenic risk scores
PANSS	Positive and Negative Syndrome Scale
DTI	Diffusion tensor imaging
GNM	Generative network model
NCT	Network control theory
TMS	Transcranial magnetic stimulation
RDoC	Research Domain Criteria
PLS	Partial least squares
CCA	Canonical correlation analysis
AA	Ambulatory assessment
EMA	Ecological momentary assessment

1 INTRODUCTION

1.1 A brief introduction to the origin, diagnosis, and treatment of schizophrenia

In 1887, Dr. Emil Kraepelin firstly defined schizophrenia as a discrete mental disorder, which he thought was primarily an illness of the brain and particularly a form of dementia (Kraepelin 1987). Thus, he named it 'dementia praecox' (early dementia) to distinguish it from other dementias, such as Alzheimer's disease. Considering that the illness was not dementia and could also occur late, Krapelin's name was misleading, so a Swiss psychiatrist, Eugen Bleuler, coined the term "schizophrenia" in 1911 (Bleuler 1911). The word "schizophrenia" translates roughly as "splitting of the mind" to describe a fragmented, disorganized thinking, which should not be confounded with split in multiple personalities. Schizophrenia remains a broad syndromic concept, like most other psychiatric disorders, although the etiology originates undoubtedly in the central nervous system (CNS) (Meyer-Lindenberg 2010a).

Currently, the diagnosis of schizophrenia still depends on the personal history of patients and the examination of the mental state. Despite decades of research on schizophrenia, the underlying neurobiological abnormalities remain elusive, mainly due to the complexity of psychiatric disorders (Kapur, Phillips, and Insel 2012). To date, there is no biomarker to establish the diagnosis of schizophrenia, in contrast to many neurological disorders, for example epilepsy, which can be diagnosed and classified using electroencephalography (Sabers and Kjær 2014). Schizophrenia is diagnosed based on the criteria of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), or the World Health Organization's International Classification of Disease (ICD) 10th revision. According to DSM 5, two or more of the symptoms (including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms, such as diminished emotional expression) should be present for more than one month, and at least one of them must be among the first three symptoms listed (Edition 2013). Similarly, ICD 10 regards persistent delusions and hallucinations, thought disorder, experiences of influence, passivity, or control as the core symptoms of schizophrenia, and signs must also persist for at least one month.

Overall, both DSM and ICD have promoted better diagnostic agreements and improved the reliability of psychiatrists' diagnosis of schizophrenia.

According to DSM 5, the lifetime prevalence of schizophrenia is approximately 1%. Schizophrenia patients suffer from different symptoms and have poorer social, educational and occupational outcomes, substantial loss in disability-adjusted life years (DALY), and lower fertility (Hjorthøj et al. 2017; Davidson et al. 2016; Haukka, Suvisaari, and Lönnqvist 2003). As the current primary treatment, antipsychotic medications, such as clozapine and olanzapine, effectively reduce "positive" psychotic symptoms, like delusions. The efficiency of these drugs primarily results from blocking dopamine receptors, particularly the D2 receptor, suggesting that increased dopamine activity may be involved in the pathophysiology of schizophrenia (Howes and Kapur 2009). However, since dopamine receptor antagonism is not an efficient treatment strategy for cognitive deficits and partly negative symptoms as well (Yang and Tsai 2017), schizophrenia patients still suffer from functional and vocational impairments in their daily life. In addition, there is a lag of two to four weeks between the blockade of dopamine receptors and clinical response, implying that acute dopamine receptor blockade might not be sufficient for solely explaining the reduction of symptoms in response to antipsychotic treatment (Marder and Cannon 2019). In recent years, more and more drugs targeting other neurotransmitter receptors, such as those for glutamate and gamma-aminobutyric acid (GABA), which can also help mitigate cognitive dysfunction and negative symptoms, are now under study (Maric et al. 2016). In summary, despite the significant progress made in recent years to improve the diagnosis and treatment of schizophrenia, we need to better understand the neurobiological alteredities underlying this complex disorder. Here, neuroimaging has established itself as a promising tool for achieving the goal, as it allows in-vivo assessment of brain functioning. In combination with genetic and neuropsychological methods, novel models of brain (dys-)function may ultimately advance our understanding of brain alteredities in schizophrenia, paving the way for new therapeutic interventions and prevention strategies.

1.2 Genetic and cognitive research of schizophrenia

Schizophrenia is a heterogeneous syndrome, which appears to result from the disruption in the interaction of genetic and environmental factors during neurodevelopment. The advances of epidemiology, pharmacology, imaging, and

genetics make it possible to put these insights together for further scientific advance and even optimization of clinical practice.

1.2.1 Genetic studies in schizophrenia

Genetic epidemiological studies suggest that the heritability of schizophrenia is about 80% (Hilker et al. 2018). The introduction of high-throughput sequencing has made genome-wide experiments possible to investigate the molecular genetics of schizophrenia. The largest multi-stage schizophrenia genome-wide association study (GWAS) to date identified 128 independent genetic loci ('Biological insights from 108 schizophrenia-associated genetic loci' 2014). These significant associations were enriched for genes distributed mainly in three clusters: neurotransmitters, immune system and potentially neurotrophic factors, which adds evidence for the link of these processes with schizophrenia pathophysiology. Recent work suggests that studies of genetic susceptibility in schizophrenia might be enhanced by identifying so-called “intermediate phenotypes”, which are quantitative traits that are reliable and heritable and show greater prevalence in unaffected relatives of patients than in general population. These phenotypes are believed to be related more intimately to fundamental aspects of brain dysfunction in heritable mental disorders.

1.2.2 Cognitive dysfunction in schizophrenia

Historically, schizophrenia was first called dementia praecox, a term focusing on the cognitive deterioration accompanying the syndrome. Later, the defined core symptoms shifted towards the core symptoms of psychosis, such as delusions and hallucinations, perhaps because they stand out most and appear most disturbing to the social environment and society. Since current antipsychotics do not have much effect on cognitive dysfunction, true functional and vocational rehabilitation is difficult for patients with schizophrenia. Consequently, it becomes more and more critical to develop new treatments that can also remediate cognition except for mitigating psychosis (van Os and Kapur 2009). Neuroimaging is a promising tool to explore the neurogenetics risk and cognitive dysfunction of schizophrenia.

1.3 Neuroimaging studies of schizophrenia

Neuroimaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography, and electroencephalography, are the primary tools for understanding the biological basis for psychopathology. Unlike clinical symptoms,

neuroimaging biomarkers could serve as accessible and objective indices to help decide whether individuals suffer from a particular disease and which treatment might be optimal and best predict the treatment outcome.

1.3.1 Brief introduction of MRI

MRI is based on nuclear magnetic resonance and is a noninvasive imaging technique that can be used to describe the anatomical structure, physiological functions, and the molecular composition of tissues. Briefly, when placed in a strong magnetic field, atoms are forced to be aligned with that field. Through applying a radiofrequency current to the atoms, these atoms are stimulated and spin out of equilibrium. When the radiofrequency field is turned off, the atoms will gradually recover to the spin movements under the strong magnetic field. The recovery duration and the amount of energy released vary for different brain tissues, therefore differentiating grey and white matter and enabling to acquire high-dimension structural images. Functional MRI measures a proxy of brain neural activity based on the blood-oxygen-level-dependent (BOLD) signal. The BOLD signal measures the hemodynamic response - a lagged signal (about 2 seconds delay) and physiological consequence of neural activity. At regions of neural activity, neurons require an increased amount of oxygen, which causes changes in the level of oxyhemoglobin and deoxyhemoglobin. Hemoglobin has different magnetic properties in its oxygen binding, where deoxygenated hemoglobin is paramagnetic and oxygenated hemoglobin is diamagnetic, both of which can be detected using MRI. Even though functional MRI is an indirect measure of neural activity, it can provide high spatial resolution whole-brain functional images (around 3mm) that measure both resting-state (baseline) and task-state brain activity. Diffusion weighted imaging (DWI) is another MRI technique allowing for the reconstruction of neural tracts by measuring the restricted diffusion of water in brain tissue. DWI can be used to describe the integrity of white matter fibers and infer structural connectivity between brain regions.

1.3.2 Disconnection hypothesis of schizophrenia

More than one century ago, Wernicke first suggested that schizophrenia arises from aberrations of the brain’s association fibers (Wernicke 1906). The advent of neuroimaging techniques provided powerful tools to test and extend these ideas by mapping brain structure and function. First evidence of functional differences in brain metabolism was detected by Ingvar et al. using a Xenon-based imaging technique,

who found an altered distribution of frontal blood flow in patients with chronic schizophrenia (Ingvar and Franzén 1974a, 1974b). In line with these findings, structural differences in brain morphology were first described based on computed tomography scans: Johnstone found increased lateral ventricle volume in schizophrenia patients compared to age-matched controls (Johnstone et al. 1976). Since schizophrenia was suggested as a disorder of brain connectivity, exploring the interactions of regional brain activity may provide important insights into the neural alteredities in this disorder. Volkow first reported the disturbing correlation of metabolic patterns among different brain areas under both resting and task conditions in chronic schizophrenics (Volkow et al. 1988). The advent of modern neuroimaging techniques, particularly MRI, enabled researcher to quantify structure and function of human in-vivo without any potentially harmful side effect. These early neuroimaging studies showing altered brain connectivity in schizophrenia were candidate circuit analyses based on previous knowledge of pathophysiology, testing the dyadic connectivity between two single brain regions using seed-based connectivity analyses. One prominent example described an impaired decoupling between prefrontal regions and the hippocampus during working memory. These early accounts provided experimental evidence in humans for the “dysconnection hypothesis” of schizophrenia by Friston and Firth (Friston and Frith 1995), followed by more general characterizations of schizophrenia as a dysconnection disorder (Pettersson-Yeo et al. 2011; Stephan, Friston, and Frith 2009). The idea of dyadic interactions has been further developed into a network perspective, providing a more powerful tool to describe functional interactions at a whole brain level simultaneously, and not only between two single brain areas.

1.3.3 Basic concepts of connectomics

In recent years, connectomics has provided prominent tools for the studies of altered connectivity in schizophrenia. Connectomics was initially referred to a complete structural description of the brain’s physical wiring and was later extended to refer to a map of the brain functional interactions (Biswal et al. 2010). The central principle of connectomics is to describe the entire set of connection of the brain as a connectivity matrix. For analysis purposes, the connectivity matrix can be represented in an abstract representational space, called a graph. A graph consists of nodes (which represent brain regions) and edges (which represent the connections between brain regions). The most common way to define nodes is to use a priori brain parcellation,

such as Automated Anatomical labeling (Tzourio-Mazoyer et al. 2002). The approach to defining edges depends on the data modality one uses to construct the connectivity matrix. For functional MRI, edges can be the correlation of mean time-series of two brain areas, while in DWI data, edges reflect the reconstructed white matter tracts based on the diffusion of water molecules in brain tissue. After building the connectivity matrix, one can directly compare the connectivity strength (how strongly the activity of one region is synchronized with the activity of another, or the number of fiber tracts between two regions) between groups or use tools from graph theory to investigate the local and global aspects of brain network organization. For example, one of most basic metrics from graph theory is degree, which is the sum of connections attached to a given node. High-degree nodes are called hubs and can be thought of being important in a network, as they are important for communication processes. Brain regions that are commonly found to have a high degree are for example the medial prefrontal cortex and the posterior cingulate cortex. Another common metric, clustering coefficient, is defined as the number of existing triangle connections around a given node divided by the number of all possible triangles. Clustering indicates how well a node is integrated with its neighboring nodes, conveying important insight about the local connectivity structure. These graph metrics can be used to describe large-scale functional aspects of the brain's architecture, such as segregation and integration. Segregation in the brain is the ability for specialized processing within interconnected groups of brain regions, while integration is the ability to combine specialized information from distributed brain regions.

With the variable metrics provided by graph theory, human brain networks have been found to be organized in a highly efficient small-world manner: high level of local clustering for local information processing and the existence of long-range connections ensuring global communication efficiency and integrating information between different brain regions (Sporns et al. 2004). Furthermore, normalized path length (shortest path distance between two nodes) between frontal and parietal areas was correlated with intellectual quotient, indicating a strong association between the global efficiency of brain network and intellectual performance (van den Heuvel et al. 2009). Research in the network topology has gained new knowledge about the fundamental principles underlying the human connectome organization. Therefore, it

is worthwhile to extend this research to investigate the altered connectome in schizophrenia.

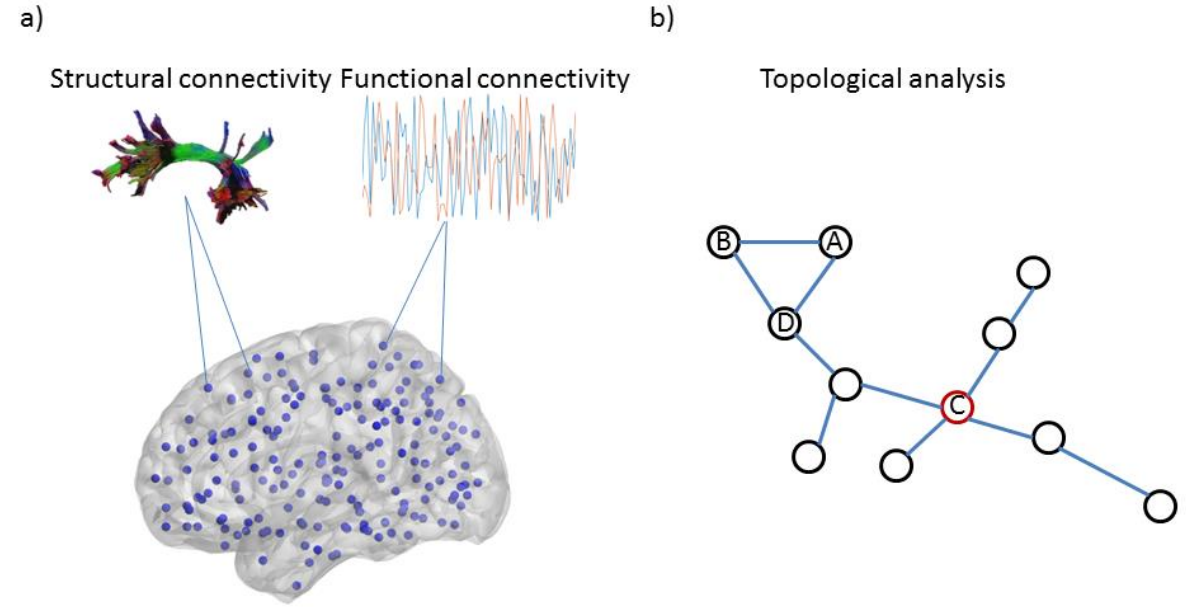

Figure 1.1 Basic concepts and measures of connectome and graph theory. (a) Structural connectivity can be fiber tracts between two brain regions constructed by DWI, while functional connectivity can be the correlation of time series of two regions. (b) Circles represent nodes, and lines represent edges. A and B are two different brain regions. The edge between them could be functional connectivity represented by the correlation between their time series, or white matter fiber tracts reconstructed with diffusion tensor imaging. The degree of node C is 4, which is higher than other nodes and could be regarded as the hub of this network. The clustering coefficient of node D is 0.33, indicating that 2 of 3 neighbors have one connection. The picture of fiber tracts comes from DSI Studio (http://dsi-studio.labsolver.org/).

1.3.4 Neuroimaging connectomics in schizophrenia

Relative to candidate circuit analysis, connectome-wide analysis can evaluate all possible connections simultaneously, therefore providing comprehensive mapping of disease-related changes. Previous findings indicate a relatively diffuse and context-independent reduction of functional connectivity in schizophrenia (Fornito et al. 2011; Zalesky et al. 2011; Supekar et al. 2019; Alexander-Bloch et al. 2010; Bassett et al. 2012), particularly affecting the functional interactions among the hubs of the human connectome, for example frontal cortex and posterior regions (Crossley et al. 2014). There is also a more circumscribed and context-dependent increase in functional connectivity (Fornito et al. 2012). And early work indicates that these functional alteredities have an anatomical basis.

Besides directly comparing connectivity strength between schizophrenia patients and healthy controls, previous studies have also reported the topological disturbances of structural and functional brain networks in schizophrenia. Brain networks in schizophrenia may be characterized by a subtle randomization showing reduced

clustering (Liu et al. 2008; Kim et al. 2014; van den Heuvel et al. 2010; Bassett et al. 2008) and modularity (Alexander-Bloch et al. 2010) and increased topological integration (Whitfield-Gabrieli et al. 2009) and robustness (Lynall et al. 2010b) as well as altered rich club organization (van den Heuvel, Sporns, Collin, Scheewe, Mandl, Cahn, Goñi, et al. 2013; Collin et al. 2014). In addition, brain networks show affected dynamic reconfiguration (Braun, Schäfer, et al. 2016; Du et al. 2018; Sun et al. 2019), which may underlie altered brain function and clinical symptoms observed in schizophrenia. In summary, a connectome perspective on schizophrenia has provided important insights about the dysfunction of specific brain regions, candidate brain circuits, and sub-networks in addition to emphasizing the importance of conceptualizing schizophrenia as a disorder of disrupted interconnected complex systems. These findings deepen our understanding of schizophrenia as a disorder of disconnection.

1.3.5 Linking gene and cognition to brain network

Imaging genetics has increased our understanding of the neurogenetic mechanism of schizophrenia (Meyer-Lindenberg 2010b). Imaging genetics combines genetics and neuroimaging to investigate the effect of genetic risk variants on brain structure and function. Early studies used genetic risk variants that come from candidate genes or top hits from GWAS. For example, healthy carriers of rs1344706 in ZNF804A, which is the first common genetic variant showing genome-wide association with schizophrenia, exhibit significant gene dosage-dependent changes in the functional correlation between dorsolateral prefrontal cortex and hippocampus (Esslinger et al. 2009), which corresponds to the findings in schizophrenia patients (Schneider et al. 2017; Rasetti et al. 2011). Considering that hundreds of common genetic polymorphisms each confer only very small effects to the overall risk for schizophrenia, novel measures were developed to represent the cumulative influence of each locus on the genetic risk for developing schizophrenia. One simple but widely used method is polygenic risk scores (PRS), which models the additive effect of alleles associated with a disorder status and allow the application of the power of large-scale GWAS to small samples (Dima and Breen 2015). PRS for schizophrenia were found to be associated with the activity of the dorsolateral prefrontal cortex during a working memory task (Miller et al. 2018) and cortical gyrification (Liu et al. 2017) in healthy controls. These findings validate the disturbed brain structure and function as intermediate phenotypes in schizophrenia. These intermediate

phenotypes lie between risk genotypes and disease phenotypes and are closer to gene function than the disease itself, representing therefore useful targets for molecular genetic studies.

Previous studies have found associations between brain network efficiency and intelligence (van den Heuvel et al. 2009), and the connectivity deficits in offspring (Collin et al. 2017) and siblings (Collin et al. 2014) of schizophrenia patients. Furthermore, using a longitudinal dataset, Collin found that affected local connectivity organization was related to longitudinal increase in overall Positive and Negative Syndrome Scale (PANSS) scores and decrease in total intelligence quotient (Collin et al. 2016). Thus, neuroimaging studies of cognition dysfunction in schizophrenia may predict the course of illness and help to find neurobiological biomarkers as treatment targets.

1.4 Novel network tools

However, current neuroimaging connectomic studies of schizophrenia have not yet found neurobiological biomarkers that can significantly impact the diagnosis or treatment of individual patient. To move beyond the simplicity of descriptive and associative mapping of human brain networks using graph theory, we need more realistic and mechanistic network models that characterize the brain as a complex system. Gaining a more causal understanding of the pathophysiological processes on the neural network level may help identifying novel treatment targets that could truly improve diagnosis and treatment.

1.4.1 Necessity of novel network tools

While graph theory and connectomics help us to identify some fundamental principles of the brain organization that might underlie normative cognitive function, these insights are usually derived from statistical differences in graph theory parameters or from correlations between these parameters and behavior or cognitive measures. However, these parameters do not offer any information on how the brain is organized to support so many cognitive (dys-)functions, and correlations do not allow inferences on causal relationships. For example, the functional network in schizophrenia shows reduced clustering, implying decreased local integration, but this findings does not tell us when and why the reduced clustering happens or how it leads to different symptoms. Therefore, to move beyond these graph-theoretical

parameters to causal factors, we need newly generative or even mechanistic network models rather than current descriptive models in schizophrenia research.

1.4.2 Introduction of generative network models

There are many models for seeking mechanisms underlying the evolution and development of the network. One of them is the generative network model (GNM), a flexible framework for generating networks based on a set of wiring rules that may suggest the mechanisms underlying how the network functions, develops, and evolves. Generative models have been used widely to investigate the worldwide web, social system, and evolution of protein interaction networks (Betzel and Bassett 2017).

To construct the generative models of the brain network, one needs to define two essential elements: the generative algorithm and the objective function. The generative algorithm is the probability function of connection formation, which could be the combination of different wiring rules. For example, ‘the rich get richer’, namely that the connectivity between high-degree nodes is more likely to form than between low-degree nodes; the closer two nodes are, the higher likelihood there is a connection between them. And the objective function is to perform quantitative comparisons between synthetic networks created by generative models and empirical networks constructed from neuroimaging. There are different methods to define the objective function, which are suited to answer different research questions. One can regard edge overlap as the objective function, which accounts for the exact configuration of nodes and edges. While it is useful to compare synthetic and observed networks based on edge configuration, this has also significant flaws. For example, a small-world network, which could be represented by a ring lattice plus a few shortcut connections that can reduce the characteristic path length of the network, matches most of the edges in the lattice network. However, the global efficiency of these two networks is profoundly different: the small-world network is more suitable for information communication because of the shortcut connections. So from a structural perspective, these two networks are nearly perfect matches, but from a functional point, the two networks are highly dissimilar. Another potential approach is to compare a set of topological properties between the synthetic and the observed networks (Vértes et al. 2012; Betzel, Avena-Koenigsberger, Goñi, et al. 2016). This approach is flexible and can include different sets of network metrics. However, we need to note that many network metrics are correlated with each other.

And even though synthetic networks match the observed network in terms of topological properties, this does not mean that they share the same set of edges. Therefore, one needs to define the proper probability function of connection formation and objective function of network comparison based on their specific research question or based on previous studies. After determining the generative algorithm and the objective function, one can start to optimize the objective function by selecting model parameters.

There has already been a couple of application of generative models to large-scale brain networks in humans. Vertes defined different generative models with varying combinations of wiring rules and found that compared to other models, one two-factor model could better simulate a set of critical topological properties of grouped functional brain network (Vértes et al. 2012). There were two competing factors in this model: a distance penalty on wiring cost of building and maintaining long-range connections; and a topological term favoring edges between brain areas with similar connection patterns. In addition, slightly detuned model parameters could reasonably simulate the same set of altered topological properties of brain networks in the schizophrenia group. Another study on the generative model of the human brain connectome found that the same set of wiring rules can optimally simulate a set of topological features of individual structural brain network (Betzel, Avena-Koenigsberger, Goñi, et al. 2016). Furthermore, with a lifespan dataset, the authors of the study found that model parameters change progressively, implying a rebalancing of generative factors underlying human connectome during aging. These studies provide potential chances to dig deeply into the mechanisms underlying the dysfunction in the human connectome by simulating the altered formation of brain networks with models like GNMs.

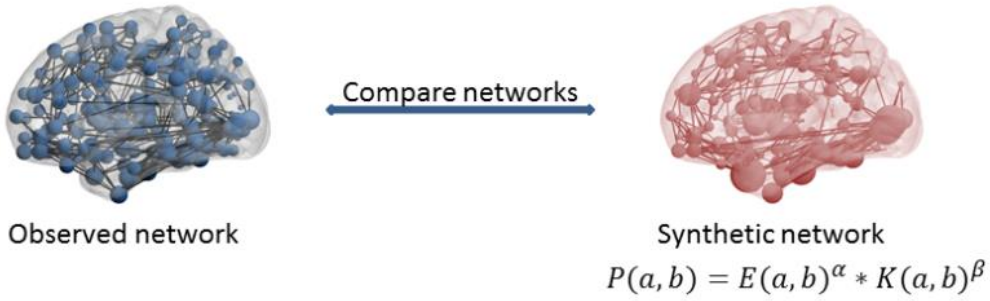

Figure 1.2 Framework of the generative network model. After setting up the probability function of connection

formation $P(a, b)$(a and b are two brain regions), one can construct the synthetic network. In the probability function, E and K are two different factors representing varying wiring rules. α and β are the model parameters that control the influence level of the corresponding factor on connectivity formation. And they need to be picked up so that the synthetic network will optimally simulate the edge configuration or topological properties of the observed network. The synthetic network will then be compared to the observed network based on the objective function that one defines. Brain networks are drawn with BrainNet Viewer (Xia, Wang, and He 2013).

1.4.3 Thesis goals and publications

Given the evidence reviewed above, it is adequate to conclude that there is a lack in research that investigates the altered formation of individual brain network in schizophrenia, or genetic factors or functional consequences of the altered formation. In this thesis I aim to elucidate:

1) what the differences in the process of brain network formation between schizophrenia patients and healthy controls are,

2) whether genetic risk factors contribute to the altered formation,

3) whether the altered formation has an influence on cognitive function.

To answer these questions, I construct generative network models across patients, relatives and healthy controls and compare the model parameters between groups. I will apply polygenic risk scores and endophenotype to explore the effects of genetic factors and correlate model parameters with cognitive measures to explore the influence on cognition.

The findings reported in this thesis form the basis of two published peer reviewed first-author papers of the doctoral candidate:

1) Xiaolong Zhang, Urs Braun, Heike Tost, Danielle S. Bassett. Data driven approaches to neuroimaging analysis to enhance psychiatric diagnosis and therapy. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2020 Jan 7. pii: S2451-9022(19)30355-6. doi: 10.1016/j.bpsc.2019.12.015.

2) Xiaolong Zhang, Urs Braun, Anais Harneit, Zhenxiang Zang, Lena S. Geiger, Richard F. Betzel, Junfang Chen, Janina I. Schweiger, Kristina Schwarz, Jonathan Rochus Reinwald, Stefan Fritze, Stephanie Witt, Marcella Rietschel, Markus M. Nöthen, Franziska Degenhardt, Emanuel Schwarz, Dusan Hirjak, Andreas Meyer-Lindenberg, Danielle S. Bassett, Heike Tost. Generative network models identify biological mechanisms of altered structural brain connectivity in schizophrenia. NeuroImage. 2020 Nov 5; 225:117510. doi: 10.1016/j.neuroimage.2020.117510.

2 STUDY 1: DATA DRIVEN APPROACHES TO NEUROIMAGING ANALYSIS TO ENHANCE PSYCHIATRIC DIAGNOSIS AND THERAPY

2.1 Abstract

Combining advanced neuroimaging with novel computational methods in network science and machine learning has led to increasingly meaningful descriptions of structure and function in both the normal and altered brain, thereby contributing significantly to our understanding of psychiatric disorders as circuit dysfunctions. Despite its marked potential for psychiatric care, this approach has not yet extended beyond the research setting to any clinically useful applications. Here we review current developments in the study of neuroimaging data using network models and machine learning methods, with a focus on their promise in offering a framework for clinical translation. We discuss three potential contributions of these methods to psychiatric care: (i) a better understanding of psychopathology beyond current diagnostic boundaries, (ii) individualized prediction of treatment response and prognosis, and (iii) formal theories to guide the development of novel interventions. Finally, we highlight current obstacles and sketch a forward-looking perspective of how the application of machine learning and network modeling methods should proceed to accelerate their potential transformation of clinically useful tools.

2.2 Introduction

For the past several decades, neuroimaging techniques such as MRI, positron emission tomography, near-infrared spectroscopy, and electrophysiology, have leveraged an expanding array of available tools to evaluate human brain structure and function. These techniques have proven essential for extending cognitive neuroscience (Shine et al. 2016; Braun et al. 2015), delineating new mechanisms in pathophysiology (Lo et al. 2015), verifying long-standing pathophysiological hypotheses (Laruelle et al. 2005), and characterizing macro-circuit contributions to (dis)ordered human behavior (Esslinger et al. 2009; Buchel and Dolan 2000). Although, neuroimaging research in psychiatry has revolutionized the clinical perspective on the pathophysiology of major psychiatric disorders, diagnostic neuroimaging remains confined to the academic environment. As part of clinical care in psychiatry (Mayberg 2014; Macqueen 2010), it is mainly used as a tool to rule out

potential “organic” origins of psychiatric symptoms such as tumors, trauma, or inflammation. The reasons for lack of translation are many, and range from general to neuroimaging-specific. General reasons include the large heterogeneity within diagnostic entities, and the long established use of a phenomenological rather than a biological classification of disorders; reasons specific to neuroimaging include the common use of rather simplistic models of brain function, descriptive rather than predictive tools, and group-level analysis.

Changing perspective, it might be useful to ask: What are the most pressing challenges currently faced by clinicians? Psychiatric diagnostics often resemble working assumptions, with a patient presenting a variety of symptoms such as hallucinations, delusions, and neurocognitive impairments. In stark contrast to other medical disciplines that use laboratory tests and diagnostic imaging to offer a diagnosis within hours, a thorough psychiatric investigation can span days to weeks, requiring a third-party history and the building of a trusting patient-physician relationship to reveal symptom details and the extent of functional impairment. Experienced clinicians often foresee the most probable diagnosis, but they still face unpredictable challenges as to what medication the patient will most likely respond to and what course his or her disease will take in the future. In navigating these challenges, current psychiatric research has increasingly turned to new data driven approaches with the aim of developing expeditious and more accurate predictors of diagnosis and treatment.

Here we describe novel data driven approaches to neuroimaging with a focus on network science and machine learning, discuss current obstacles in study design and analysis strategies, and highlight potential future directions that might provide useful clinical applications. The specific content that we review was identified by a literature search for keywords including both methodological terms “network model” and “machine learning”, as well as outcome measures such as “prediction” and “subtypes”. Furthermore, we focused on a subset of that literature comprised of studies that integrate both analysis methods: network science and machine learning. The reader may also be interested in other more extensive reviews that focus separately on either network neuroscience in psychiatry (Fornito, Zalesky, and Breakspear 2015; Braun et al. 2018) or machine learning in psychiatry (Janssen, Mourao-Miranda, and Schnack 2018). Here, we seek to describe the unique potential of combining both approaches to advance subtype detection and prediction.

In particular, we begin by describing how network science can provide increasingly more realistic, biologically valid, and useful models of brain function. We then turn to a discussion of how these models can be used to (i) gain a better understanding of brain dysfunction and psychopathology beyond established diagnostic boundaries, (ii) provide valuable information about individual treatment and prognosis, and (iii) guide future development of novel interventions. We acknowledge that our scope is broad and we must inevitably pass over many important details. We encourage the interested reader to peruse our extensive bibliography (and the bibliographies within them) for further study.

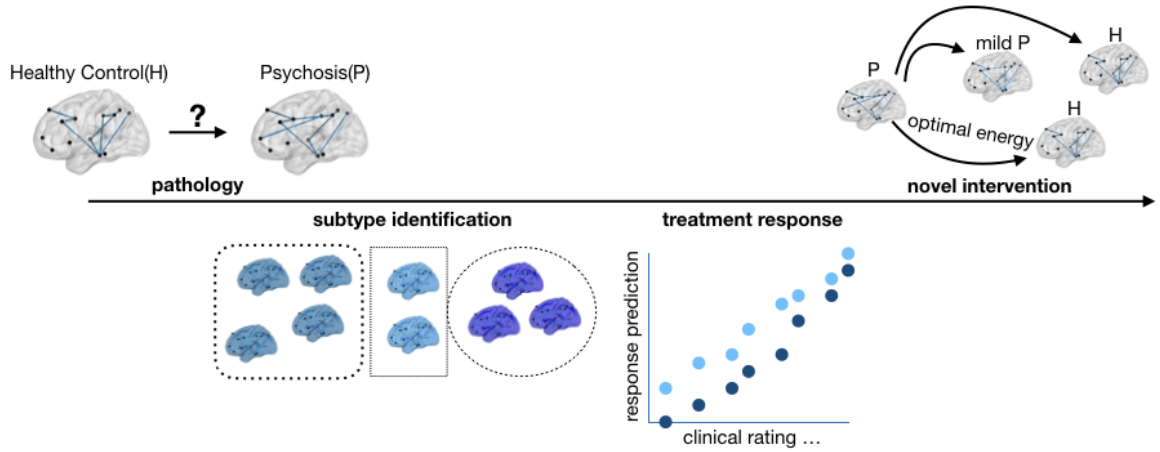

Figure 2.1 Room for improvement: Schematic of potential applications of network neuroscience and machine learning to enhance psychiatric care. Current applications concentrate on identifying neural correlates of the pathology of diagnostic entities. However, clinical and scientific data favors the idea of a dimensional description of mental disorders. Therefore, identifying subtypes or internally homogenous groups will help unravel the complicated mechanisms involved and inform the selection of different treatment options for different subgroups. The prediction of individual response to various treatments could assist clinicians in choosing the most promising therapeutic option for individual patients. Finally, a mechanistic understanding of dynamic brain processes will be useful for developing novel interventions. Brain network maps were made with BrainNet Viewer (Xia, Wang, and He 2013). H means healthy controls and P means psychosis.

2.3 Networks as increasingly realistic models of brain (dys-)function

Converging evidence from decades of neuroscience research supports the notion that brain function arises from the complex interaction of multiple components, from individual neurons to large-scale areas (Cajal 1995; Swanson 2003). In the 19th century, pioneers like Wernicke, Meynert, and Dejerine put forward the idea that psychiatric disorders arise from disruptions in highly coordinated interactions. This notion continues to shape the modern conception of psychiatric disorders as disconnection syndromes or brain circuit dysfunctions (Catani and ffytche 2005).

Simultaneously, neuroimaging models of mental disorders have shifted from emphasizing dysfunction of specific brain regions (Braak and Braak 1991; Weinberger et al. 2001) to characterizing disruptions of interconnected neural systems, paralleling the rapid advances in connectomics (Sporns, Tononi, and Kotter 2005).

In recent years, the neuroimaging community has constructed increasingly accurate maps of these structural and functional connections with unprecedented detail (Hagmann et al. 2007; Cole et al. 2014). In combination with new analytical tools from the field of network science, these approaches have given rise to a new field of research referred to as connectomics or network neuroscience (Bassett and Sporns 2017). The map of large-scale connections within the brain is termed a “connectome” or “brain network,” and offers a comprehensive description of whole-brain interactions (Fornito and Bullmore 2015). Careful study of such networks has offered an increasingly precise account of brain function, and how that function relates to inter- and intra-individual differences in cognition, emotion, and behavior. The application of connectomes has also enabled detailed descriptions of how mental disorders affect brain structure and function, which in turn has offered new insights into the shared traits of different brain disorders (Bullmore and Sporns 2012; Crossley et al. 2014). With this knowledge, investigators may be able to transform conventional descriptions of case-control differences in neurobiological measures to novel inferences regarding the underlying pathophysiological mechanisms of psychopathology (Fornito, Zalesky, and Breakspear 2015).

2.4 Novel network approaches to understanding mechanisms of disease

Despite marked advances, these network approaches have remained rather static and descriptive, and generally ignored the complex dynamics of brain function, thereby failing to provide mechanistic insights. To better probe mechanisms, a novel set of tools has recently been adapted that allow increasingly realistic and mechanistic models of brain dynamics and function.

2.4.1 The previous application and potential direction of generative network models

One particularly promising tool is GNM, which offers an appealing framework to uncover mechanisms of function in brain networks (Betzel and Bassett 2017). GNM formalizes the stepwise development, growth, or evolution of networks based on

different wiring rules, each comprising a posited network mechanism (Bertolero and Bassett 2019). Examples include a rule penalizing distance or a rule enforcing a topological property; note here that a network's topology is the architecture of its connectivity pattern. These wiring rules, which can be chosen to reflect neurodevelopmental factors such as the time of development or to reflect neurobiological factors such as brain function (Park and Newman 2004; Newman 2010), determine the likelihood that a specific connection is instantiated. Once constructed, one can then compare the synthetic networks generated by the models to the real networks estimated from neuroimaging data, thereby explicitly testing different mechanistic explanations of the observed topology. The approach thus allows the identification of potential neurobiological and developmental processes that drive the growth and evolution of brain networks. Previous research has provided convergent evidence in favor of a growth model that penalizes long-distance connectivity and, at the same time, favors complex topological features (Vertes et al. 2012); the implicit balance falls in line with current theories of an economic trade-off between minimizing wiring cost and forming valuable topological patterns in the development of brain networks (Bullmore and Sporns 2012). Importantly, GNM has been used to capture age-related changes in network architecture during healthy brain development: the penalty for long-distance connections weakens with age (Betzel, Avena-Koenigsberger, Goni, et al. 2016), consistent with a preferential decrease in the number of short-distance fiber tracts over time (Lim et al. 2015). These observations make GNM an attractive approach for explaining and predicting aberrant brain development in psychiatric disorders as they aim to provide insight into underlying mechanisms leading to observed data.

Although applications to mental disorders are rare, the few existing applications of GNM to brain network dysfunction are promising. Studies in schizophrenia have found that brain networks in disease can be equally well modeled with the same (simple) set of parameters as healthy networks (Zhang et al. 2019), but the contributions of these parameters to the formation of brain networks differ significantly. Most prominently, schizophrenia patients show a decreased penalty for long-distance connectivity (Vertes et al. 2012), allowing for a greater abundance of long-distance connections. Notably, this empirical finding is consistent with previous observations showing a greater proportion of long-distance connections in schizophrenia than in healthy controls (Bassett et al. 2008; Alexander-Bloch et al.

2013). Importantly, a recent study links these aberrant network formation processes to polygenic risk for schizophrenia and cognition, emphasizing the role of impaired genetic processes in the neurodevelopment of large scale brain networks (Zhang et al. 2019).

GNM is in some sense a computational sandbox in which to perform numerical experiments that may be difficult to perform with state-of-the-art empirical technologies. Specifically, with well-established generative models based on biologically grounded wiring rules, one could manipulate or perturb the networks in targeted ways (Betzel and Bassett 2017) to evaluate neurodevelopmental alterations (e.g., autism, schizophrenia) (Vertes and Bullmore 2015; Braun et al. 2018). Such manipulations are accessible to in silico approaches but impossible in vivo; yet, they are critical for identifying and probing the underlying causal mechanisms that might explain how psychiatric disorders develop. For example, computational models based on structural brain networks can be used to predict specific effects of dynamic lesions (Alstott et al. 2009), or the multifactorial interaction and spread of pathological processes in neuro-degenerative diseases that integrate multiple data modalities (Iturria-Medina et al. 2017). An additional field of application lies in the development of longitudinal GNM, which could be used to study the reconfiguration or adaption of brain networks in response to genetic and environmental factors.

2.4.2 Evaluate brain states with network control theory

A second novel framework for mechanistic inquiry is network control theory (NCT): a powerful approach with which to investigate the controllability of complex biological systems (Campbell et al. 2015). Here, the term controllability refers to the potential for a dynamical system to be driven to particular states, and is frequently accompanied by a study of the control inputs necessary for the system to reach those states. NCT is built upon a dynamic system model that serves to explain how changes in the activity of a single node in a network can, over time, result in spatially diffuse and system-level effects depending on the structure of the white matter network (Kim et al. 2018). The network itself, along with the dynamics of the system, serves to define the energy landscape that the system traverses. That landscape may be characterized by low valleys, along which the system easily walks, or high hills, which the system cannot traverse without additional energy injected from exogenous sources.

STUDY 1: DATA DRIVEN APPROACHES TO NEUROIMAGING ANALYSIS TO ENHANCE PSYCHIATRIC DIAGNOSIS AND THERAPY

Applying control theory to large-scale neuroimaging data (Gu et al. 2017), recent studies have found that brain areas in the default mode system are ideally wired to facilitate transitions into easy-to-reach brain states; formally, such states are those that require little input energy, such as performing easy tasks. In contrast, areas in the cognitive control system are ideally wired to facilitate transitions into hard-to-reach states (Gu et al. 2015). Moreover, energetically optimal target states are reminiscent of activation in the default mode system, suggesting that the baseline of the brain is optimized for the swift enactment of common state transitions (Betzel, Gu, et al. 2016). Notably, these control properties undergo significant changes during development: human brains appear to optimize controllability (to both near and distant states) while sacrificing global synchronizability, which is a structural predictor of the ability of regions to support the same dynamic pattern in the network (Tang et al. 2017). Intuitively, this trade-off supports the emergence of diverse dynamics, which is a requirement for complex human cognition. Applying network control theory to the study of altered cognition, evidence demonstrates a decreased specificity in control processes following mild traumatic brain injury (Gu et al. 2017). Schizophrenia patients display decreased controllability and stability of working memory network dynamics compared to healthy controls, consistent with the notion that alterations in cognitive function can stem from an altered energy landscape of the underlying network architecture (Braun et al. 2019).

In addition to the ability of NCT to study intrinsic control properties of human brain networks, the framework of NCT can be used to ask how external perturbations can be optimally delivered to drive the system into a desired state. This capability is particularly important as neurostimulation treatments, such as deep brain stimulation and transcranial magnetic stimulation (TMS), are increasingly considered as circuit-based treatments for psychiatric disorders (Krystal and State 2014). Imaging research has recently made headway in trying to understand the mechanisms underlying the clinical response to stimulation therapies by comparing the functional connectivity of different regions of interest (e.g., dorsolateral prefrontal cortex, subgenual anterior cingulate cortex) before and after stimulation (Philip, Barredo, Aiken, et al. 2018; Philip, Barredo, van 't Wout-Frank, et al. 2018). Yet, these studies have been limited by their ability to offer a mechanistic account of how focal simulation impacts both local and distant brain areas, and by extension global brain dynamics. Here, NCT has begun to offer exciting pathways to more accurately model

and predict the impact of local perturbations as delivered by neurostimulation and related approaches (Taylor et al. 2015).

By applying NCT to whole-brain structural networks derived from diffusion weighted imaging data, one recent study constructed a model of large-scale human brain network dynamics in the form of regional changes in signal power (Stiso et al. 2018). Incorporating electrocorticography (ECoG) data collected from the same sample during direct electrical simulation, the model predicts the brain state transitions induced by stimulation, and the energy required for different state transitions. A full 93% of the variance in the required energy could be explained by three variables (two from the white matter connectome and one from the ECoG signals): the determinant ratio (quantification of the relation between the strength and heterogeneity of direct connectivity from the controlling node to others), the persistent modal controllability, and the initial brain state. Such studies demonstrate the promise of NCT in developing models that can predict a patient's response to brain stimulation, and can be used to optimize that stimulation to achieve a target brain state (Bassett, Xia, and Satterthwaite 2018).

2.4.3 Future direction of network models

The field now stands at an exciting juncture in which the measures from these network models can be usefully combined with our heightened understanding of genetic risk for psychiatric disorders. In the simplest and most direct of approaches, one can evaluate the correlation between network measures and (i) gene expression or co-expression estimates, (ii) disease-specific polygenetic risk scores, and (iii) estimates of neuromodulatory receptor expression levels from cutting-edge imputation methods utilizing genotype data across the whole genome (Zhang et al. 2019). Such efforts can be naturally extended by incorporating information from multivariate methods, such as partial least squares (PLS) (Grellmann et al. 2015), to further increase our understanding of the network manifestations of genetic risk for psychiatric disorders.

While these modern network methodologies have greatly improved our mechanistic understanding of neuropsychiatric disorders and offer exciting possibilities for translation to new diagnostic or therapeutic tools in psychiatry, their application will remain limited if they are applied to traditional group comparison paradigms that do not respect the dimensional nature of psychiatric disorders. Therefore, in the

following paragraphs we aim to illustrate how the integration of novel data-driven approaches can facilitate or even redefine the nature of brain-behavior relationships.

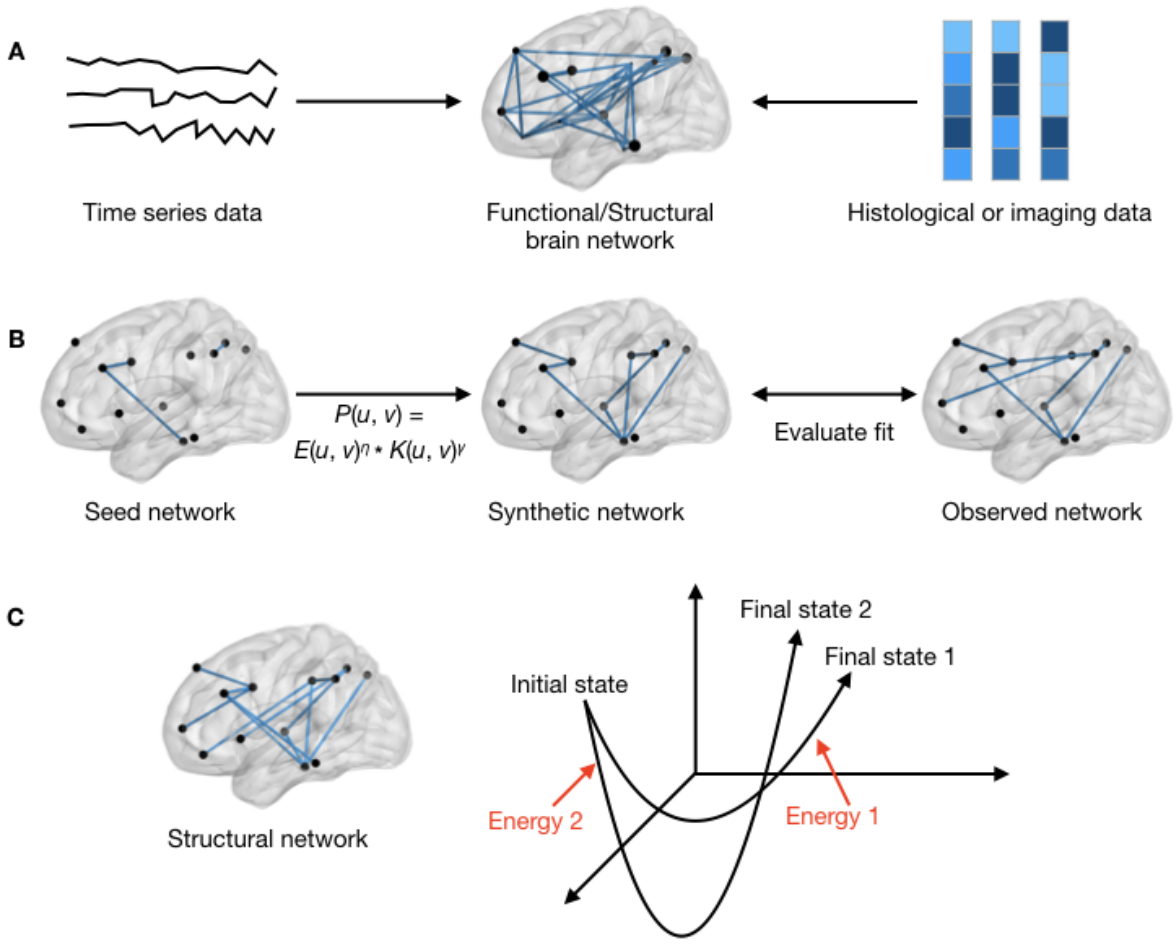

Figure 2.2 Introduction to brain networks and overview of novel network modeling approaches. (A) A structural brain network can be constructed by estimating the location of white matter fibers using diffusion tensor imaging data. A functional brain network can be constructed by computing the correlation between two regional time series using functional magnetic resonance imaging data. (B) Generative network models (GNM) simulate the development of brain networks based on simple, biologically interpretable rules. Starting from a seed network, GNMs add connectivity by estimating the probability (P) of connection formation until the number of connections in the synthetic network is the same as that in the observed network. Then, by evaluating how similar the synthetic network is to the observed network, GNMs can be used to test different wiring rules. (C) Constructed from a structural connectome, network control theory can help investigate how the stimulation of one brain region impacts the activity of other local and distant regions through the underlying pattern of white matter tracts. Brain network maps were made with BrainNet Viewer.

2.5 Crossing diagnostic boundaries and identifying disease subtypes

Current categorical definitions of psychiatry are based on observable signs and symptoms. As the standard for clinical practice, they are catalogued in the ICD (santé et al. 1992) and the DSM (Association 2013). However, the nature of psychiatric nosology impedes progress towards elucidating and treating mental disorders as

biological entities: different mechanisms may lead to the same disorder, and multiple symptoms can occur within one patient (Feczko et al. 2019; Hyman 2010; Insel and Cuthbert 2015). Therefore, the National Institute of Mental Health has launched the Research Domain Criteria (RDoC) project to understand the nature of mental health and illness in terms of biological dimensions that can span from genetics to circuits to behaviors (Insel 2014; Insel et al. 2010). Admittedly, RDoC's focus on neurobiologically anchored constructs and systems does not require that these constructs and systems be transdiagnostic, nor that they explain subtypes. Nevertheless, RDoC does provide a useful perspective that may help us to achieve the ultimate goal of realizing precision medicine for psychiatry -- a diagnostic system based on a deeper understanding of the biological and psychosocial basis of the disorders, that can better explain patient heterogeneity. Notably, population heterogeneity is a key challenge in psychiatric research, and has motivated the search for more homogeneous subtypes defined by biological variables or clinical features. However, subtypes defined purely from biology may miss important architectural motifs characteristic of clinical features, while subtypes defined purely by clinical features may miss important organizational principles of biology.

2.5.1 The application of bifactor models to psychopathology

Many prior studies have used bifactor models to evaluate the structure of psychopathology (Bonifay, Lane, and Reise 2017; Simms et al. 2008). By parsing diverse components of symptoms, such work sheds light on how such disorders are assessed, described, and studied. Bifactor models enforce a hierarchy resulting in a set of orthogonal latent factors that explain residual variances along the hierarchy. Such factors are arguably more interpretable than raw scores. Bifactor models have repeatedly identified a general liability factor for psychopathology underlying the shared risk for many mental disorders; this factor has been coined the 'p factor' in analogy to the general 'g factor' in the study of human intelligence (Gottfredson 1998). By relating these factors to brain network data, mounting evidence suggests that this common liability, as well as a few specific latent factors from these models, are related to brain network organization (Braun 2018). Specifically, the general liability factor tracks alterations in visual-fronto-parietal connectivity and cerebellar connectivity (Romer et al. 2018; Elliott et al. 2018). Interestingly, the anatomical pattern of these effects differs from those tracking cross-diagnostic brain alterations

(Goodkind et al. 2015), a distinction which might be due to the large heterogeneity within diagnostic categories (Wolfers et al. 2018). The distinction further highlights the potential of dimensional approaches to align better with biological entities (Sheffield et al. 2017).

2.5.2 Dimensional methods for linking psychopathology to brain network

Many researchers have argued that such dimensional approaches are likely closer to the underlying biological causes. Yet, progress remains slow because dimensional approaches require large datasets spanning several categorical diagnostic domains as well as marked dimensional variation in psychopathology. With large datasets, one can begin to link psychopathology to brain networks using such promising approaches as PLS (Kebets et al. 2019) and canonical correlation analysis (CCA) (Smith et al. 2015). In contrast to previous work defining subtypes based purely on symptoms (Van Dam et al. 2017; Maglanoc et al. 2019) or neuroimaging features (Clementz et al. 2016), a pioneering study of a neurodevelopmental cohort applied sparse CCA to link a wide range of symptoms to functional brain networks, and found four dimensions of psychopathology across clinical diagnostic boundaries: mood, psychosis, fear, and externalizing behaviors. Each dimension was related to specific patterns of functional connectivity; for example, compared to a null model, the psychosis dimension exhibited stronger connectivity and weaker segregation between the default mode system and the fronto-parietal and salience systems. The results suggest that sparse CCA may help to elucidate the high heterogeneity within each diagnostic category and high comorbidity among psychiatric disorders (Xia et al. 2018). Another study, which focused on patients with depression, first used CCA to identify two linear combinations of functional connectivity features (similar to principal components) that were associated with specific combinations of clinical symptoms. By applying hierarchical clustering to these two components (Drysdale et al. 2017), the study identified four subtypes in the participant population. After identifying subtypes, it is important to determine whether they have some external validity and utility (Williams 2017), such as predicting response to treatment (Etkin 2019). Thus, the study went on to demonstrate that the subtypes could be diagnosed with high specificity and sensitivity in individual patients and could be used to predict the patient’s response to TMS therapy. Collectively, these findings suggest that the identification of subtypes with neuroimaging biomarkers transcends current

diagnostic boundaries and may be useful in selecting therapies for specific patients (Abi-Dargham and Horga 2016; Williams 2016).

2.5.3 Hybrid ways for identifying subtypes

It is important to note that supervised approaches are biased towards the assumptions made and unsupervised approaches are sensitive to wrong or incomplete data, which may result in unusual groupings (Feczko et al. 2019). Hybrid approaches, such as functional random forest (Feczko et al. 2018) and surrogate variable (Leek et al. 2012) analysis, have been developed to overcome these limitations. Hybrid approaches take both continuous dimensions and latent classes into account, and also allow for a direct comparison of model fit (Borsboom et al. 2016; Eaton et al. 2014; Whalen 2017). In a hallmark study of this kind, an exploratory factor analysis was performed on 49 subscales from 10 questionnaires and a hybrid hierarchical clustering was applied to the resultant factor scores (Van Dam et al. 2017). The investigators found two, four, and eight nested groups: the highest clustering level differentiated between functionally adaptive and maladaptive groups, and the middle clustering level separated problem type (internalizing vs. externalizing problems) and behavioral type (sensation seeking vs. extraverted/emotionally stable). Such hybrid approaches, which can delineate homogenous subgroups spanning disease severity, can yield clinically meaningful groups showing important neurobiological differences (Georgiades et al. 2013). By identifying subtypes tied to outcomes, hybrid approaches may ultimately help to refine psychiatric nosology (Feczko et al. 2019).

2.5.4 Necessity of ambulatory assessment to evaluate dynamic symptoms

While these novel tools have shown great promise in detecting novel dimensional brain-behavior relationships, they still rely on single time point questionnaires and scores that are acquired in clinical and laboratory settings, and therefore might not accurately capture intra-subject dynamics in behavior, emotions, and mood (Cornblath, Lydon-Staley, and Bassett 2019). Ambulatory assessment (AA) is an important research tool that can minimize retrospective biases while collecting ecologically valid data including behavior, biological and physiological data, and self-reports through so-called ecological momentary assessment (EMA), usually assessed via electronic diaries on smartphones (Wilhelm, Perrez, and Pawlik 2012),

capturing life as it is lived (Bolger, Davis, and Rafaeli 2003). Furthermore, AA can also provide indices for emotional dynamics, for example the standard deviation of time series and emotional inertia (Ram and Gerstorf 2009; Waugh et al. 2017). AA has been widely used in clinical psychology (Trull and Ebner-Priemer 2013; Trull and Ebner-Priemer 2020) to investigate the mechanisms and dynamics of psychopathological symptoms (Ebner-Priemer et al. 2007), predict psychopathological symptoms (Wichers et al. 2010), monitor treatment effects (Geschwind et al. 2011), predict treatment success (Peeters et al. 2010), prevent relapse (Spaniel et al. 2008) and administer interventions (Clough and Casey 2011; Nahum-Shani et al. 2018). Combining neuroimaging with AA could therefore provide a promising avenue to evaluate the ecological validity of neuroimaging findings (Wilhelm and Grossman 2010; Forbes et al. 2009).

In addition to improving measurement and capturing dynamics in symptoms, combining AA with neuroimaging may provide insights into the complex interactions between psychiatric symptoms in real life and their underlying neurobiological correlates. To more fully understand interactions between symptoms, recent work building on the network perspective of psychopathology (Borsboom 2017; Borsboom et al. 2018) has demonstrated that it is feasible to model the dynamical and reciprocal interactions of symptoms within psychiatric patients (Pe et al. 2015; Bringmann et al. 2015). The use of these models for clinical practice is currently being examined (Groen et al. 2019; Wichers et al. 2017). Investigators in this area note the difficulties in identifying common causes for disorders and present an alternative to common cause perspectives of psychiatric disorders by highlighting the intuitive notion that symptoms of disorders causally interact, an interaction which can in principle be measured with EMA/AA (Borsboom 2017; Lydon-Staley, Barnett, et al. 2018). From this perspective, once a symptom is triggered by an event or set of events, symptom activation spreads through the symptom network via causal symptom associations. Strongly connected symptom networks contain feedback loops that lead to the reverberation of symptom activity (Yang et al. 2018; Borsboom, Cramer, and Kalis 2018). Symptom activity then becomes self-sustaining, and this persistent activation of symptoms in the absence of triggering events reflects a state of psychiatric disorder. First steps towards using individual symptom networks to better guide psychotherapeutic intervention have been made, demonstrating that the interaction and dynamics of individual symptoms provide additional information that

the group means do not offer (Ebner-Priemer et al. 2015; Dejonckheere et al. 2019). This effort seems particularly important, as the perspective focuses on the interaction between symptoms and likely involves additional mechanisms/aspects of brain (dys)function. Therefore, it could prove fruitful in the future to combine neuroimaging and real-life assessments of psychiatric symptoms using EMA/AA to uncover novel neural signatures of symptom interactions that, by facilitating the sustained reverberation of symptom activity over time, are responsible for maintaining states of psychiatric disorders (Lydon-Staley, Kuehner, et al. 2018).

2.5.5 Summary

Altogether, dimensional approaches that can relate dynamic behavioral measures to brain networks may help identify psychiatric subtypes, crossing the current diagnostic boundaries. These more homogeneous subgroups could then be used to investigate the underlying neurobiological mechanisms for specific symptoms and also help guide the selection of treatment options.

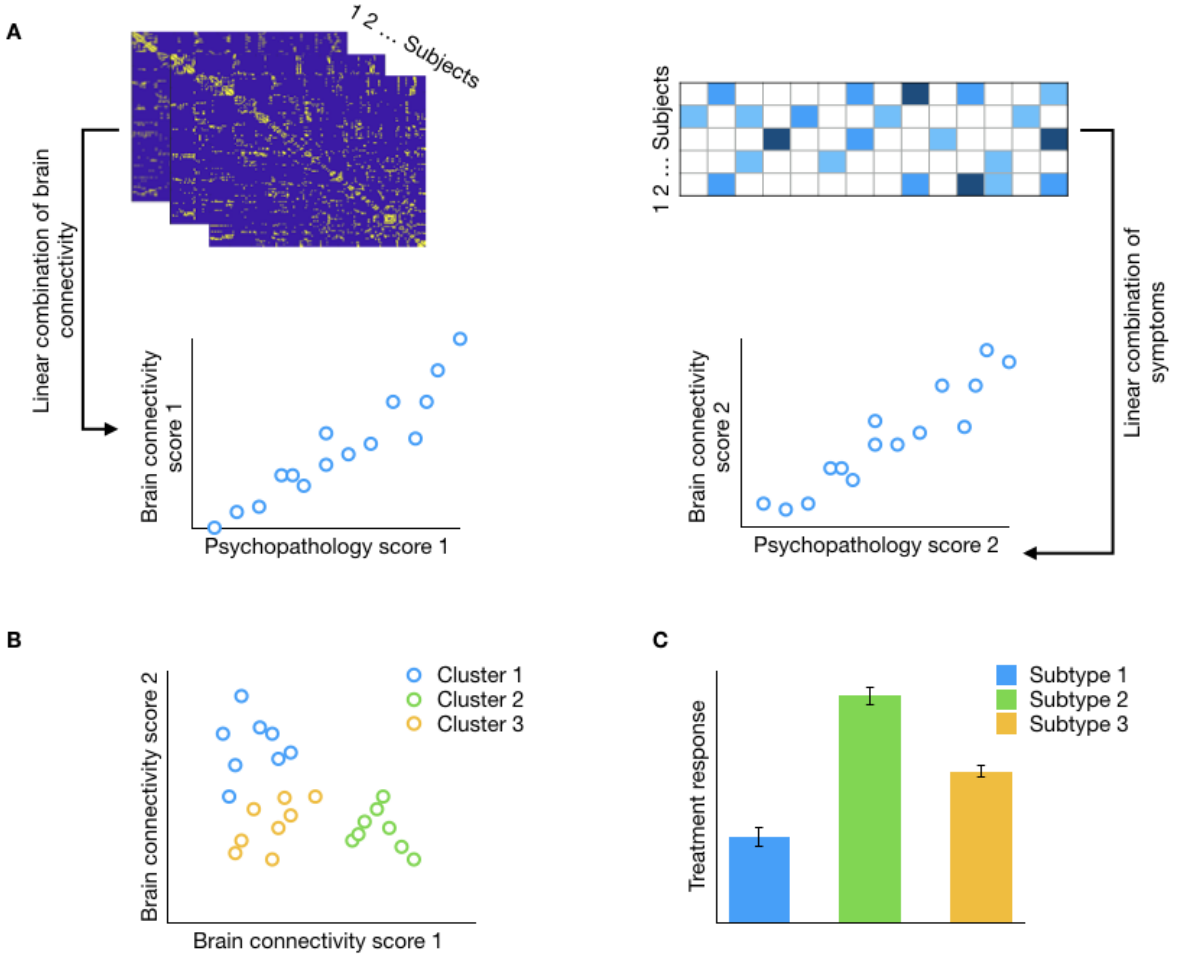

Figure 2.3 Schematic of sparse canonical correlation analysis (sCCA) and its application to subtype identification. (A) sCCA seeks the linear combinations of brain connectivity and clinical symptoms that

maximize their correlation and identifies components that are linear combinations of connectivity features correlated with linear combinations of clinical symptoms. (B) The scatterplot of the components can help identify subgroups of a given population of interest. (C) After identifying different subtypes, it is important to test validity and evaluate utility, such as by predicting patient response to treatment.

2.6 Prediction of treatment response

Although a number of treatment alternatives are available for all psychiatric disorders (Ridding and Rothwell 2007; van Os and Kapur 2009; Sabella 2018), innovation in the development of novel therapeutic options has been slow in the past several decades. The side effects of antipsychotic drugs are still the main reason for discontinuation of drug treatment causing relapse (Fikreyesus, Soboka, and Feyissa 2016). Moreover, other current therapeutic options including psychotherapy or electroconvulsive therapy work well, but much time is lost in finding the appropriate therapy for an individual patient. Currently, there exists no objective (bio-)markers that predict which treatment would be optimal for a particular patient (Abi-Dargham and Horga 2016). A reliable, individualized prediction of the treatment outcome could help clinicians and patients avoid unnecessary costs of ineffective treatment, and weigh the chances of recovery against the risk of possible adverse effects. Previous studies have found that antipsychotics, such as ketamine, dextromethorphan, and paroxetine, can affect brain activation (Abler et al. 2011; Francois et al. 2016), connectivity (Grimm et al. 2015; Zang et al. 2018), and network topology (Braun, Schafer, et al. 2016). Other complementary studies have found that TMS can also alter connectivity (Bilek et al. 2013). Collectively, this work suggests that brain network features are sensitive to pharmacology and neural stimulation, and can be used to predict individual treatment response. In further support of this potential, there have been several large-scale clinical trials, such as the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) (Pizzagalli et al. 2018), the International Study to Predict Optimized Treatment-Depression (iSPOT-D) (Maller et al. 2018), and other studies (Morgieve et al. 2014; Ball, Stein, and Paulus 2014) that have identified biomarkers predicting specific response to a range of interventions by assessing the statistical relationships between treatment improvement and pre-therapy brain structure and function. While these studies have demonstrated the major potential of predictive approaches to develop potential prognostic biomarkers for predicting response to treatment, many were limited in predicting outcomes only at the group level and not

at the individual level, and often lacked validation in an independent sample, thus not demonstrating enough specificity, sensitivity and generalizability to transfer the findings to clinical practice (Ball, Stein, and Paulus 2014).

As the application of network science and machine learning methods to psychiatry grows, an increasing number of studies demonstrate individual-level prediction of treatment response using methods like support vector machines, structural equation modeling, and random forest (Mourao-Miranda et al. 2011; Ball et al. 2018; Koutsouleris et al. 2018; Reggente et al. 2018). Testing on samples ranging from dozens to several hundred, some even from multiple sites, studies have shown the capacity to classify responders from nonresponders with an accuracy of 82% on an individual level (Hahn et al. 2015). However, 82% still means that almost one fifth of patients received the wrong treatment, and thus larger datasets are needed to train the prediction model to improve accuracy. Moreover, in clinical practice the problem is even more complicated because doctors need to be able to select among several therapeutic options. Therefore, future work is needed to evaluate approaches to compare a single patient's predicted response to different treatments (Dunlop et al. 2017). Before translating these findings into actual clinical practice (Siegle 2011), researchers need to assess whether these biomarkers work well in psychiatric patients at different stages of disease or from different genetic, racial, socioeconomic, or ethnic backgrounds, and whether data preprocessing and analysis methods have an effect on the performance of these biomarkers (Passos and Mwangi 2018; Braun et al. 2012).

2.7 Future Perspectives

Promising tools from network science and machine learning to obtain neuroimaging biomarkers may refine the nosology of psychiatric disorders and optimize individualized treatment selection (Bzdok and Meyer-Lindenberg 2018; Passos, Mwangi, and Kapczinski 2016). But before such methods can make an impact on clinical practice, they need to be validated and replicated with large, independent samples (Janssen, Mourao-Miranda, and Schnack 2018). While using these large-scale datasets, it is important to improve the measurement reliability within individual samples (Ball et al. 2017), for example by assessing the minimum data requirements and optimizing analytic strategies (Esteban et al. 2019). Such efforts are essential while searching for clinically useful biomarkers and can reduce the sample size

required for targeted effect size (Zuo, Xu, and Milham 2019). Emerging methods, such as generative network modeling and network control theory, can help gain insights into the mechanisms underlying how brain networks function, or grow and evolve, and can provide tools to manipulate and perturb brain networks in targeted ways (Betzel and Bassett 2017; Bassett, Xia, and Satterthwaite 2018). Longitudinal data from both healthy individuals and clinically high-risk samples offer a precious chance to investigate the formation of normal and altered brain networks, which might help us to better understand the time-varying nature of many psychiatric disorders (Cannon 2015; McInnis and Greden 2016).

2.8 Conclusion

Here we have reviewed a set of key studies that apply machine learning and network science to neuroimaging data to deepen the mechanistic understanding of psychiatry, identify dimensional subtypes with brain-behavior relationships, and predict individual treatment response. We suggest that the emerging methods could not only promote psychiatric research, but also provide biomarkers that improve the precision of diagnosis and personalized treatment. Such inspiring future prospects will only be realized by a concerted and continued effort in the field to bridge the gap between emerging methodological approaches and their clinical application. Because resources are scarce, each emerging methodological approach will need to be stringently evaluated for its potential before being chosen for additional development towards translation.

3 STUDY 2: GENERATIVE NETWORK MODELS OF ALTERED STRUCTURAL BRAIN CONNECTIVITY IN SCHIZOPHRENIA

3.1 Abstract

Alterations in the structural connectome of schizophrenia patients have been widely characterized, but the mechanisms remain largely unknown. Generative network models have recently been introduced as a tool to test the biological underpinnings of altered brain network formation. We evaluated different generative network models in healthy controls (n=152), schizophrenia patients (n=66), and their unaffected first-degree relatives (n=32), and we identified spatial and topological factors contributing to network formation. We further investigated how these factors relate to cognition and to polygenic risk for schizophrenia. Our data show that among the four tested classes of generative network models, structural brain networks were optimally accounted for by a two-factor model combining spatial constraints and topological neighborhood structure. The same wiring model explained brain network formation across study groups. However, relatives and schizophrenia patients exhibited significantly lower spatial constraints and lower topological facilitation compared to healthy controls. Further exploratory analyses point to potential associations of the model parameter reflecting spatial constraints with the polygenic risk for schizophrenia and cognitive performance. Our results identify spatial constraints and local topological structure as two interrelated mechanisms contributing to regular brain network formation as well as altered connectomes in schizophrenia and healthy individuals at familial risk for schizophrenia. On an exploratory level, our data further point to the potential relevance of spatial constraints for the genetic risk for schizophrenia and general cognitive functioning, thereby encouraging future studies in following up on these observations to gain further insights into the biological basis and behavioral relevance of model parameters.

3.2 Introduction

Schizophrenia is a highly heritable neurodevelopmental disorder (Sullivan, Daly, and O'Donovan 2012; Lee et al. 2012; Sullivan, Kendler, and Neale 2003) characterized by abnormalities in perception, cognition, affect, behavior, and social functioning (van Os and Kapur 2009). Converging evidence supports the notion that wiring disruptions of brain networks may partially underlie these alteredities (Fornito et al. 2012;

Fitzsimmons, Kubicki, and Shenton 2013; van den Heuvel and Fornito 2014). Previous studies have found marked differences in the brain network architecture in schizophrenia (van den Heuvel, Sporns, Collin, Scheewe, Mandl, Cahn, Goni, et al. 2013; van den Heuvel et al. 2010) and delineated alterations in their structural development (Zalesky et al. 2015). More generally, human brain networks show a complex architecture favoring topologically advantageous properties while minimizing material and metabolic costs, in line with the proposal that the developmental architecture of the human brain connectome results from an economic trade-off between minimizing wiring costs and allowing adaptively valuable topological features (Bullmore and Sporns 2012). Indeed, there is evidence for alterations in both connection distance (Alexander-Bloch et al. 2013; Bassett et al. 2008) and network topology including reduced local clustering and modularity (Liu et al. 2008; Alexander-Bloch et al. 2010) in schizophrenia, consistent with a biased trade-off between wiring cost and topology (Bullmore and Sporns 2012). However, the principles by which brain networks form and facilitate disturbances in schizophrenia are poorly understood.

Current network neuroscience approaches predominantly focus on descriptive individual or population-level differences, offering little insight into the mechanisms that give rise to network alterations in brain disorders (Vertes and Bullmore 2015; Braun et al. 2018). The recent adoption of generative network models (GNMs) may help to address some of these limitations. For example, predictive (Beul, Grant, and Hilgetag 2015) and random network models (Kaiser, Hilgetag, and van Ooyen 2009; Samu, Seth, and Nowotny 2014; Song, Kennedy, and Wang 2014) have been used to investigate cortical wiring principles, and applications of generative network models to brain network across species have substantially increased our understanding of preserved and species-specific evolutionarily features (Horvat et al. 2016; Kaiser and Hilgetag 2004). GNMs formalize the stepwise development, growth, or evolution of networks, which can potentially be linked to brain development if the wiring rules mimic neurodevelopmental factors (Kaiser and Hilgetag 2004; Betzel and Bassett 2017). One can then compare synthetic networks generated by the model to empirical brain networks reconstructed from neuroimaging data, thereby explicitly testing different mechanistic explanations that might govern their (disordered) structural formation (Betzel and Bassett 2017; Bassett and Sporns 2017). Two recent examples have tested different wiring rules of healthy brain networks, finding

converging evidence for a two-factor model where one factor accounts for the spatial embedding of brain networks by penalizing spatially distant connections while the other factor enhances the complexity of local topological organization (Betzel, Avena-Koenigsberger, Goni, et al. 2016; Vertes et al. 2012). The model parameters could be potentially linked to biological processes as they account for the metabolic cost of wiring and the strength of a Hebbian-like wiring rule, in part buttressed by the fact that they undergo progressive changes over the lifespan and show alterations in disease states (Betzel, Avena-Koenigsberger, Goni, et al. 2016; Vertes et al. 2012).

In addition to their biological plausibility and developmental sensitivity, an appropriate model of brain network architecture might illuminate genetic aspects underlying network alterations and formation in mental disorders. An important strategy is the examination of unaffected first-degree relatives of patients, who have an increased familial risk for developing the disorder (Erk et al. 2014; Rasetti and Weinberger 2011; Collin et al. 2017). This strategy allows for the identification of intermediate brain phenotypes linked to psychiatric risk independent of potential disease-related confounders (Rasetti et al. 2011). In addition, the genetic contributions to these phenotypes can be studied with modern genetic approaches utilizing the potential of cumulative genetic risk scores.

Here, we combined GNMs with imaging genetics to identify potential developmental mechanisms promoting the altered formation of structural brain networks in schizophrenia. Building on a family of previously described and validated generative models (Betzel, Avena-Koenigsberger, Goni, et al. 2016), we first replicated their optimal-fitting model in a healthy sample, and subsequently applied it to a group of unaffected first-degree relatives and schizophrenia patients. Following the hypothesis of an aberrant balance between wiring cost and topological properties during network formation in schizophrenia, we tested whether these model parameters show the quality of an intermediate phenotype. Moreover, on an exploratory level we examined the model parameters for potential associations with schizophrenia polygenic risk and cognitive function.

3.3 Materials and Methods

3.3.1 Participants

Patients were recruited from the Department of Psychiatry and Psychotherapy at the Central Institute of Mental Health in Mannheim, Germany. Diagnoses were made by

staff psychiatrists. Clinical evaluation included ascertainment of personal and family history, and detailed physical and neurological examination. Patients were excluded if: (i) they were aged <18 or >65 years, or (ii) they had a history of brain trauma or neurological disease. We studied 152 healthy controls (HC) without a first-degree relative with mental illness (mean [SD] age, 30.32 [10.28] years; 94 women), 32 unaffected first-degree relatives (REL) of patients with schizophrenia (33.25 [11.50] years, 19 women), and 66 unrelated patients satisfying DSM-IV-TR criteria for schizophrenia (SZ, 32.77 [9.26] years; 20 women). All participants provided written informed consent for the protocols approved by the local Ethics Committee of the University of Heidelberg.

3.3.2 Neuroimaging data acquisition and processing

Diffusion Weighted Imaging (DWI) data were acquired with a 3-T Siemens Trio scanner using two echo planar imaging (EPI) sequences with different parameters: 1) 32 channel multi-array head-coil, TE/TR = 86/8400 ms, 2 mm slice thickness, field of view (FOV) = 256*256 mm2, 64 slices, and 46 diffusion directions at b-value of 1000 s/mm2; 2) 12 channel coil, TE/TR = 86/14000 ms, 2 mm slice thickness, FOV = 256*256 mm2, 64 slices, and 60 diffusion directions at b-value of 1000 s/mm2. A total of 163 participants were scanned with the first sequence and 87 participants were scanned with the second sequence.

DWI data were preprocessed with standard routines implemented in the software package FSL (https://fsl.fmrib.ox.ac.uk/fsl/) including correction for head motion and eddy currents, extraction of non-brain tissues (Smith 2002), and linear diffusion tensor fitting. After estimating the diffusion tensor, we performed deterministic whole-brain fiber tracking using a modified FACT algorithm (Yeh et al. 2013). When performing deterministic whole-brain fiber tracking, we initiated 1,000,000 streamlines for each subject and removed those with a length of less than 10 mm. To construct the structural connectome, the cerebral cortex was parcellated into 360 areas (Glasser et al. 2016) and the number of streamlines connecting every pair of brain areas was used as an estimate of structural connectivity. Notably, if the number of streamlines connecting two regions was less than 5, we set the connection weight to zero to minimize bias due to false positives (Zhang et al. 2015; Zhu et al. 2019) and to enforce an averaged network density of ~2.5% across subjects. As inter-hemispheric connections cannot be adequately modeled, we focused on the right

hemisphere (180 areas) following the precedent set in related prior work (Betzel, Avena-Koenigsberger, Goni, et al. 2016; Vertes et al. 2012). To compare the structural connectome between groups and retain connections not only according to weight but also according to length, every connection was required to be present in at least 70% of subjects (Roberts et al. 2017).

3.3.3 Construction of generative network models

For each subject, we constructed synthetic networks using generative models (Figure 1). After defining a seed network consisting of all edges that were consistently identified across all subjects, edges between nodes were added one at a time until the number of edges in the synthetic network conformed to that of the observed network. The relative probability of edge formation was evaluated at each step according to the equation:

$$(1) \qquad P(u,v) = E(u,v)^{\eta} * K(u,v)^{\gamma}.$$

Here $E(u,v)$ denotes the fiber distance between brain areas u and v, which was obtained using a streamline-based quantification of distance (Roberts et al. 2017). Note that η controls the edge length; when η is negative, short-distance edges are favored, whereas when η is positive, long-distance edges are favored. The term $K(u,v)$ represents the topological relationship between brain areas u and v, and γ represents the relative importance of the topological term. Importantly, $K(u,v)$ can be varied to realize different wiring rules. All topological parameters are defined in Table S2 and were computed using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/Home) as implemented in MATLAB.

In this study, we limited our analysis to four generative models, each representing one of four previously-studied classes: the geometric model, the degree-product model, the clustering-product model, and the matching index (MI) model (Betzel, Avena-Koenigsberger, Goni, et al. 2016). In the geometric model, the probability of forming a connection between two brain regions is a function of their fiber distance (represent by the spatial parameter: η), based on the intuition that brain regions are less likely to be connected if they are further apart. In the degree-product, clustering-product, and MI models, the connection probability function includes an additional topological term (represent by the parameter γ) which is the product of degrees

(number of connections of a brain region) between two nodes, the product of clustering coefficients (fraction of connected triangles around a brain region) between two nodes, or the normalized number of nearest neighbors in common between two nodes (homophily), respectively. Here, the intuition would be that two brain regions are more likely to be connected if their connectivity profiles are similar rather than dissimilar.

To evaluate the fitness of synthetic networks and to optimize models, we define an energy function that measures how dissimilar a synthetic network is from the observed network as follows:

$$(2) \qquad E = \max\left(KS_k, KS_c, KS_b, KS_e\right),$$

Here, each term is a Kolmogorov-Smirnov statistic that compares degree (k), clustering coefficient (c), betweenness centrality (b), and edge length (e) distributions of synthetic and observed networks. Since we defined energy as the maximum of the four statistics, smaller energy indicated greater fitness.

We used classical Monte Carlo methods to find the parameters (η, γ) that generated networks with minimal energy, i.e. networks that were most similar to the observed networks. The procedure starts from randomly sampling 2000 points from the defined parameter space. Then, by computing the energy at each point and dividing the whole parameter space into a subset of Voronoi cells, we sample points preferentially within Voronoi cells with low energy. We repeated this procedure five times until it converged to a (locally) optimal solution. Further details regarding this process can be found in Ref. (Betzel, Avena-Koenigsberger, Goni, et al. 2016).

To explore whether our optimal-fitting model could capture other structural network alteredities in schizophrenia, we also calculated the global efficiency, modularity (Q, the degree to which the network may be subdivided into such clearly delineated groups where edges are more likely within groups than between groups, Newman's community detection algorithm with default resolution parameter, gamma=1 (Newman 2004)) and hub degree (defined as the mean degree of the top 10% highest-degree nodes), and then compared them between HC and SZ in both synthetic and observed networks.

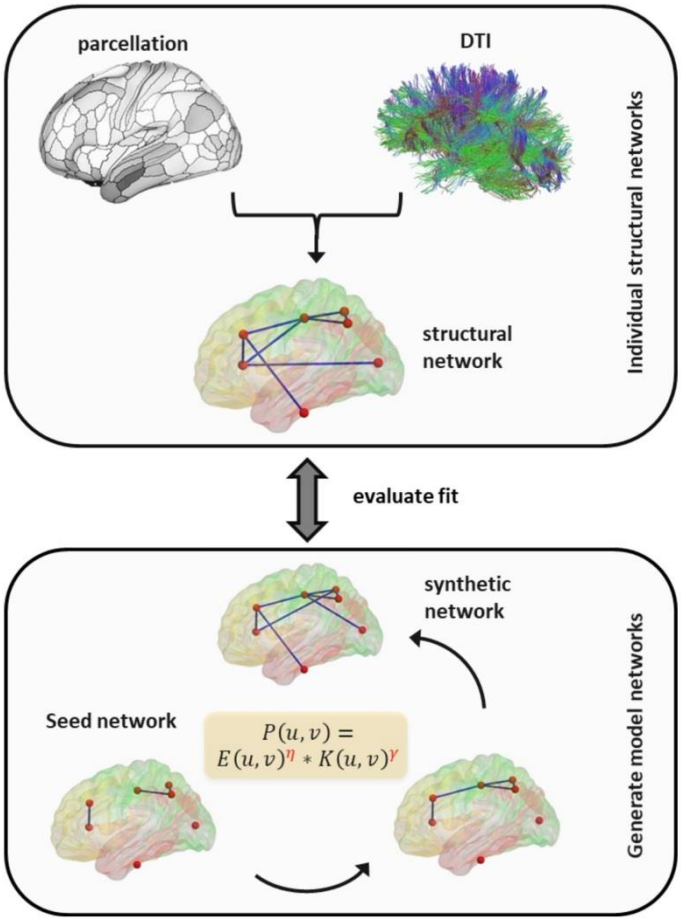

Figure 3.1 Overview of generative network models. Deterministic whole-brain fiber tracking was performed to reconstruct white mater pathways, from which we constructed structural networks linking 180 regions of interest. By retaining edges present in all subjects, a seed network was created and then edges were added stepwise with a certain probability of edge formation, $P(u,v)$, until the number of connections in the synthetic network was the same as that in the observed structural network. The fitness of the synthetic network was evaluated by comparing the degree, clustering coefficient, betweenness centrality, and edge length distributions between the synthetic network and the observed structural network. We used BrainNet viewer to visualize brain networks (Xia, Wang, and He 2013).

3.3.4 Cognitive assessment and factor construction

In a subset of 120 individuals (74 healthy controls, 21 relatives, and 25 patients), we assessed a range of cognitive subdomains frequently impaired in schizophrenia (including attention and psychomotor speed, executive function, memory, impulsivity, and social emotional cognition) using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Mesholam-Gately et al. 2009; Barch and Ceaser 2012). Because the CANTAB measures displayed significant shared variance, we performed a principal component analysis (PCA) to reduce the redundancies and minimize potential for Type I error (Levin et al. 2013). For this purpose, we selected two main outcome measures per test and performed a PCA, which resulted in five

components whose eigenvalues were larger than 1. The first component accounted for 27.1% of the variance, and factor loadings with lower factor values indicated better individual cognitive performance and captured mainly executive function and memory. The detailed description of methods and a full list of included outcome measures and cognitive factors are provided in the supplementary methods and table S1.

3.3.5 Polygenic risk score

We used standard methods to extract genomic DNA from Ethylenediaminetetraacetic acid blood to perform genome-wide SNP (single nucleotide polymorphism) genotyping of all individuals using the Infinium PsychArray (Illumina Inc). Quality control (QC) and imputation was performed with Gimpute (Chen, Lippold, et al. 2018) including the following steps: Removal of SNPs with sex chromosome heterozygosity, a missing rate greater than 0.05, deviation from Hardy-Weinberg equilibrium in controls ($P < 10\text{-}6$) and autosomal heterozygosity deviation of greater than 0.2 as well as removal of samples with a missing rate greater than 0.02. Phasing and imputation were conducted using SHAPEIT and IMPUTE2 (Howie, Donnelly, and Marchini 2009; Howie et al. 2012; Delaneau, Zagury, and Marchini 2013) with the imputation reference panel from the 1000 Genome Project dataset (August 2012, 30,069,288 variants, release “v3.macGT1”). After imputation, we only retained SNPs with an imputation INFO score larger than 0.6, minor allele frequencies larger than 0.01 and successfully imputed in at least 20 individuals. The proportion of alleles shared identity-by-decent estimated using PLINK(Chang et al. 2015) (www.cog-genomics.org/plink/1.9/) was used to identify relatedness for all pairs of samples. A threshold of $\pi\hat{} > 0.2$ was used to identify related pairs of samples and exclude one member of each pair at random.

To control for population stratification, we performed a PCA on the linkage-disequilibrium pruned set of autosomal SNPs using GCTA (Yang et al. 2011). Then we excluded outliers whose principal components were larger than six standard deviations from the group mean and used the first five principal components as covariates in the following association analyses of model parameters.

We computed the polygenic risk score with PRSice v-2, while the expected value of the missing genotypes was imputed based on the sample allele frequency (Euesden, Lewis, and O'Reilly 2015). In this study, genome-wide association (Schizophrenia

Working Group of the Psychiatric Genomics 2014) nominal $P < 0.05$, was used to achieve a balance between the number of false-positive and true-positive risk alleles (Wray et al. 2014; Agerbo et al. 2015). The association analyses were repeated for thresholds of nominal $P < 0.01$ and of nominal $P < 0.1$.

3.3.6 Olanzapine equivalents

To investigate the effect of antipsychotics on the results, we converted the daily doses of patients' antipsychotic medication to olanzapine equivalents (OLZe) according to the classical mean dose method presented by Leucht and colleagues (Leucht et al. 2015). This method is based on the analyses of 13 oral second-generation antipsychotics, haloperidol, and chlorpromazine compared with olanzapine 1 mg/d. To obtain OLZe, we weighted the mean dose of each antipsychotic by the study's sample size and finally divided by the weighted mean olanzapine dose.

3.3.7 Statistical analysis

For each participant, we tuned the parameters (η, γ) to the range where the generative model always produced synthetic networks with near-lowest energy, i.e. networks that were most similar to the observed structural brain networks, by using the Monte Carlo methods mentioned above. Within this range, we analyzed the top 1% minimal-energy synthetic networks (100 networks per participant, 10,000 networks in total). We compared individual averaged energy of these top 1% lowest-energy synthetic networks between the four types of generative models and between different groups of participants using a repeated-measures analysis of variance (ANOVA) with the Statistical Package for the Social Sciences 24. We compared the parameters of the optimal-fitting model between groups using a general linear model.
In order to exclude the effect of antipsychotics on our results, we computed individual olanzapine equivalents and then assessed the correlation coefficient between those values and the model parameters.
Furthermore, to investigate the genetic association of the model factors and to circumvent the potential effect of confounding factors not related to the genetic risk for the disorder in patient populations (Chen, Ursini, et al. 2018), we assessed the correlation between the parameters of the optimal-fitting model and polygenic risk scores in healthy controls only while controlling for age, sex, DWI protocol, temporal

signal to noise ratio (tSNR) (Roalf et al. 2016), and the first five principal components of population structure. To evaluate the behavioral relevance of the identified model parameters, we assessed the correlation coefficient between the parameters of the optimal-fitting model and the individual cognitive factor loadings, while controlling for age, sex and tSNR in the three groups separately.

3.4 Results

3.4.1 Sample characterization

The groups were matched for age, education, tSNR, and head motion, but not for sex and acquisition protocol (see detailed demographic and clinical characteristics as well as image quality control parameters in Table 1). To account for the group differences in these latter variables, we included sex and DWI protocol as covariates in all analyses that included multiple groups. The demographic and neuroimaging characteristics for the participants of the different acquisition protocols are provided in Table S3.

Table 1: Demographic, clinical and neuroimaging characteristics

	Healthy controls (n = 152)	First-degree relatives (n = 32)	Schizophrenia patients (n = 66)	F or χ^2 value	P value
Demographic characteristics					
Age (years)	30.32 ± 10.28	33.25 ± 11.50	32.77 ± 9.26	1.977	0.141
Sex (male / female)	58/94	13/19	46/20	18.95	< 0.001
Acquisition protocol (32/12 channel coil)	76/76	21/11	66/0	50.71	< 0.001
Education (years)	15.40 ± 1.60	15.19 ± 2.34	14.86 ± 2.17	1.881	0.155
Clinical characteristics					
PANSS positive	n.a	n.a.	14.61 ± 7.54	-	-
PANSS negative	n.a	n.a	14.51 ± 8.27	-	-
PANSS general	n.a	n.a	31.70 ± 11.42	-	-
PANSS total	n.a	n.a	60.82 ± 23.51	-	-
Duration of illness (years)	n.a.	n.a.	10.44 ± 8.34	-	-
Olanzapine equivalents (n= 52)	n.a.	n.a.	15.04 ± 8.91		

QC parameters					
DTI: mean relative root-mean-square displacement (mm)	0.31 ± 0.10	0.33 ± 0.12	0.35 ± 0.18	1.844	0.160
DWI: tSNR	5.85 ± 0.29	5.76 ± 0.25	5.85 ± 0.26	1.491	0.227

PANSS = Positive and Negative Syndrome Scale (Kay, Fiszbein, and Opler 1987). tSNR = temporal signal to noise ratio, QC = quality control

3.4.2 Generative Network models

Comparison between the four network models revealed significant differences in mean energy (repeated measures ANOVA: $F(3,453) = 2964.277$, $p < 0.001$) in HC, with the MI model showing the lowest energy level (see Figure 2). The Akaike information criterion is -746 for the one-factor (spatial) model and -1219 for the two-factor (MI) model. Inline with this result, the Bayesian Information Criterion of the one-factor model is -742, and of the two-factor model is -1212. Both results imply that the quality of the two-factor model is superior to that of the one-factor model (see Supplementary Results for further details). Importantly, when including all diagnostic groups in the analysis, the group-by-model-type interaction was not significant (repeated measures ANOVA with group as a between-subjects factor, and with sex and DWI protocol as covariates: $F(6,735) = 0.870$, $p = 0.516$), arguing for the same pattern across all groups. We did not find a sex-by-model interaction ($F(3,735) = 1.155$, $p = 0.326$). We however found a significant protocol-by-model interaction effect ($F(3,735) = 26.37$, $p < 0.001$), which comes from the spatial and clustering-product models (see Supplementary Figure 6 for more details). Hence, in our subsequent investigation we focused on the analysis of the MI model, as among the four tested classes of generative network models it provided the optimal fit to the individual, experimentally-derived structural networks across diagnostic groups. We show the energy landscape and the parameter distribution of the MI model for different groups in the supplement (Figure S2). Compared to MI models for the randomized networks, MI models for observed network showed lower energy and significantly different parameters distributions (Figure S4), implying that the MI model contains meaningful information that is worth investigating further. To show how similar the synthetic networks and observed networks were at the edge level, we calculated the percent in edge overlap and the percent of correctly-modelled subjects for each edge among different groups (Figure S3).

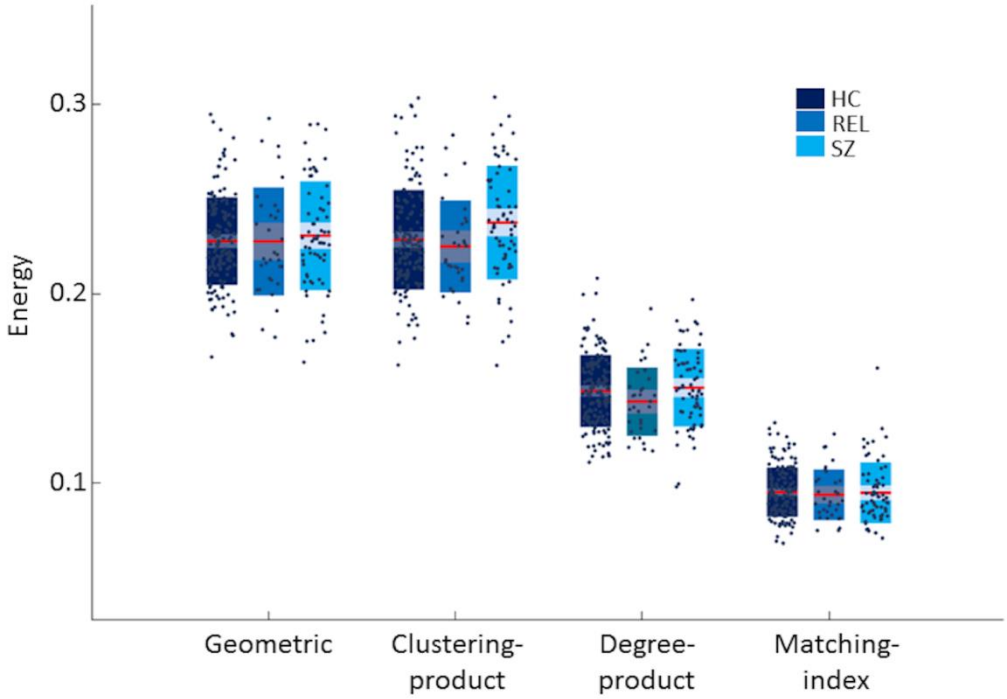

Figure 3.2. Four classes of GNMs: Individual energy was significantly different among the four types of models ($p < 0.001$) without a significant model by group interaction ($p = 0.516$). The matching index model showed the lowest energy.

When comparing global efficiency, modularity, and hub degree between groups, we detected significant between-group differences in global efficiency (ANOVA, with same covariates; $F(2,245) = 5.289$, $p = 0.006$) and in hub degree (ANOVA; $F(2,245) = 3.875$, $p = 0.022$) in the observed networks. In the synthetic networks, we also detected a marginal between-group difference in hub degree (ANOVA; $F(2,245) = 2.751$, $p = 0.066$), and a significant difference in global efficiency (ANOVA; $F(2,245) = 3.967$, $p = 0.02$). No group differences were found in modularity for either the observed data (ANOVA; $F(2,245) = 0.088$, $p = 0.916$) or the synthetic network (ANOVA; $F(2,245) = 0.039$, $p = 0.962$, see Figure 3A). Our definition for hub degree ensures that every network has the same number of hubs. Importantly, our results are robust to variation in the threshold that defines hubs. Specifically, we find that when using a threshold of 8%, the hub degrees of healthy controls are higher than the hub degrees of patients and relatives for both the observed networks ($F(2,245) = 3.462$, $p = 0.033$) and for the synthetic networks ($F(2,245) = 2.408$, $p = 0.092$).

Similarly, when using a threshold of 12%, the hub degrees of healthy controls are higher than the hub degrees of patients and relatives for both the observed networks ($F(2,245) = 4.138$, $p = 0.017$) and the synthetic networks ($F(2,245) = 2.578$, $p = 0.078$). The findings are consistent with what we see at the threshold of 10%. Please see Figure S5 for scatterplots of observed networks (data) and synthetic networks (model) in hub degree, global efficiency and modularity for each group.

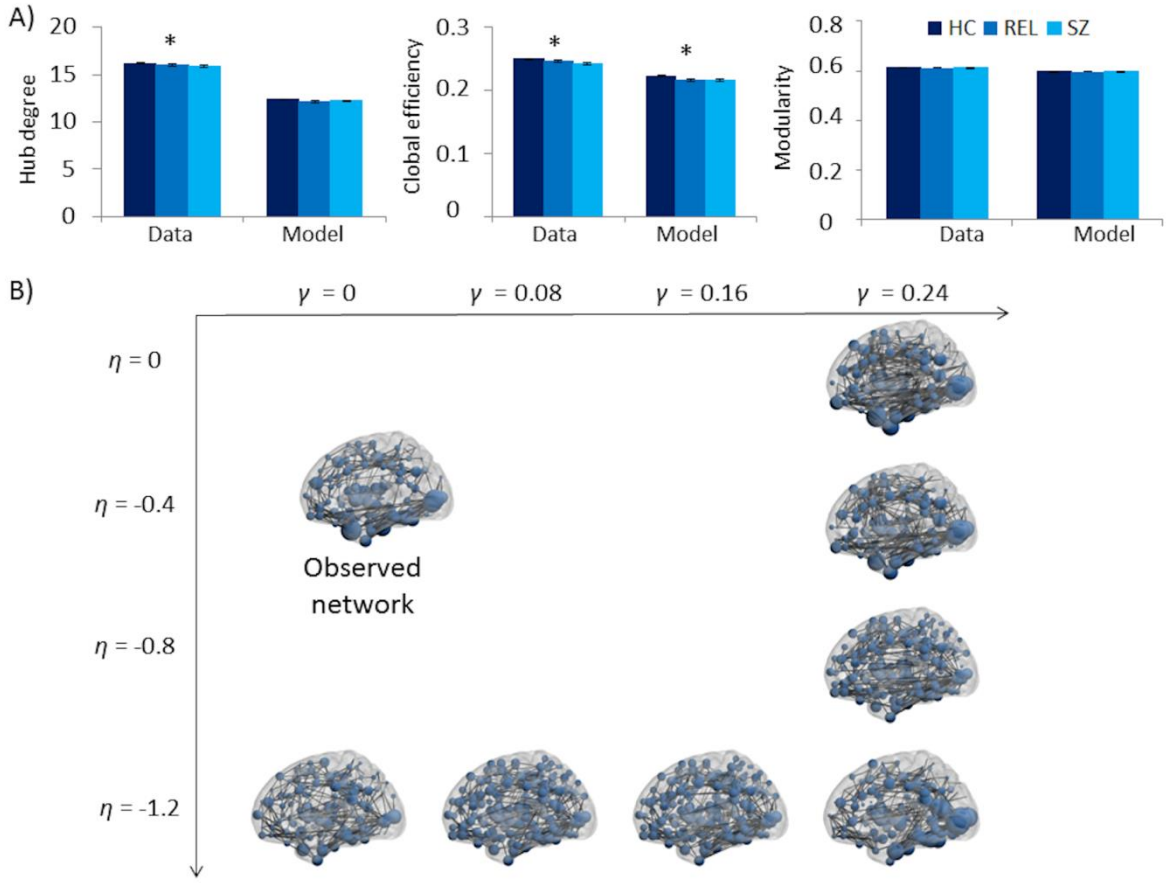

Figure 3.3 Topological characteristics in health and disease. (A) Comparison of several network characteristics in data and model between healthy controls (HC), relatives (REL) and schizophrenia patients (SZ). The matching index model captured the altered hubness and global efficiency in SZ well, while also modeling no modularity difference between groups. The deep blue bars represent the global efficiency, modularity, and hub degree of the synthetic network (model) and observed network (data) in HC, respectively, while the blue bars represent REL and light blue bars represent SZ. Bars indicate mean values. Error bars indicate 95% confidence intervals. Asterisks denote significant difference between diagnostic groups. (B) Visualization of parameter effects on network structure for a single subject. The topological parameter γ mainly influences the degree distribution with larger γ corresponding to the occurrence of more and larger hubs, while the distance parameter η mainly affects the edge distance distribution. Here, $\eta = -1.2$ and $\gamma = 0.24$ correspond to the optimal-fitting model.

In Figure 3B, we illustrate the synthetic network structure of a single subject at different parameter values, thereby offering an intuition regarding the roles of each

parameter in the MI model. As expected, the two parameters η and γ are strongly anti-correlated (Pearson correlation: r = -0.613, p < 0.001) in HC, and this relation was conserved across diagnostic groups (relatives: r = -0.535, p = 0.002, patients: r = -0.492, p < 0.001). Investigating the between-group differences of the two parameters, we found a significant between-group effect on the distance parameter η (ANOVA, with sex and DTI protocol as covariates; F(2,245) = 4.777, p = 0.009) and also on the topological parameter γ (ANOVA, same covariates; F(2,245) = 3.054, p = 0.049, see Figure 4). The effect sizes (Partial Eta Squared) of the significant group difference were 0.038 (η) and 0.024 (γ). Post-hoc analyses confirmed significant differences between HC and SZ (η: F(1,214) = 3.956, p = 0.048; γ: F(1,214) = 4.707, p = 0.031) as well as between HC and REL in η (F(1,180) = 8.970, p = 0.003), but not in γ (F(1,180) = 2.609, p= 0.108). We found no significant correlation between individual olanzapine equivalents and model parameters in SZ (η: r = -0.121, p = 0.393; γ: r = 0.092, p = 0.517). We did not find any significant correlation between model parameters and positive or negative syndrome scale scores (see the Supplementary Results for further details). While the varying size of parcellations in the atlas can potentially impact the number of successive streamlines, this factor did not influence our main results (see Supplementary Results).

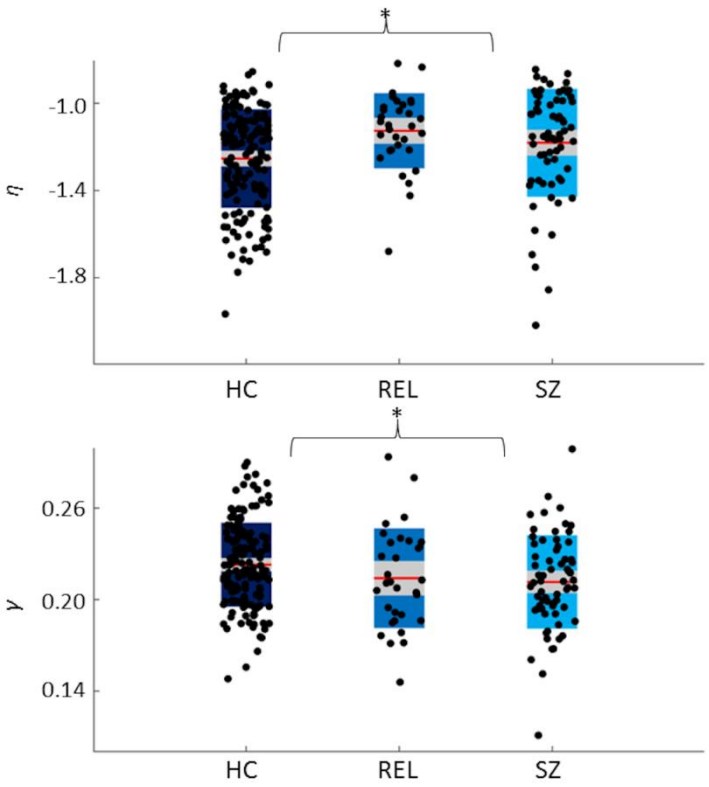

Figure 3.4. Group differences in parameters: in the matching index model, there was a significant between-group effect on the distance parameter η ($p = 0.009$) and on the topological parameter γ $p = 0.049$) correcting for sex and DTI protocol. Red lines indicate mean values and boxes indicate one standard deviation from the mean. Asterisks denote significant difference between all diagnostic groups.

3.4.3 Polygenic risk score

Based on the observed alterations in topological network formation in schizophrenia patients and healthy individuals at familial risk for schizophrenia, we further examined, on an exploratory level, potential associations to polygenic risk for schizophrenia. All healthy controls were of Caucasian ethnicity. A PCA plot to account for potential population stratification is provided in the Supplement (Figure S1). There was a significant group-difference in the genetic risk scores (ANOVA; $F(2,194) = 7.685$, $p = 0.001$) with SZ showing the highest risk scores. To characterize the influence of genetic risk for schizophrenia on both model parameters, we correlated the individual participants' risk scores with η and γ. We found a significant positive association for the distance parameter η ($rpar = 0.173$, $p = 0.045$, where "rpar" refers to a partial correlation that treats age, sex, and principal components as covariates. Figure 5A) and a weaker, trend-wise negative association for the topological parameter γ ($rpar = -0.154$, $p = 0.073$) in HC for all genetic variants with a nominal genome-wide significant association to schizophrenia ($P < 0.05$, uncorrected). The 95% confidence interval of the correlation coefficient for PRS and η estimated by bootstrapping is (0.003, 0.345). Supplemental analyses confirmed the robustness of this finding to the choice of significance threshold used for polygenic risk score computation: for a nominal $P < 0.01$, we obtained $rpar = 0.154$ and $p = 0.074$ for η, and we obtained $rpar = -0.156$ and $p = 0.071$ for γ, while for a nominal $P < 0.1$, we obtained $rpar = 0.196$ and $p = 0.022$ for η, and we obtained $rpar = -0.174$ and $p = 0.043$ for γ.

3.4.4 CANTAB

Based on the observed alterations in topological network formation in schizophrenia patients and healthy individuals at familial risk for schizophrenia, we further examined, on an exploratory level, potential associations to cognitive function. Exploring the correlation between the individual participants' scores of the first component and the distance parameter η (or the topological parameter γ), we found

a significantly negative association for η (r = -0.261, p = 0.029, Figure 5B) and no association for γ (r = 0.108, p = 0.374) in HC. The 95% confidence interval of the correlation coefficient for the first component and η estimated by bootstrapping is (-0.482, -0.014). No association was found in relatives (η: r = -0.137, p = 0.589; γ: r = 0.035, p = 0.890) or in patients (η: r = 0.261, p = 0.240; γ: r = -0.133, p = 0.556). As expected, healthy controls showed lower factor loadings compared to relatives and patients (F(2, 115) = 7.680, p = 0.001). We did not detect any correlation between the other four cognitive components and the network model parameters.

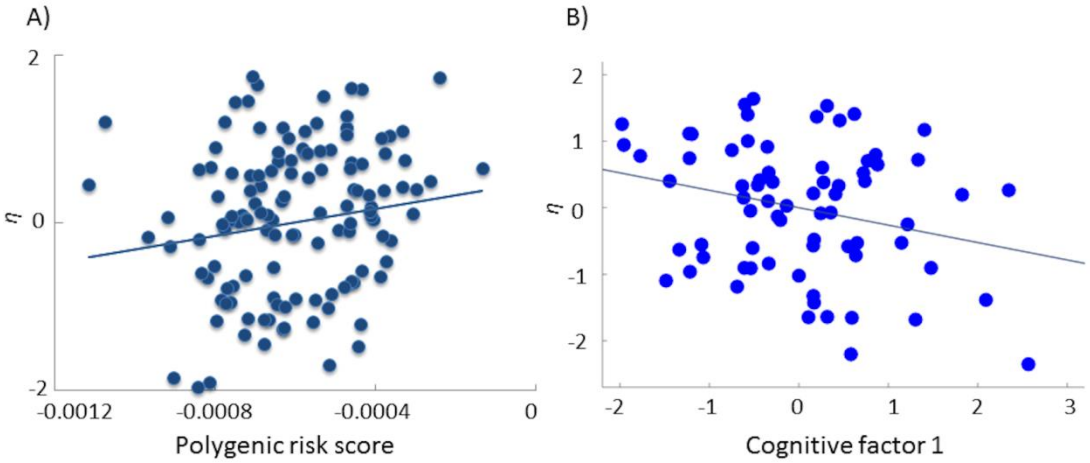

Figure 3.5. Correlation of polygenic risk score and cognition. (A) Individual polygenic risk score for schizophrenia was significantly positively associated with η (rpar = 0.173, p = 0.045). Here η denotes the residuals after regressing out covariates. (B) After performing principal component analysis on 13 main outcome measures of the neuropsychological test battery, we obtained five components whose eigenvalues were larger than 1, and we found a significant negative correlation between the first component and η (r = -0.261, p = 0.029) in healthy controls. As in panel (A), η denotes the residuals after regressing out covariates.

3.4.5 Influence of data quality measures and DTI protocol

We did not detect a significant correlation between model parameters and head motion (η: r = —0.008, p = 0.906; γ: r = -0.001, p = 0.983) or temporal signal to noise ratio (η: r = 0.069, p = 0.28; γ: r = 0.006, p = 0.923).

Limiting our analysis to the subset of individuals acquired with the same DTI protocol (32 channel coil), we still found a significant between-group effect on η (ANOVA, with sex as a covariate: F(2,159) = 4.827, p = 0.009), and a trend-wise significant between-group effect on γ (ANOVA, with sex as a covariate: F(2,159) = 2.798, p = 0.064). We list the network density for each group and each protocol separately (Tables S4 and S5).

3.5 Discussion

In this study, we replicate prior work in GNM (Betzel, Avena-Koenigsberger, Goni, et al. 2016) by demonstrating that the resulting synthetic networks simulate many properties of structural brain networks in both health and disease. We further identify significant differences between healthy controls, first-degree relatives and schizophrenia patients for the two optimally-fitting model parameters in a pattern that aligns with the increasing familial risk for schizophrenia. Specifically, these differences imply lesser geometric constraints and lesser topological constraints in the processes driving network formation in schizophrenia. Moreover, additional exploratory analyses suggest potential associations between network formation parameters, schizophrenia polygenetic risk and latent features of cognitive functioning, respectively. Notably, these observations highlight a potential plausible explanation of how genetic risk contributes to the malformation of brain networks and cognitive dysfunction, although future studies are needed to validate the biological basis and behavioral relevance of model parameters.

Our study extends the current state of the field in several notable ways. Firstly, our data replicate previous accounts of a superior performance of a model integrating geometric constraints and topological complexity of structural brain networks (Betzel, Avena-Koenigsberger, Goni, et al. 2016). This observation aligns well with the current theory that the regular formation of brain networks follows an important evolutionary rule (Chklovskii, Schikorski, and Stevens 2002; Kaiser and Hilgetag 2006; Chklovskii and Koulakov 2004) by minimizing the metabolic cost of building and maintaining long-range axonal connections(Chklovskii 2004) while preserving the adaptive properties of the human connectome, such as the capacity for information processing (Costa Lda, Kaiser, and Hilgetag 2007) through formation of topological features (Bullmore and Sporns 2012).

Secondly, when extending this framework to model mechanisms of connectome formation in schizophrenia patients and first-degree relatives, we detected no significant between-group differences in the fit between the synthetic networks and the observed networks across models. Importantly, this suggests that the same wiring rules can equally well describe both normal and altered brain network formation. Previous studies have found increased connection distance of brain networks (Alexander-Bloch et al. 2013; Bassett et al. 2008) and altered network topology including reduced clustering and modularity (Liu et al. 2008; Alexander-

Bloch et al. 2010; Lynall et al. 2010a) in schizophrenia (see Figure 3A). In line with this prior work, theoretical accounts suggest that the altered organization of brain networks in schizophrenia may result from a biased trade-off between generative factors of homophilic attraction and distance penalization in the process of brain network formation (Bullmore and Sporns 2012). To probe further, we tested whether individual model parameters contributed differently to network formation in all three study groups. We identify smaller values of the distance parameter η in HC than in relatives and patients, while values of the topological parameter γ were higher in HC than in relatives and patients. This said, larger η values in relatives and patients indicate a lower distance penalization, thus increasing the edge length distribution, which is consistent with the increased connection distance of brain networks in schizophrenia (Alexander-Bloch et al. 2013; Bassett et al. 2008). Since the topological parameter mainly influences the degree distribution (see our Figure 3B), smaller γ values in patients and relatives indicate the presence of fewer and smaller hubs) (Vertes et al. 2012). This observation corroborates previous findings suggesting that brain networks in schizophrenia are less clustered and have fewer hubs (Bassett et al. 2008; van den Heuvel et al. 2010). Notably, the presence of decreased spatial constraints and homophilic association in our sample of unaffected first-degree relatives suggests that these network mechanisms may resemble intermediate phenotypes, i.e., relate to the increased familial risk for schizophrenia rather than being epiphenomena of potential confounds such as antipsychotic medication.

Thirdly, we explored the associations between model parameters and schizophrenia polygenic risk in healthy individuals. We identified a weak, but nominally significant positive correlation between polygenic risk and the distance parameter η. In addition, we detected a trend-wise negative association between polygenic risk and the topological parameter γ. Together these findings suggest that increasing genetic risk load for schizophrenia leads to a diminished distance penalization and local homophily of the structural brain connectome. While these effects are small and do not survive correction for multiple comparison, they are in the range of commonly observed effect sizes for polygenetic risk associations (Dudbridge 2013) and provide an interesting observation that could potentially guide replication efforts in future studies. In general, two interconnected factors are thought to contribute to the formation of long distance connections in the brain: a) neurons connect to each other

at an early stage of neurodevelopment when the neural system is small in scale, and b) at later stages, axons follow developmental pathways already established by earlier pioneer neurons (fasciculation) (Kaiser 2017). Studies in animals models suggest that most neurons already form early connections in a spatially localized system (Varier and Kaiser 2011) where navigation through differential expression of guidance molecules is feasible. Importantly, the genes coding for such guidance molecules have been repeatedly implicated in the pathophysiology of schizophrenia (Aoki-Suzuki et al. 2005; Eastwood and Harrison 2008; Shi et al. 2004). It is interesting to speculate that altered spatial expression of guidance molecules imposes less spatial constraints on brain network formation, and these fine-scale mechanisms are reflected in our large-scale model parameters. However, these observations critically require replication in larger datasets and further call for integrating novel, spatially differentiated methods of gene-expression such as the Allen Brain Atlas.

Moreover, we additionally sought to investigate the association of the generative network parameters with a broad and general marker of cognition in an exploratory manner. We found a negative correlation between the distance parameter η and individual scores of the first principal cognitive factor, predominantly capturing converging aspects of executive function and memory, in HC. In particular, we observed that larger values of η (reflecting less geometric constraints, thus a higher probability of long distance connections) were associated with better cognitive performance. Healthy human brain networks usually contain only a small fraction of long-distance shortcuts preferentially linking hub regions (Alexander-Bloch et al. 2013; Bullmore and Bassett 2011). Although these long-distance connections are expensive in terms of material and metabolic cost, they greatly reduce the path-length of information transfer between spatially remote regions, thus increasing the potential for efficient information processing in a binary network (Buzsaki et al. 2004; Bullmore and Sporns 2012). A number of previous studies have shown that more topologically efficient structural and functional networks are associated with enhanced cognitive performance (Giessing et al. 2013; Breckel et al. 2013). Cross-species comparisons of connectome have suggested that modifications of human brain connectivity that are beneficial for higher cognitive function may also render humans vulnerable to brain dysfunction (van den Heuvel et al. 2019). On one hand, long-range connections are essential to maintain the integrity of the expanding brain

network and are therefore under positive selection pressure (Hofman 2014). On the other hand, these long range connections are at an increased vulnerability (Crow 1997) due to their increased metabolic cost and also due to their topological importance. Hence brain disorders such as schizophrenia manifest themselves in alterations of these long-range connections. Indeed, previous studies have shown an increased proportion of long-range connections in schizophrenia resulting in brain networks shifted towards random networks (Lo et al. 2015). The association of the distance parameter η and cognition was not detectable in schizophrenia patients and first-degree relatives, suggesting an optimum in the number of long-range connections potentially exceeded in those populations, meaning that a higher proportion of long-range connections in patients and relatives may not lead to higher network efficiency, but subtle randomization (Lo et al. 2015).

There are a number of methodological considerations that deserve discussion. Firstly, even complete correspondence of two networks does not necessarily imply that both models have been shaped by the same biological mechanism(s). While we have attempted to limit interpretational restraints by external validation with other well-established network features, it is important to note that generative models can be used to offer candidate mechanisms for an observed topology, but cannot conclusively prove that a given candidate mechanism actually occurred in the developing organism (Betzel and Bassett 2017). Secondly, while GNMs can provide insights into the formation of structural brain networks, they do not explicitly model neurodevelopmental processes. Such investigations are warranted, and will require longitudinal datasets as well as the use of an advanced GNM framework explicitly modeling variant developmental processes within subjects. Finally, our sample size used here is relatively small for investigating associations between model parameters and polygenic risk score and cognitive scores, calling for bigger sample sizes and replications in independent samples in future studies.

In conclusion, we show that the distinct wiring rules can simulate normal and altered network formation in humans, resemble intermediate connectomic phenotypes for schizophrenia familial risk and manifest as altered spatial and topological characteristics of brain connectome formation in schizophrenia and first-degree relatives. We further demonstrate preliminary evidence that the GNM model parameters can be linked to schizophrenia polygenic risk and explore their relevance for cognitive functions frequently disturbed in schizophrenia. Together, these data

suggest that brain network formation is under genetic control, is potentially optimized to support cognitive functioning and is disturbed in heritable developmental disorders such as schizophrenia. While these results provide an important first step to harness the potential of GNM by linking it to neurobiologically interpretable factors, longitudinal studies in developmental cohorts are needed to further elucidate successful and aberrant brain connectome formation.

3.6 Supplements

3.6.1 Supplementary methods

Principal component analysis of CANTAB measures

CANTAB measures included Emotion Recognition Task (ERT), Pattern Recognition Memory (PRM), Spatial Span (SSP), Stocking of Cambridge (SOC), Reaction Time (RTI), Attention Switching Task (AST) and Information Sampling Task (IST). We selected two main outcome measures per test (with the exception of SOC, for which only one outcome measure is available) and performed a PCA. The first component was consistently negatively correlated with correct response rates and positively correlated with latency (or reaction times) across the seven test domains, suggesting that lower factor values indicate better individual cognitive performance. The detailed description and a full list of outcome measures across tasks and the resulting cognitive factors are provided in Table S1.

3.6.2 Supplementary results

Correlation of model parameters and PANSS scores

We did not find any significant correlations between model parameters and positive (η: $r = 0.110$, $p = 0.398$, γ: $r = -0.158$, $p = 0.223$), negative (η: $r = -0.039$, $p = 0.766$, γ: $r = 0.069$, $p = 0.595$), general (η: $r = 0.036$, $p = 0.781$, γ: $r = -0.042$, $p = 0.746$) and total (η: $r = 0.039$, $p = 0.763$, γ: $r = -0.047$, $p = 0.719$) PANSS (Positive and Negative Syndrome Scale) scores.

Akaike information criterion analysis

To quantify the bias and variance of one-factor vs two-factor models, we computed the AIC (Akaike information criterion) and Bayesian Information Criterion (BIC), which are estimators of out-of-sample prediction error and thereby the relative quality of a statistical model for a given set of data. Here, AIC = n*log(RSS/n) + 2*K, where n is

the number of subjects, K is the number of factors in the model, and RSS is the sum of squares of the maximal difference between best-fit network and observed network in terms of clustering coefficient, degree, edge length and betweenness centrality. The AIC of the one-factor (spatial) model is -746, and of the two-factor (matching index) model is -1219. Similarly, the BIC can be computed using the following formula: BIC = n*log(RSS/n) + K*log(n), but penalizes additional model factors more severely. In line with the AIC results, the BIC of the one-factor model is -742, and of the two-factor model is -1212. Both results imply that the quality of the two-factor model is superior to that of the one-factor model.

Normalizing the number of streamline by ROI size

To demonstrate the robustness of our results to the effect of correcting for ROI size, we normalized the number of streamlines by ROI size and repeated our analysis using the same methods as described in our main analysis. We found no difference between non-normalized and normalized network models in terms of energy ($F(1,249) = 0.391$, $p = 0.532$) and could replicate the observed group differences in terms of model parameters (η: $F(2, 245) = 4.516$, $p = 0.012$; γ: $F(2, 245) = 3.749$, $p = 0.025$), suggesting that our results are not driven by the variation in ROI size.

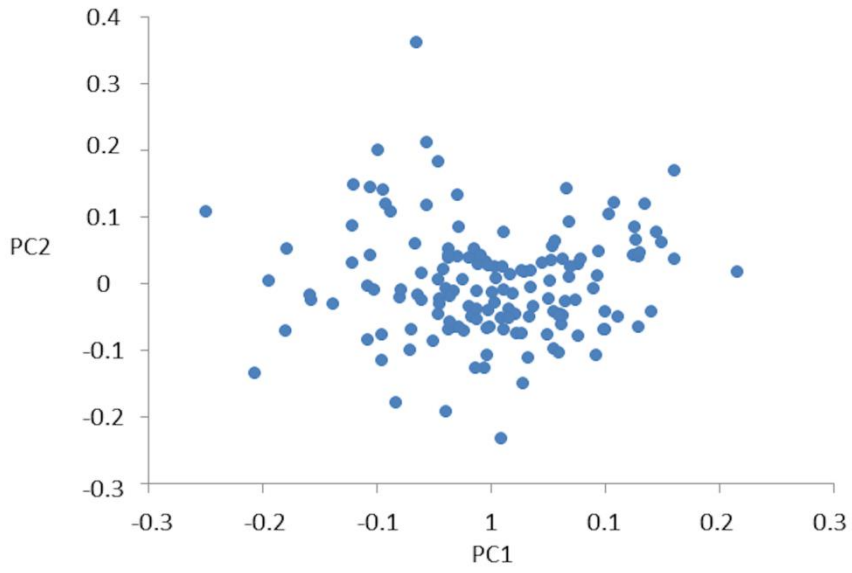

Figure S1. Scatterplot of the first and second principal components of the PCA on genetic data.

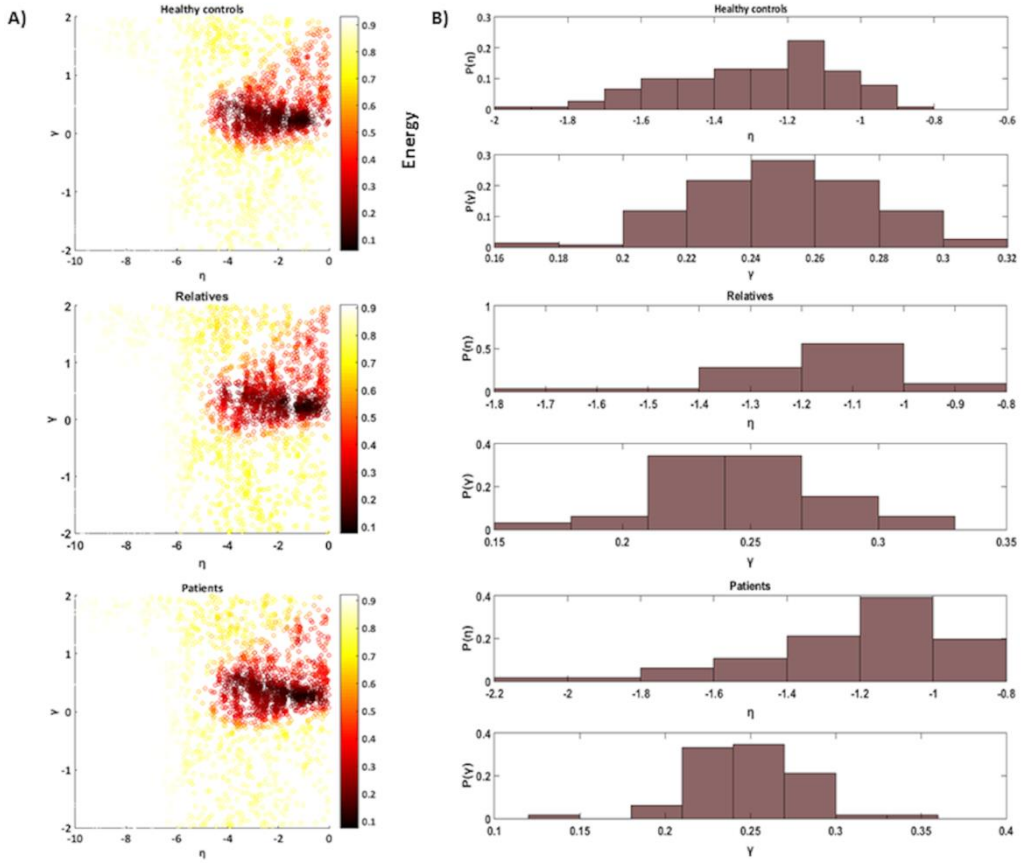

Figure S2. Energy landscape of matching index model (A) and distribution of parameters of optimal-fitting matching index model (B) for different groups of subjects

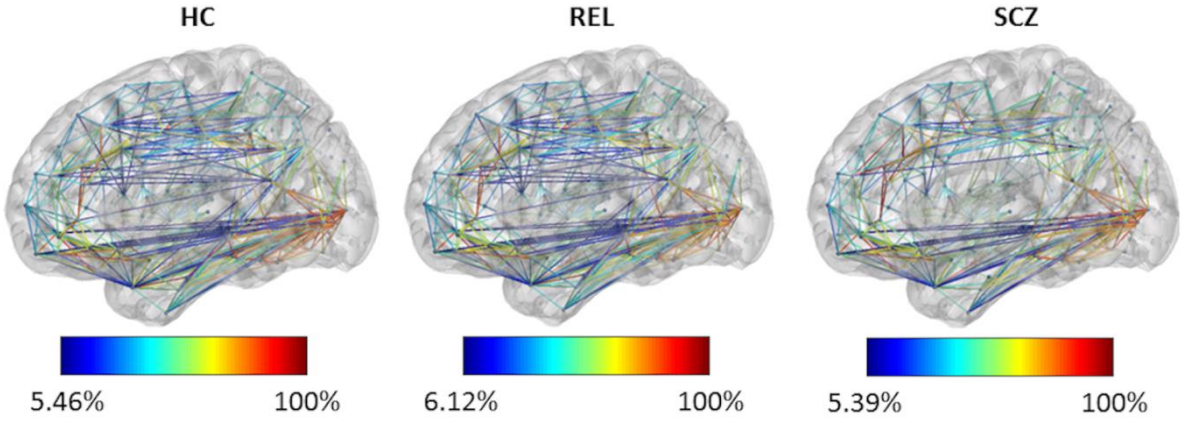

Figure S3. For each edge, the percent of correctly-modelled subjects in healthy controls (HC), relatives (REL), and patients (SCZ). We quantified the edge-level similarity between simulated and empirical graphs, reporting the percent overlap between common edges. On average, we found that edge overlap was 56.3% (57.05% for healthy controls, 55.6 % for relatives and 54.87% for patients). We did not find any significant group difference in edge overlap ($F(2, 245)= 2.255$, $p = 0.107$). This finding suggests that more than half of the edges were simulated correctly, and that our model can simulate both the formation of normal and altered brain networks from the perspective of edge overlap. We also computed the average degree for each region of both empirical networks and the best-fitting networks. Individual averaged degree for empirical networks was negatively

correlated with the relative difference in degree between empirical networks and synthetic networks ($r = -0.5548$, $p < 0.001$). This finding indicates that higher-degree regions were simulated better than regions with only few edges.

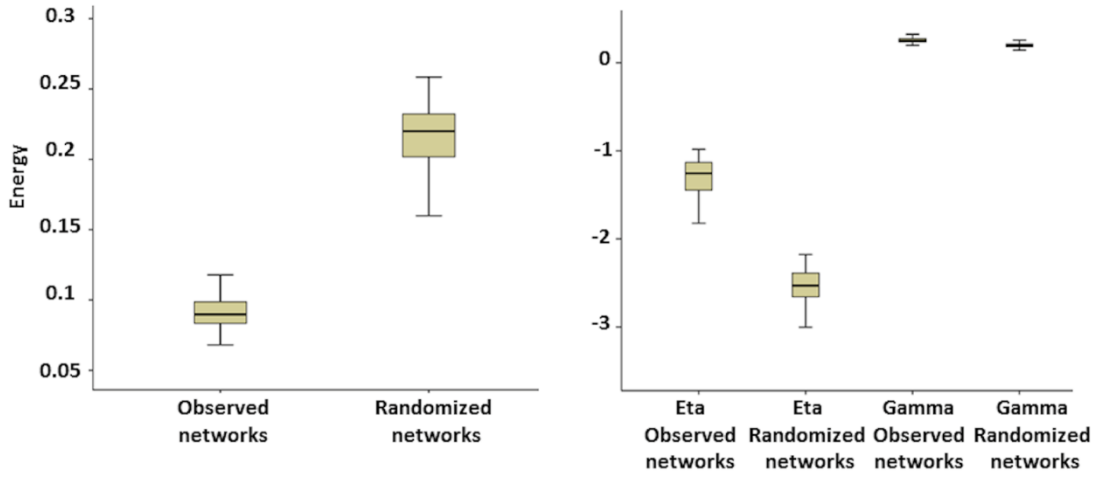

Figure S4. Distributions of model fit and model parameters for observed brain networks and randomized networks. We randomized the connectomes of the 75 healthy controls from 32 channels while preserving both the degree and edge length distribution by using codes from Betzel and Bassett (Betzel and Bassett 2018) and applied the matching index model to these randomized networks. Compared to our original model, we found a significant difference in the model fit ($F(1, 74) = 1988$, $p < 0.001$) with models for randomized networks showing lower fit. We also found a significant difference in both model parameters (η: $F(1, 74) = 1622$, $p < 0.001$; γ: $F(1, 74) = 210$, $p < 0.001$) between the best-fitting models for observed brain networks and for randomized networks.

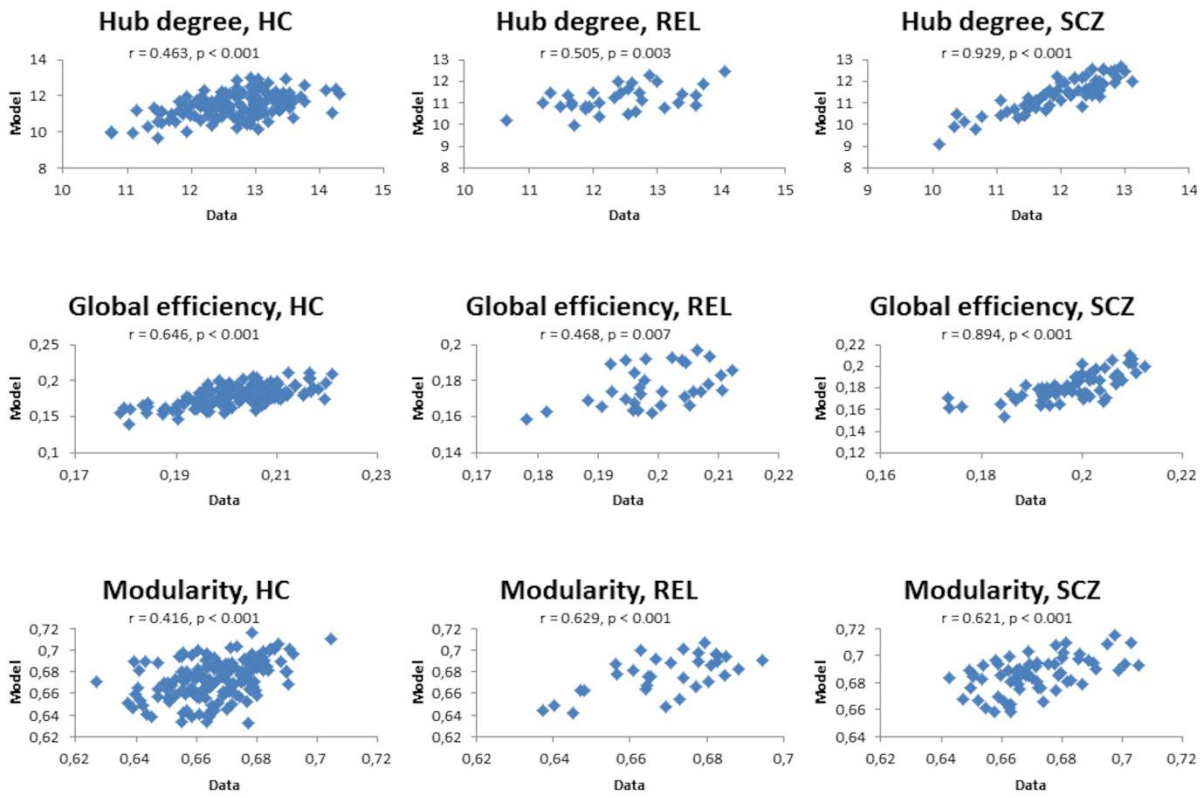

Figure S5. Scatterplots of observed networks (data) and synthetic networks (model) in hub degree, global efficiency and modularity in healthy controls (HC), relatives (REL) and patients (SCZ).

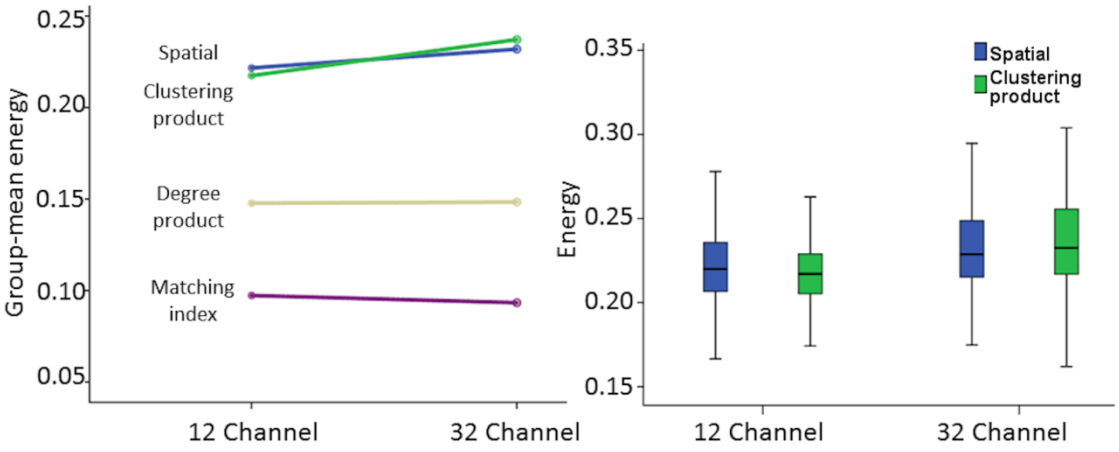

Figure S6. Protocol-by-model interaction between spatial and clustering-product models. There is a significant protocol-by-model interaction effect ($F(3,735) = 26.37$, $p < 0.001$), which comes from an interaction between the spatial and clustering-product models. This driving interaction results from a similar energy distribution of these two models and the marked between-subject variation in energy.

Table S1. Neuropsychological measures and respective factor loadings

Measures	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
SSP span length	-0.579			-0.323	0.350
SSP mean time	0.371	0.329		-0.629	
IST correct win		0.644			-0.406
IST error		-0.507	-0.340		0.458
PRM mean latency	0.670		-0.332		
PRM correct	-0.491		0.529		0.345
SOC problems solved	-0.338	0.620			
RTI movement time	0.379		0.618		0.360
RTI reaction time	0.714		0.409		
AST correct trials	-0.442	0.313		0.582	0.319
AST mean latency	0.729				
ERT mean latency	0.605	0.468			
ERT correct	-0.652				

Note: ERT, Emotion Recognition Task; PRM, Pattern Recognition Memory; SSP, Spatial Span; SOC, Stocking of Cambridge; RTI, Reaction Time; AST, Attention Switching Task; IST, Information Sampling Task.

Table S2. Definitions of complex network measures

Measure	Definition
Basic concepts	N is the set of all nodes in the network, and n is the number of nodes. a_{ij} is the connection status between node i and j.
Degree	Number of links connected to a node i, $k_i = \sum_{j\in N} a_{ij}$.
Hub degree	The mean degree of the hubs, and hubs are top 10% highest-degree nodes. $H = \frac{1}{n_h}\sum_{i\in N_h} k_i$, where Nh is the set of hubs, and $n_h$is the number of hubs.
Global efficiency	Average inverse shortest path length in the network, $E = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, j\neq i} {d_{ij}}^{-1}}{n-1}$, where $d_{ij}$is the shortest path between i and j.
Clustering coefficient	The fraction of triangles around a node i, $C_i = \frac{2t_i}{k_i(k_i-1)}$, and $t_i = \frac{1}{2}\sum_{j,h\in N} a_{ij}a_{ih}a_{jh}$, which is the number of triangles around node i.
Modularity	The degree to which the network may be subdivided into such clearly delineated groups where edges are more likely within groups than between groups (Newman's spectral community detection with default resolution parameter, gamma=1), $Q = \sum_{u\in M}[e_{uu} - (\sum_{v\in M} e_{uv})^2]$, where M is the nonoverlapping modules, and euv is the proportion of all links that connect nodes in module u with nodes in module v.
Matching index	Normalized measure of the overlap in the connection pattern of two nodes i and j, $m_{ij} = \frac{2\sum a_i.*a_j}{k_i+k_j}$, where $a_i$is the connection vector of node i, and .* means dot product.
Betweenness centrality	The fraction of all shortest paths in the network that contain a given node i, $b_i = \frac{1}{(n-1)(n-2)}\sum_{\substack{h,j\in N \\ h\neq j, h\neq i, i\neq j}} \frac{p_{hj}(i)}{p_{hj}}$, where $p_{hj}$is the number of shortest paths between h and j, and $p_{hj}(i)$ is the shortest path between h and j passing through i.

Table S3. Demographic and neuroimaging characteristics of participants for the different acquisition protocols

		12 channel coil (n = 87)	32 channel coil (n = 163)	F or χ^2 value	P value
Age (years)	HC	33.67 ± 10.21a	26.92. ± 9.23	18.16	<0.001
	REL	30.91 ± 10.97	34.48 ± 11.83	0.69	0.413
	SCZ	-	32.77 ± 9.26	-	-
Sex (male/female)	HC	32/44	26/50	1	0.316
	REL	6/5	7/14	1.347	0.246
	SCZ	-	46/20	-	-
Education (years)	HC	15.34 ± 2.02	15.45 ± 1	0.18	0.67
	REL	14.95 ± 2.72	15.31 ± 2.18	0.162	0.691
	SCZ	-	14.86 ± 2.17	-	-
DTI: mean relative root-mean-square displacement (mm)	HC	0.32 ± 0.07	0.31 ± 0.12	0.903	0.343
	REL	0.32 ± 0.05	0.34 ± 0.14	0.185	0.67
	SCZ	-	0.35 ± 0.18	-	-
DTI: temporal signal to noise ratio	HC	5.74 ± 0.33	5.96 ± 0.19	24.65	< 0.001
	REL	5.61 ± 0.26	5.84 ± 0.21	7.04	0.013
	SCZ	-	5.85 ± 0.26	-	-

Values denotes mean ± standard deviation.

To explore the effect of scanning protocol on our results, we compared the two model parameters from the matching model between different protocols. We did not find any significant difference in eta ($F(1,145) = 0.461$, $p = 0.498$) or in gamma ($F(1,145) = 3.838$, $p = 0.052$) for different protocols in healthy controls, which suggests that the sample size affects the group-difference in eta and gamma when limiting our analysis to subjects from the same protocol.

Table S4. Network density for each group

	Healthy controls	Relatives	Patients	F value	P value
Density of seed network	0.21%	0.21%	0.21%	-	-
Density of target network	2.69% ± 0.12%a	2.62% ± 0.12%	2.61% ± 0.21%	8.345	< 0.001
Number of added connections	800 ± 38	776 ± 39	773 ± 68	8.345	< 0.001

Valuea denotes mean ± standard deviation.

We computed the correlation between the number of added connections and energy, detecting no significant association ($r = -0.008$, $p = 0.902$). This result implies that the number of added edges do not influence the model fit.

Table S5. Empirical network density for different acquisition protocols and groups

	12 channel coil	32 channel coil	F value	P value
Healthy controls	2.68% ± 0.1%	2.71% ± 0.13%	2.321	0.13
Relatives	2.69% ± 0.11%	2.58% ± 0.11%	6.856	0.014
Patients	-	2.61% ± 0.21%	-	-
F value		8.218	-	-
P value		< 0.001	-	-

Valuea denotes mean ± standard deviation.

Network density was not correlated with model energy ($r = 0.161$, $p = 0.404$), implying that protocol-effect on network density did not affect model fit. There were significant differences in the network density between different groups for 32 channel coil ($p < 0.001$) after controlling for temporal signal-to-noise and head motion, implying that group-differences in density are not due to noise, but the clinical difference of groups.

4 GENERAL DISCUSSION

4.1 Results summary

This thesis is based on two original first author publications of the doctoral candidate. Firstly, I reviewed studies of network models and machine learning that could potentially promote the transfer from lab experiments to clinical practice. I then applied one of these promising methods: the generative network model, to investigate the altered brain network formation in schizophrenia and the link to genetic risk and cognitive dysfunction.

The first study aimed to describe novel data-driven methods, mainly focusing on network models and machine learning, which may overcome the obstacles in current psychiatric study design and promote the clinical transfer of lab findings. The advent of neuroimaging techniques and the application of connectome and graph theory have provided numerous useful tools for psychiatric research and greatly improved our understanding of the underlying psychopathology of mental disorders by exploring related alterations in brain structure and function. However, these findings currently do not have significant influence on psychiatric diagnosis and therapy yet. The reasons for the lack of translation range from general to neuroimaging-specific. Therefore, the thesis reviewed psychiatry studies that adopted novel network models and machine learning methods, different from conventional case-control comparisons of descriptive measures. Firstly, network models can help gain an in-depth understanding of the psychopathology of the complex and dynamic disorders beyond current diagnostic boundaries. For example, one can establish generative models based on biologically meaningful wiring rules and then manipulate or perturb networks in targeted ways to investigate the neurodevelopmental changes during the disease process. And it is also possible to predict the spreading process of neurodegenerative diseases with computational models. A second network method, network control theory, is built on a dynamic system model and mainly studies how the activity of one node can affect the rest of the system. Derived from diffusion-weighted imaging and working with electrocorticography data, NCT could estimate the energy needed for different states transitions (Stiso et al. 2018). The application of NCT may help explain the function mechanism of neurostimulation therapy, such as transcranial magnetic stimulation, and then improve individual treatment outcome. Secondly, dimensional approaches, such as CCA, could define psychopathological

subgroups by linking psychopathology to brain network with a transdiagnostic dataset. These subgroups show different psychopathological dimensions and distinct patterns of brain connectivity (Xia et al. 2018). Importantly, these subgroups may help select treatment options for individuals (Drysdale et al. 2017). Thirdly, individualized prediction of therapy outcomes using machine learning methods also provides the potentials to select personalized therapy solutions. In summary, these emerging methods could provide neurobiological biomarkers that improve the precision of diagnosis and personalized treatment after they are stringently evaluated for their potentials.

In the second study, based on different wiring rules, we applied generative models to simulate a set of critical topological properties of structural brain networks in healthy controls, patients with schizophrenia, and relatives of patients. We found that the matching index model, a combination of geometric constraints and a homophilic attachment rule, works optimally among the four tested classes of generative models. There were significant differences in the two parameters of the matching index model, which control the level of geometric and nongeometric constraints respectively, between healthy controls and patients as well as the relatives, suggesting that model parameters fulfil indeed some of the basic requirements of a promising intermediate phenotype. Notably, the group differences are consistent with previous findings that there was a higher proportion of long-range connections in schizophrenia (Bassett et al. 2008) and that brain networks in schizophrenia are less clustered and have fewer hubs (van den Heuvel et al. 2010). Therefore, the dysfunctional brain network in schizophrenia could be simulated with the generative models. Furthermore, in the following exploratory study, we found the associations of the model parameter to genetic risk for schizophrenia and cognitive function. These findings may help explain altered brain network formation in schizophrenia, and help elucidating some of the “driving” genetic factors and resulting cognitive disturbances.

4.2 Novel network models and machine learning methods for clinical psychiatry

4.2.1 Novel network models for understanding mechanism of disorders

Understanding the organization principles of the human brain network has long been the main challenge for neuroscience. In the past decades, graph theory has provided many new methods to analyze the complex anatomical and functional brain networks. Brain networks have been found to show specific topological properties:

small-worldness, the existence of hubs, modular structure, among others. Neuropsychiatric disorders are nowadays recognized as dysconnectivity syndromes, and graph theory has been applied to investigate the altered properties of structural and functional networks in disorders. Although brain network research in psychiatry has revolutionized the clinical view on the pathophysiology of psychiatric disorders, diagnostic and therapeutic markers are still confined to use in research environments. Except for the highly heterogeneous character of current psychiatric diagnosis, network metrics widely used are descriptive, oversimplifying the complex dynamics of brain function, thereby providing limited mechanistic insights, not to mention the clinical translations.

Novel network models and machine learning methods have been adopted to promote current psychiatric research further and look for neurobiological biomarkers for psychiatric diagnosis and treatment. One promising network tool, generative network models, produces synthetic networks showing the same properties of empirical networks on the basis of different wiring rules, each representing a posited mechanism. The application of generative models to the *Drosophila* protein interaction network suggested that different mechanisms, such as duplication-mutation-complementation and linear preferential attachment, were suitable for reproducing different sets of subgraphs (Middendorf, Ziv, and Wiggins 2005), validating the potentials to infer growth mechanisms with GNMs. While for large-scale brain networks in humans, generative models with two competing wiring rules could simulate a group of important topological properties of the human functional network (Vertes et al. 2012). On the one hand, the two competing constraints correspond to the economic trade-off of brain organization between minimizing wiring cost and allowing the emergence of valuable topological principles, which accompanies the evolution, growth and adapting to changing cognitive demands of brain networks (Bullmore and Sporns 2012). On the other hand, both model factors show some degree of face validity as biological mechanisms underlying brain network formation. Penalty on connectivity distance may be caused by that axonal growth cones detect the gradients of increasing concentration of guidance molecules towards the source (Song and Poo 2001), and that the concentration of the molecules decays exponentially as the square of the distance between growth cone and source (Goodhill 1997). The homophilic attachment is compatible with Hebb’s law that neuronal groups share common inputs from the same neighboring group are more

likely to be activated simultaneously and therefore to form direct connections between them. After applying the established generative model to the schizophrenia-group functional connectome, Vertes found that the altered network topology could be simulated with detuned model parameters. Combining the same generative model and a lifespan dataset, Betzel found model parameters show progressive changes with age, suggesting a rebalancing of growth factors underlying the brain network formation across the lifespan (Betzel, Avena-Koenigsberger, Goñi, et al. 2016). With well-constructed generative models on the basis of biologically meaningful wiring rules, we can perturb the networks in targeted ways to investigate the neurodevelopmental alternations in disorder process, and also predict the pathological development, thus potentially informing interventions in psychiatric disorders in which wiring patterns have disrupted.

Another novel network model, which is suitable for evaluating the dynamic system of the human brain, is network control theory. NCT mainly studies how the activity or input of a single node impacts the rest of the system over time through the white matter anatomical network. By applying NCT to neuroimaging data, recent studies have investigated the intrinsic control properties and also the neurodevelopmental changes: brain regions in the default mode system are ideally wired for the transitions into easy-to-reach “unchallenging” brain states while regions in the cognitive control system are ideally wired for hard-to-reach “demanding” states (Gu et al. 2017; Gu et al. 2015); human brains optimize controllability while sacrificing global synchronizability during development (Tang et al. 2017). In addition to general principles in healthy controls, NCT may also offer mechanistic explanations for the effect of neurostimulation treatments in psychiatric disorders and further provide models that can predict the impact of local perturbations delivered by neurostimulation. In one recent study, the NCT model predicts the brain states transitions induced by direct electrical stimulation, thus having the potential to optimize the stimulation to achieve a target brain state.

4.2.2 Identifying disorders subtypes across diagnostic boundaries

Current discrete definitions of psychiatry are on the basis of signs and symptoms, which hinders researchers from elucidating psychiatric disorders as biological entities: disorders share altered brain structure and function and cognitive dysfunction. Dimensional approaches, such as CCA and PLS, which link psychopathology to brain networks, can define more homogeneous subgroups that

show both distinct dimensions of psychopathological characteristics and brain features. By applying CCA to a neurodevelopmental cohort, Xia identified four dimensions of psychopathology across diagnostic boundaries: mood, psychosis, fear and externalizing behaviors, each related with specific patterns of functional connections (Xia et al. 2018). After identifying two components that correspond to specific combinations of functional connectivity features and clinical symptoms using CCA, the other study applied hierarchical clustering to the components and defined four subtypes of depression (Drysdale et al. 2017). More importantly, these subtypes could be diagnosed in individual patient and predict the response to TMS therapy, which offers vitally external validity and clinical utility. These novel approaches may help to solve the heterogeneity problem existing in the field of psychiatry: different causal mechanisms may link to the same disorder, and multiple symptoms can happen to one individual. The identified subgroups are beneficial for understanding the physiological and biological correlates of specific cognitive function and mental health, and may also help guide the treatment for typical subtypes of patients.

4.2.3 Prediction of treatment response

There are different treatment options for psychiatric disorders, such as antipsychotics and neural stimulations. However, the side effects of the antipsychotics can lead to impaired patient compliance and drug discontinuation, thereby causing relapse. Therefore, reliable individual-prediction of treatment outcome will help doctors select the suitable treatment that optimizes the chance of recovery and minimizes adverse effects. Previous studies have found that both antipsychotics and stimulation can impact brain network features and that there have been several large-scale clinical trials that identify biomarkers that may predict the response to different interventions (Pizzagalli et al. 2018; Maller et al. 2018). The main analysis approach is linking the treatment performance to pre-therapy brain structure and function. The reason why these studies have not influenced clinical practice is lack of specificity, sensitivity, and generalizability. This is explained, at least in parts, by the abundant focus of analyses on group level (and not individual level) results and the lacking validation of findings in independent datasets. Then machine learning methods start to play a role in predicting individual-level treatment response, and some of these models can achieve an accuracy of 82% on individual level while separating responders from nonresponders (Hahn et al. 2015). Despite this, there are still parts of patients for which information on optimal treatment is

lacking to date. Before individual-prediction of response to treatment can be applied to clinical practice, there are still some issues that need to be considered, for example, the response to different treatment options, patients at different stages of the disease, and coming from different genetic, racial or socioeconomic backgrounds, and the stability of analysis process.

Except for applying novel network models and machine learning methods to psychiatric research, we should also take the measurement reliability within individual samples into account, which will reduce the sample size required for target effect size (Zuo, Xu, and Milham 2019). Only when we narrow the gap between these emerging approaches and clinical application gradually with continued efforts, will the identified neurobiological biomarkers significantly improve the precision of diagnosis and personalized treatment.

4.3 Application of generative network models in schizophrenia

Schizophrenia is a complex neurodevelopmental and highly heritable disorder that manifests altered behavior, cognition, and social functioning, which may result from altered brain connections (van Os and Kapur 2009). Neuroimaging studies have found significant differences in the brain network architecture ranging from specific connections to topological measures in schizophrenia (van den Heuvel et al. 2010; Fornito et al. 2012). However, these studies focused on descriptive measures, which provided limited information for the altered formation of brain networks. Therefore, based on our review above that introduces novel network models and machine learning methods, we chose to apply the generative network model to investigate the potential mechanisms underlying the dysfunctional formation of structural brain networks in schizophrenia.

We firstly constructed the structural brain networks in healthy controls, unaffected relatives of patients with schizophrenia and schizophrenia patients, and then simulated individual structural network with four classes of generative models representing different combinations of wiring rules. After that, we evaluated the fitness of different classes of models by comparing a set of topological metrics between observed and synthetic networks, thus selecting an optimal-fitting model. Then we compared the parameters of the optimal-fitting model between different diagnostic groups. At last, we also explored the association of network formation parameters, the polygenic risk for schizophrenia, and latent features of cognitive function.

We did not find any significant difference in the model fitness between groups, implying generative models could equally simulate both the normal and altered formation of structural brain networks. Among four tested classes of generative models, the optimal-fitting model consists of two competing factors: one favors short-range connections; the other supports connections between nodes sharing similar connection patterns. This is consistent with the current theory for the formation of brain networks: the economic trade-off of brain network organization between minimizing wiring cost and favoring adaptively valuable topological properties (Bullmore and Sporns 2012). Through comparing the parameters of the optimal-fitting model, we found decreased distance penalty and lower topological facilitation in relatives and patients. Decreased distance penalty is consistent with a higher proportion of long-range connections in schizophrenia (Bassett et al. 2008), while lower topological facilitation corresponds to fewer hubs in schizophrenia (van den Heuvel et al. 2010), implying a biased trade-off between distance penalty and hemophilic attraction in the process of brain network formation. The difference in the model parameter between healthy controls and relatives suggests parameters of network formation as a potential neuroimaging intermediate phenotype signaling familial genetic risk. Apart from the influence of disease risk on model parameters, there was also a nominally significant and positive association of individual polygenic risk with the distance penalty parameter in healthy controls. The association may be related to genes coding guidance molecules in the formation process of long-distance connections, since these genes are also implicated in the pathophysiology of schizophrenia (Eastwood and Harrison 2008; Aoki-Suzuki et al. 2005). So I speculate that different gene expression of guidance molecule leads to less spatial constraints on brain network formation in schizophrenia, which need to be evaluated in larger datasets. In my second publication, my coworkers and myself reported a significantly negative correlation between distance parameter and cognitive performance, namely that a higher proportion of long-range connections was related to a better cognitive function. Long-distance connections could greatly decrease the path length of information transfer between remote brain regions, thus improving potentially the efficiency of information processes in brain networks (Buzsáki et al. 2004). And the higher efficiency of brain networks is correlated with increased cognitive function (Giessing et al. 2013). Therefore, a higher proportion of long-range connections is related to both higher genetic risk for schizophrenia and higher

cognitive performance. While initially apparently counterintuitive, these observations may correspond to findings from cross-species comparisons of the brain connectome, which suggested that modifications of human brain connections, on the one hand, are beneficial for higher cognitive function, but on the other hand, may make human brains vulnerable to dysfunction (van den Heuvel et al. 2019).

4.4 Limitations and Future directions

The results reported in this dissertation bear several limitations worthwhile discussing. Firstly, even though the matching index model successfully simulated a set of importantly topological properties optimally among four tested classes of generative models, this does not implicate that the formation of observed and simulated synthetic networks is underpinned by the same biological mechanism. So my findings can only offer candidate mechanisms for the tested topology, but cannot conclusively prove a given candidate mechanism. Secondly, while generative models can provide information on the formation of the brain network, they do not explicitly simulate the neurodevelopmental processes.

Therefore, in the future, to identify the biological mechanisms underlying the formation of the brain network in more detail, the field should add biologically-grounded factors into the generative models (Betzel and Bassett 2017). Once establishing those more biologically valid generative models, researchers could perturb, or manipulate networks (e.g., by brain stimulation methods or in drug challenges) to investigate the perturbation process of the connectome in healthy individuals and patients. What is more, building generative models for a longitudinal dataset could simulate the dynamic neurodevelopmental process and further provide insights into the dynamic process of disease.

5 SUMMARY

Schizophrenia is a serious and chronic mental disorder, which brings not only suffering to patients, but also much burden to families and society. Current diagnosis is mainly based on criterion-based systems, including ICD and DSM, which describe various symptoms of schizophrenia, and antipsychotic drugs are only relatively effective for positive symptoms, but not for negative symptoms and cognitive dysfunction. Previous neuroimaging studies have not provided stable biomarkers for clinical practice. Part of the reason lies in the focus of analysis on group-level, static, and descriptive research approaches.

To improve this situation, I firstly reviewed novel network models and machine learning methods that have the potentials to dig deeply into the mechanisms of disease, define psychopathological subgroups across current diagnostic boundaries, and predict individual response to treatment. Secondly, I chose and applied one promising network tool, generative model, to investigate the altered brain network in schizophrenia. Among the four classes of models, one two-factor model combining spatial constraints and topological facilitation could equally simulate the normal and altered formation of brain networks. By comparing the model parameters, relatives and schizophrenia showed lower spatial constraints and topological facilitation, which is consistent with the topological perturbation in disease. And spatial constraints in healthy controls may be linked to polygenic risk for schizophrenia and cognitive function. In sum, this thesis provides promising analysis approaches and application examples that may help elucidate the complex and dynamic neurodevelopmental process of mental disorders. The reported insights have been published in two peer-reviewed first-author publications by the doctoral candidate.

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7 PUBLICATIONS

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Braun U., Harneit A., … Zhang X., ... Tost H.. Brain state stability during working memory is explained by network control theory, modulated by dopamine D1/D2 receptor function, and diminished in schizophrenia. Under review

8 CURRICULUM VITAE

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