

Aarhus University
School of Communication and Culture

Common cause or direct network interactions? Investigating the covariance structure of genetic, clinical, and cognitive observables in schizophrenia

Author

Line Elgaard Kruse Danielsen
B.Sc. Cognitive Science
Student ID: 201608877

Supervisor

Riccardo Fusaroli
Associate Professor at School of Communciation
and Culture, Aarhus University.
Interacting Minds Center, Aarhus University

Co-Supervisors

Lars Tjelta Westlye
Professor and Head of Research at Department
of Psychology, University of Oslo
NORMENT

Dag Alnæs

Senior Researcher at the Faculty of Medicine,
University of Oslo
NORMENT

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Contents

SUMMARY	4
ACKNOWLEDGEMENTS	5
ABBREVIATIONS	6
1. INTRODUCTION	7
1.1. The complexity of schizophrenia	9
1.2. Network topology	11
1.3. Models of symptom covariance in mental disorders	14
1.3.1. Latent Variable Models	14
1.3.2. Psychometric network models	16
1.3.3. Latent Variable Network Models	20
1.4. The current study	23
2. METHODOLOGY	26
2.1. Participants	26
2.2. Data	27
2.2.1. Clinical symptoms	27
2.2.2. Neurocognition	28
2.2.3. Genotype	29
2.3. Analysis	31
2.3.1. Network-based stratification of genetic sub-profiles	31
2.3.2. Model estimation	33
2.3.3. Confirmatory Factor Models (CFA)	33
2.3.4. Gaussian Graphical Model (GGM)	35
2.3.5. Latent Network Models (LNM)	37
2.3.6. Residual Network Models (RNM)	37
2.4. Model comparison	38
2.5. Visualization	38
3. RESULTS	39
3.1. Network based stratification	39
3.2. Three-factor versus five-factor model comparisons	39

3.3.	Gaussian Graphical Model (GGM)	40
3.4.	CFA model	41
3.5.	Latent Network Model (LNM)	42
3.6.	Residual Network Model (RNM)	43
3.7.	Model comparisons	45
4.	DISCUSSION	46
4.1.	Limitations and methodological considerations	53
4.2.	General discussion	57
4.2.1.	<i>Constituent elements of the networks</i>	57
4.2.2.	<i>Hybrid models</i>	60
4.3.	Further directions	61
4.3.1.	<i>Temporal Networks</i>	61
4.3.2.	<i>Variability networks</i>	63
4.3.3.	<i>Early Warning-Signals</i>	63
4.3.4.	<i>Moderator effects</i>	64
5.	CONCLUSION	65
REFERENCES		66
APPENDIX		76

Summary

Empirical evidence suggest unequivocally that clinical symptoms of schizophrenia are highly associated with a range of cognitive impairments (Seidman et al., 2017; Irani et al., 2012), and these dynamics appear to be under strong genetic influence (Wang et al., 2018; Harrison and Weinberger, 2005). However, investigations of the nature of these relationships, and the role they play in symptom development, maintenance and recovery have yielded mixed findings, indicating that causal pathways between genetics, cognition, and clinical symptoms may be complex and numerous. The observed co-occurrence of these observables in patients could arise from shared causal pathways, as implied by common cause models, from direct causal pathways between deficits, as implied by recent network approaches, or from a combination of the two.

The current project aimed to disentangle these dynamics assessing the covariance structure underlying 3 genetic, 12 cognitive, and 7 clinical items associated with schizophrenia. We compared four models of covariance; a factor model; a Gaussian Graphical Model (GGM); a latent network model (LNM); and a residual network model (RNM). Models were estimated on a general population youth sample and compared on confirmatory out-of-sample fit.

Results suggested that the RNM best described the covariance structure of genetic, clinical, and cognitive measures, indicating that these co-occur in part due to common underlying pathways and in part due to direct pairwise interactions. The model indicated that three latent factors explained most of the covariance within cognitive, clinical, and genetic items, respectively, however no shared latent variables were observed across categories. Further, cognitive and clinical components formed two distinct clusters in a network structure with many within-cluster connections. To the extent that components interact across clusters, this appeared to pass through attention-related mechanisms, suggesting a central role of attention in potential causal pathways between cognitive deficits and clinical symptoms in development of schizophrenia.

While specific interpretations of the identified structures should be made with caution, results highlight the importance of accounting for potential direct interactions between clinical and cognitive impairments, when investigating causal pathways underlying schizophrenia.

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Abbreviations

SNV	Single Nucleotide Variant
SNP	Single Nucleotide Polymorphism
CNV	Copy Number Variant
PGRS	Polygenic Risk Score
RDoC	Research Domain Criteria
MAGNA	Meta-Analytic Gaussian Network Aggregation
PCA	Principal Component Analysis
GGM	Gaussian Graphical Model
EFA	Exploratory Factor Analysis
CFA	Confirmatory Factor Analysis
LNM	Latent Network Model
RNM	Residual Network Model
SEM	Structural Equation Modeling
NBS	Network-Based Stratification
PNC	Philadelphia Neurodevelopmental Cohort
SD	Standard Deviation
dbGaP	Database of Genotypes and Phenotypes
SIP	Structural Interview for Prodromal Symptoms
Kiddie-SADS	Kiddie-Schedule for Affective Disorders
CNB	Computerized Neurocognitive Battery
WAIS-III	Wechsler Adult Intelligence Scale III
GWAS	Genome-Wide Association Studies
PPI	Protein-Protein Interaction
NMF	Non-Negative Matrix Factorization
GNMF	Graph Non-Negative Matrix Factorization
RMSEA	Root Mean Squared Error Approximation
BIC	Bayesian Information Criteria
FIML	Full-Information Maximum Likelihood
ML	Maximum Likelihood
WLS	Weighted Least Squares
df	Degrees of freedom
CBT	Cognitive Behavioural Therapy
MCT	Metacognitive Therapy
GVAR	Graphical Vector Autoregression
BDI-II	Beck Depression Inventory II
EWS	Early-Warning Signals
MNM	Moderator Network Model
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ICD-10	International Classification of Diseases
BD	Bipolar Disorder

1. Introduction

Research in the clinical, genetic and neurobiological literature on schizophrenia has created increasing awareness of the exceptional complexity associated with the disorder, not only in terms of its clinical manifestation (Dickinson et al., 2018), but also susceptibility patterns (Bustamante et al., 2017), neurodevelopmental pathways (Alnæs et al., 2019), and treatment response (McCutcheon et al., 2019). Beyond clinical symptoms of psychosis, schizophrenia is a disorder characterized by stable and generalized neurocognitive dysfunction (Irani et al., 2012). While these impairments have consistently been found to have strong predictive value of clinical symptoms and functional outcome in schizophrenia, the exact nature of the relationship between clinical and cognitive components remains largely unresolved. Further, schizophrenia is associated with high heritability (~80%), and disease susceptibility is largely determined by genetic variation (Harrison and Weinberger, 2005). Genetic variation has been found to correlate with both symptoms of psychosis and a range of cognitive dysfunctions (Isvoraru et al., 2020b; Wang et al., 2018). Hence, it is generally acknowledged that all symptoms, cognition, and genetics are interrelated and play important roles in the development of schizophrenia, however, the exact pathways of influence between them remains unclear. Are all symptoms equally subjected to genetic susceptibility? Do clinical symptoms, such as hallucinations and blunted affect, cause cognitive dysfunctions or vice versa? Is the former direction in play for some symptoms and the latter direction for others? Does genetic variation increase susceptibility of psychosis through cognitive dysfunction? It has recently been proposed that mental disorders can be understood in terms of complex network systems. Most natural, social and technological phenomena organize in complex systems, where multiple components connect to each other in networks of causal and reciprocal interactions (Barabasi, 2016); from the metabolic processes in our bodies, the financial flow in our societies, to the relationships of our social lives, and ever larger-scale structures of internet and transportation on which the global world resides. Characteristic of such systems is that their behavior cannot be understood from its individual components or causal effects between them but must be considered as an emergent behavior of the system as a whole. Network theory has proven to play a crucial role in understanding many natural phenomena, providing statistical tools to describe and analyze the structure and dynamics of complex systems in terms of network graphs (Boguña et al., 2003). Graph theory has its roots in physics and describes networks as a graph of nodes connected by edges (Barabasi, 2016). The connectivity patterns between nodes in the graph and the individual role of each node can be assessed statistically, informing about how information flows through the

system causing the emergence of different behaviors. In the context of mental disorders, this implies a model where the disorder is understood as an emergent behavior from complex interaction patterns between symptoms and other components, which can cause self-sustaining loops of pathological activation (Epskamp et al., 2018). This approach contrasts with standard approaches to psychopathology, where mental disorders are commonly conceptualized from common cause models. Here, an underlying entity, a latent unobserved variable, is assumed to cause the manifest symptoms, similar to how most somatic disorders are understood. In the latent variable approach, co-occurrence between symptoms is commonly modelled with factor analysis, explaining correlation between items as arising from having a common cause of variance; the latent factor (Borsboom, 2017). However, recent advances in network modelling have highlighted that the two approaches are not mutually exclusive, and that modelling shared variance caused by latent variables while taking into account variance arising from direct pairwise interactions might provide a more detailed and precise model of symptom co-occurrence (Bringmann and Eronen, 2018). The current project investigated the covariance structure underlying clinical, cognitive, and genetic observables in schizophrenia. Applying a factor model, a network model, and two generalizations hereof that combines aspects of both, the current project investigated which covariance structure provide a better description of the co-occurrence between the observed measures. The aim was to address the extent to which elements load on shared underlying dimensions, the manner in which these latent dimensions are related, and the extent to which co-occurrence can be attributed to direct interactions between pairs of components. Exploring such structures among individual components may provide more detailed insight into the causal dynamics underlying the development of schizophrenia.

The paper is structured as follows. First, the disorder of schizophrenia is described and previous findings on the interrelations between symptoms, cognitive dysfunctions and genetic risk variants are reviewed. Second, the concept of psychometric networks is introduced, including the underlying graph theory and network topology, their contrast to latent variable models of mental disorders, and previous applications of network models to other mental disorders. Third, a novel framework is presented that combines latent variable approach and network approach in two novel models of covariance. These four models of covariance are applied to components of schizophrenia measured in a general population sample, and results are compared and evaluated. Lastly, the general utility

of network theory for investigating causal pathways underlying schizophrenia, and mental disorders in general, is discussed.

1.1. The complexity of schizophrenia

Schizophrenia is a mental disorder on the psychosis spectrum, characterized by disruptions in the perception or expression of reality (National Center for Biotechnology Information). Symptoms of schizophrenia manifest as alterations of an individuals' thinking, sense of self and perception of others and the world, and is generally divided into positive symptoms (as hallucinations, delusions, formal thought disorder, and disorganized behavior) and negative symptoms (as affective flattening, alogia, avolition/apathy, and anhedonia/asociality) (American Psychiatric Association, 2013). In addition to psychological alterations the disorder is associated with stable neurocognitive impairments, which are evident in the vast majority of patients from early in disease development and across the lifespan (Irani et al., 2012). These dysfunctions span a wide range of cognitive domains including executive functions, memory and perception, and social cognitions (Seidman et al., 2017). It is now widely appreciated that susceptibility to develop schizophrenia is under significant genetic control, with heritability estimates of up to 80% (Harrison and Weinberger, 2005). Twin studies have shown that if one identical twin develops schizophrenia the other has approximately 50% chance of developing the disorder (National Center for Biotechnology Information). The attempt to identify single genes responsible for the increased disease liability has been largely inconclusive, partly explained by an ever-expanding number of identified genes associated with the disorder (Smeland et al., 2020), and partly by an increased appreciation of remarkable heterogeneity in the genetic risk profiles across individuals (Yuan et al., 2020). However, it is well established that common single-nucleotide polymorphisms (SNPs) contribute significantly to disease liability, and their cumulative additive effects, which can be represented by polygenic risk scores (PGRS), yield risk profiles with predictive value of clinical manifestation (Gilman et al., 2012).

Patients with schizophrenia exhibit exceptional heterogeneity in both phenotypic and genotypic expression (Vaskinn et al., 2020; Seidman et al., 2017), and the disorder is now considered a developmental neuropsychiatric disorder that should be understood as a dynamically evolving psycho-biological system (Seidman et al., 2017). Recent empirical evidence suggests unequivocally that genetic variation, cognitive abnormalities, environmental factors, and interactions between

these all play a role in the etiology, maintenance and recovery from schizophrenia (Seidman et al., 2017). However, investigations into the causal relationships between these and their role in disease etiology have yielded mixed findings. Several studies have concluded that cognitive impairments occur very early in the premorbid phase, often preceding the onset of psychosis by several years (Vaskinn et al., 2020; Seidman et al., 2017). These early cognitive abnormalities are strong predictors of both disorder manifestation and functional outcome in patients with schizophrenia (Irani et al., 2012), suggesting that neural mechanisms of cognition may play a causal role in the development of clinical symptoms and not vice versa. However, while cognitive impairments are evident in the vast majority of patients, the degree of dysfunction varies greatly from almost no impairment to severe dementia-like syndromes independent of symptom severity (Seidman et al., 2017). Hence, if cognitive impairments indeed have a causal role in symptom development, this effect is likely to be moderated by other factors to some extent. Another explanation may be that cognitive functions exert distinct effects on different symptoms. This is supported by evidence suggesting that cognitive function in psychosis is primarily associated with negative symptom profiles and severity (Devoe et al., 2021; Gupta et al., 2021; Kaneko et al., 2018), suggesting that the two constructs may share an underlying pathophysiology distinct from positive symptoms. Engen and colleagues (2019) reported that a group of patients with no negative symptoms did not differ from healthy control subjects on any cognitive measure, while patients with sustained negative symptoms performed worse across cognitive domains than patients with mild negative symptoms. Further, a meta-analysis found reductions in negative symptoms following cognitive remediation (Cella et al., 2017), while other studies have reported no relationship between improvements in cognition and negative symptoms (Bell et al., 2006). In contrast to earlier findings, there is now increasing evidence that cognitive alterations are also strongly associated with psychotic symptoms. Simonsen and colleagues (2021) found that cognitive abnormalities in inference were related to both positive and negative symptoms of schizophrenia, suggesting that these may arise from common underlying atypicalities. Thus, the literature points to a highly complex causal structure, where some individual cognitive functions and symptoms may share common underlying pathologies, while others may exhibit distinct causal pathways and interactional patterns, motivating a research approach focusing on the individual behavior of different components.

While the phenotype of schizophrenia is known to be largely under genetic influence (Gilman et al., 2012), molecular measures of genetic variation explain merely a fraction of the heterogeneous disease profiles observed across patients (Isvoraru et al., 2020b). Further, evidence collectively indicate that the mechanisms of genetic susceptibility may operate in heterogeneous ways across the spectrum of symptoms as well as cognitive functions. Isvoraru and colleagues (2020b) assessed the pairwise correlations of PGRS and individual symptoms of psychosis in a network model, and found that PGRS was primarily related to the spectrum of positive psychotic symptoms. Further, high heritability of cognitive deficits is well established, and the fact that these deficits tend to manifest prior to disease onset raises the possibility that genetic variations may increase psychosis susceptibility through their effects on cognitive functions (Wang et al., 2018). The role of cognitive function as a potential endophenotype of schizophrenia is supported by evidence of a strong association between PGRS and alterations of social cognition (Germine et al., 2016) and executive functions (Clementz et al., 2016) observed early in development and pre-onset of psychosis. These findings raise the possibility that early perturbations in neurocognitive development may mediate the impact of genetic variation on liability to develop psychotic symptoms. However, in light of evidence suggesting that cognition is primarily related to negative psychotic symptoms, and that PGRS was primarily related directly to the spectrum of positive symptoms, it is plausible that cognition may mediate genetic impact on negative symptoms, while positive symptoms and genetic variation are more directly linked. Investigating such down-stream effects of genetic variants and how they differ between individual phenotypic aspects may thus reveal important insight into the etiology of schizophrenia. Recently, it has been proposed that network models may offer the necessary tools to assess such complex dynamics of psychometric features in mental disorders.

1.2. Network topology

Relying on insights from graph theory, psychometric network models provide novel statistical tools to investigate complex relationships between large numbers of observables and describe the behavior that can be expected from the way these are structured, i.e., the network topology. In graph theory a network consists of nodes where each pair of nodes are connected by an edge with probability p . Most psychometric networks, as developed in Epskamp et al. (2016), are based on the Gaussian Graphical Model (GGM); an undirected network of pairwise Markov random fields (Murphy, 2012) representing conditional independence relationships (*Figure 1*).

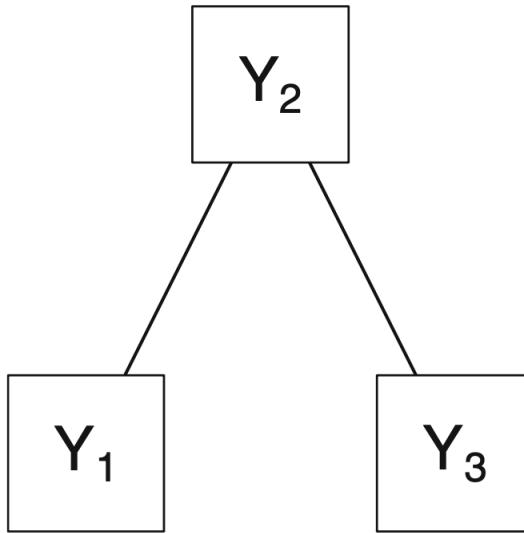


Figure 1. Example of a pairwise Markov random field model. Edges in this model indicate pairwise interactions and are drawn using undirected edges to distinguish from (bidirectional) covariances. Rather than a model for marginal associations (such as a network indicating covariances), this is a model for *conditional* associations. The network above encodes that Y1 and Y3 are independent after conditioning on Y2. Such a model allows all three variables to correlate while retaining one degree of freedom (the model only has two parameters). Figure and text from Epskamp et al., 2017b.

Two nodes are connected by an edge if they cannot be considered independent conditioning on all other nodes in the network, indicating a pairwise interaction (Epskamp et al., 2017b). A conditional independence structure, as exemplified in *Figure 1*, can arise from direct interactions between nodes, in cases where Y2 is a common cause of both Y1 and Y3, or Y2 act as a mediator on a causal path between Y1 and Y3 (Epskamp et al., 2017b). Y1 and Y3 become independent when conditioning on Y2. Networks of such structures can be described statistically in terms of local properties of individual nodes and global properties of the system as a whole, which are informative about the type of behavior that can emerge and the role of individual nodes in this behavior. In the context of psychometric networks, these statistical properties describe how likely individual components (e.g., symptoms) are to directly influence each other, how resilient their relationships are to intervention, and which components and pathways are most important for the emerging behavior. Each node can be characterized by its degree, which in undirected networks corresponds to its number of connections to other nodes. The degree distribution of the entire network then describes the distribution of the number of connections across all nodes, i.e., the probability

distribution of a randomly selected node having degree k . Random graphs are the simplest network models (Erdős and Rényi, 2011). The degree distribution of random graphs follows the Poisson distribution, implying that all nodes in the network have approximately the same number of connections (Barabasi and Albert, 1999). Most natural networks, however, organize in more complex structures with a degree distribution following a power-law. These are termed scale-free networks and are characterized by a few highly connected nodes, “hub” nodes, while the majority of nodes have a smaller degree than average (Barabasi, 2016). This structure implies efficient spread of information through the system, however, with high vulnerability to targeted attacks (e.g., interventions) on the hub nodes, as these connect most of the remaining nodes in the system. Many complex systems further organize in small-world structures, forming small clusters of tightly connected nodes, where each cluster is connected by few edges. This structure is quantified by the clustering coefficient, describing the tendency of fully connected triplets in the network. A high clustering coefficient yields short average path lengths, implying that any two nodes in the network can reach each other in very few “steps”. Short path lengths allow information to spread fast between nodes, making small-world networks ideal for efficient propagation of information through the system (Boguña et al., 2003). Further, the formation of strongly connected clusters increases the tendency of self-sustaining loops, causing prolonged activation of the system, even when the original trigger is no longer present (Borsboom, 2017). Such dynamics make the system more resilient to attacks of individual nodes, as most of the information of each node is shared within a cluster, and the system will not fragmentize easily from the removal of individual nodes. For instance, you have to remove more than 99% of the nodes composing the network of the internet in order for the system to fragmentize into smaller independent systems (Cohen et al., 2000).

The information flow can further be characterized by the global connectivity pattern, typically quantified as the mean edge weight across the entire network. Strongly connected networks will spread information more rapidly than loosely connected networks. The specific system dynamics can be quantified in terms of local properties of the nodes. Centrality metrics are particularly useful in this regard, informing about the specific influence on an individual node to the general information flow in the system. Centrality of nodes can be assessed in terms of their strength (weight of all its edges), closeness (mean distance to all other nodes), and betweenness (tendency to be part of the shortest path between any other node-pairs) (Costantini et al., 2015). Network theory thus provides several statistical metrics to inspect and quantify both global and local properties of

complex systems, which are informative of the type of dynamic behaviors that can emerge from psychometric interaction. Scale-free structure and the small-worldness have shown to be characteristic of many real-world networks, and has been demonstrated to be highly useful for understanding various disease mechanisms (Capriotti et al., 2018). It has recently been observed that psychometric networks of symptoms in several mental disorders too can be characterized as small-world networks, providing new means by which we can conceptualize and understand dynamic relationships between symptoms in the development of mental disorders.

1.3. Models of symptom covariance in mental disorders

Symptoms of psychopathology tend to co-occur (Borsboom, 2017; Boschloo et al., 2015). For instance, patients with schizophrenia experiencing hallucinations, also tend to experience difficulty concentrating and insomnia. In fact, mental disorders are diagnosed based on the presence of commonly co-occurring symptoms (Akram et al., 2017). Co-occurrence could either arise because the symptoms share the same underlying mechanisms (similar causal pathways), or as a result of direct interactions, e.g., one causing the other, between individual symptoms. The first explanation implies an underlying entity, such as a disease or dysfunction, causing various symptoms, while the second explanation assign the causal pathways to the symptoms themselves. The network approach conceptualizes mental disorders in line with the latter explanation, where symptoms, and other related components, interact directly in a complex system causing pathological patterns of development. This framework has primarily been investigated and discussed in contrast to latent variable models of psychopathology, however, recent advances indicate that the two approaches may be more complementary than previously acknowledged. The following section introduces each of the two frameworks and evaluate how they differ from each other, and how research in psychopathology may benefit from combining insights offered by both.

1.3.1. Latent Variable Models

The most widely used approach in psychopathological research is the common cause model (Li et al., 2020). The framework builds on factor models, where symptoms are modelled as indicators of an underlying source of variance, the latent factor (*Figure 2*). Following, co-occurrence between symptoms is conceptualized as being caused by a common source of variance, typically representing a disease entity (e.g., depression) (Bringmann and Eronen, 2018). This is in line with

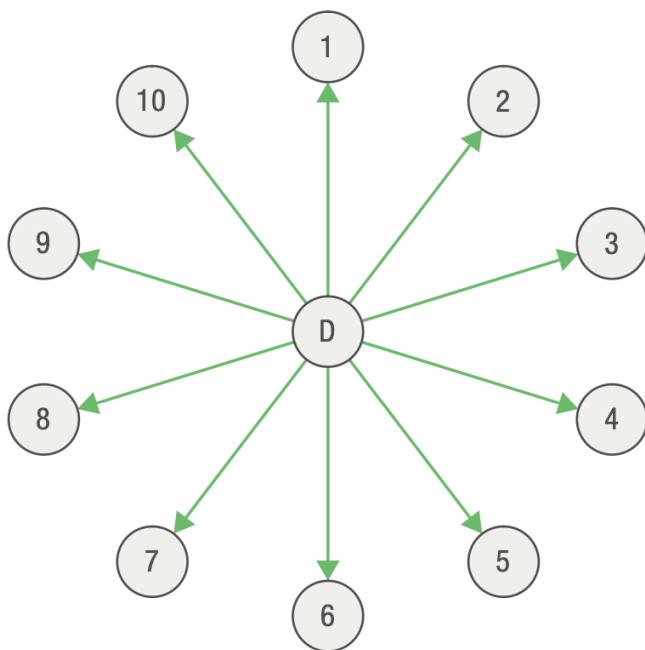


Figure 2. Latent variable model. The disorder D causes symptoms 1-10. Figure adopted from Fried and Cramer (2017).

models of most somatic disorders, where symptoms of, for example, cancer are all caused by the same underlying entity: a tumor. If you remove the tumor, all symptoms are expected to dissipate. An important assumption of this model is that individual symptoms are conditionally independent. That is, correlations between symptoms are dependent on the latent factor so that once we account for this, they will become statistically independent from each other (Bringmann and Eronen, 2018). Another common assumption is that the latent variable is the cause of the associated symptoms. As causes are by definition distinct from their effects (Pearl, 2000), this implies a conceptualization of mental disorders where the disease exists as an entity distinct from its symptoms. This assumption, however, is controversial in the psychiatric literature, as mental disorders are defined by their symptoms. It is highly difficult to imagine, for instance, a patient having depression without having any symptoms of depression. Thus, symptoms are intuitively understood as comprising the disorder itself, in contrast to most somatic disorders (Borsboom, 2017). Contrary, it seems reasonable to assume that at least some of the shared variance between symptoms is explained by a common underlying cause. For some disorders where high heritability has been observed, such as schizophrenia (Harrison and Weinberger, 2005), it is highly plausible that genetic variance for

instance can cause liability to develop several symptoms simultaneously. An important advantage of using latent variable models in psychiatric research is that they account for measurement errors in the quantification of symptom severity and other measures of dysfunction (Epskamp et al., 2017b). When treating observed symptom scores as measurements of an underlying construct, latent variable models assume that variance of measurements can be decomposed into two components; the variance that can be related to the underlying variable and the residual variance caused by random measurement error (Rhemtulla et al., 2020). Thus, latent variable models explicitly model measurement error when identifying the covariance structure between observed variables.

1.3.2. Psychometric network models

In recent years, psychometric network models have been proposed as an alternative framework for conceptualizing and studying the development of mental disorders. Based on the graph theoretical principles described earlier, the network perspective understands individual differences in psychopathology as emerging from direct causal interactions between clinical, biological, environmental components, etc. (Costantini et al., 2019). In a psychometric network model, nodes represent individual components, e.g., symptoms, while edges represent partial correlations among components. Edges are characterized by their *weight*, indicating the strength of the partial correlation and their *sign* indicating whether the relationship is positive or negative (Costantini et al., 2019). Partial correlations between two nodes are calculated by regressing out all other nodes in the network, and represent the unique shared variance between two nodes that is left when controlling for all other symptoms in the network (Boschloo, 2016). This results in a network structure comprised of direct relationships between pairs of components, where the state of a node will influence all other nodes to which it is connected. That is, activation of one symptom, for instance *insomnia*, can directly activate another symptom to which it is connected, such as *attentional deficits*, which in turn can activate more symptoms. Mental disorders are thus understood as an emerging behavior of the collective spreading of activation through the network, where symptoms become active agents in a causal system of pairwise interactions (Isvoraru et al., 2020a). Following, symptoms are conceptualized as constitutive of the disorder itself, playing a causal role in pathological development, rather than being indicators of the disease as regarded in common cause models. This framework aligns neatly with the recent Research Domain Criteria (RDoC) initiative which suggests that future research should focus on assessing the individual role

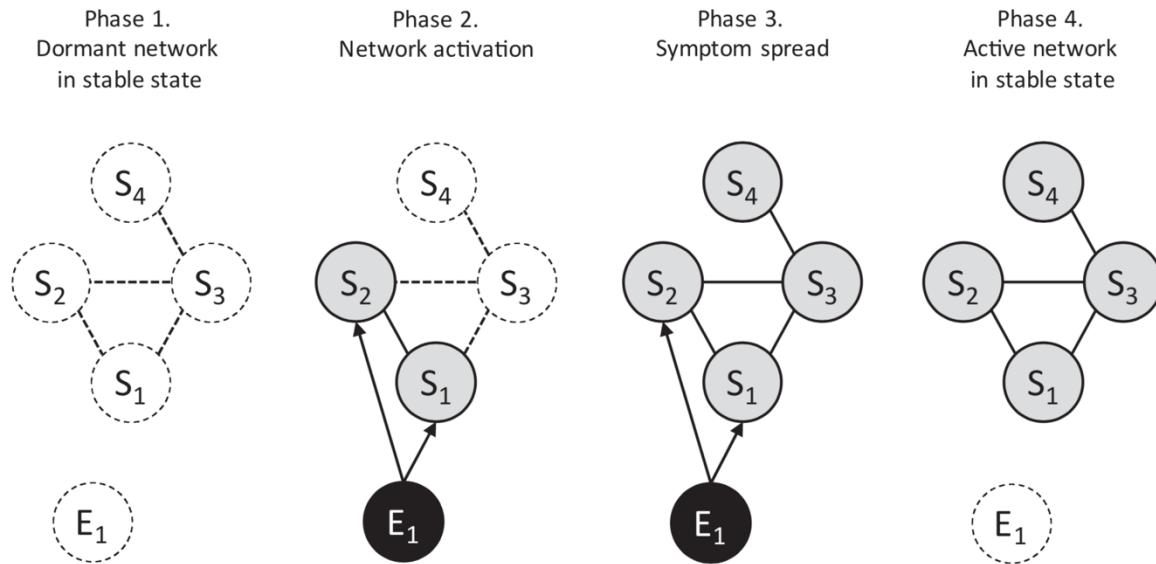


Figure 3. Example of phase-transition from healthy to disordered state according to network theory. After a state with no symptoms (phase 1) an external event (E_1) activates some of the symptoms (phase 2), which in turn activate symptoms to which they are connected (phase 3). If the network is sufficiently connected, removal of the external event does not lead to recovery: the network is self-sustaining and stuck in an active pathological state (phase 4). Figure from Borsboom (2017).

of smaller units rather than the whole disorder, when investigating causal pathways in psychopathological development (Bringmann and Eronen, 2018). Network models aim to provide more accurate and parsimonious insights into the potentially high-dimensional interplay among multiple components that constitute psychopathologies, by focusing on individual interactions in the systems and their collective behavior (Jordan et al., 2020). Applications of network models have revealed important novel insights into the relations between symptoms and demonstrated their explanatory power in terms of pathological development in a wide range of mental disorders, including major depressive disorder (Fried et al., 2016; Cramer et al., 2016; Boschloo et al., 2016), social anxiety (Heeren et al., 2016), bipolar disorder (Beard et al., 2016), obsessive compulsive disorder (McNally et al., 2017), and autism spectrum disorder (Ruzzano et al., 2015).

The central idea of this framework is that the clinical manifestation of a disorder represents a phase-transition in the system from one state to another (*Figure 3*). Phase-transitions are a common feature of complex networks from a range of fields, including medicine, global finance, and ecosystems (Scheffer et al., 2012). They reflect a tipping point in system dynamics, characterized

by increased variability and self-reinforcement among symptoms, from which the system becomes self-maintaining (Wichers et al., 2016). For psychometric networks this represents a change from a healthy stable state into one where the connectivity is so strong, and the activity of individual symptoms so high, that the system remains globally activated despite alleviation of the original cause of activation. The system dynamics underlying such pathological development are largely determined by the global topological network structure and the local role of nodes. (Li et al., 2020). Several studies have provided empirical evidence that psychopathological networks exhibit two properties characteristic of complex networks; scale-free degree distribution and small-world topology (Costantini et al., 2019; Borsboom et al., 2011). The degree distribution of psychometric networks is generally found to approximate a scale-free power-law distribution, where few nodes are highly connected while the majority of nodes has less than average degree¹ (Borsboom et al., 2011). This property implies that the connectivity structure is independent of the size of the network, and networks with fewer edges can exhibit higher connectivity than networks with more edges. Several studies have suggested that densely connected networks are more vulnerable to manifestation of psychopathology. Pe and colleagues (2015) showed that emotion networks of patients with major depressive disorder and psychosis exhibited stronger global connectivity than identical networks of healthy control subjects. Further, a longitudinal cohort study of depression found that global connectivity of symptom networks was predictive of patients who persisted treatment at follow-up and who were remitted (van Borkulo et al., 2015). Increased connectivity between symptoms of negative mood in depression was additionally found to predict a phase transition into a disordered state of depression manifestation (van de Leemput et al., 2014). In a network of psychosis symptoms it was found that symptoms were linked in a stable way independent of remission status, while the number of connections and their strength (i.e., global connectivity) were dependent on remission status (van Rooijen et al., 2018). The second property, small-world topology, is characterized by a high tendency of clustering reducing the average path lengths between any two node-pairs, and is a commonly observed feature of psychometric networks (Costantini et al., 2019). This implies that symptoms of mental disorders tend to organize in clusters, where information is efficiently shared between clusters. Thus, activation of one symptom

¹ Scale-free networks are formally defined as networks where the fraction of nodes with degree, k , follows a power law distribution, $k^{-\alpha}$, where $\alpha > 1$ (Stumpf and Porter, 2012). It has been noted that very few networks indeed meet requirements of scale-free networks in a strict sense (Broido and Clauset, 2019), including most psychometric networks. Scale-free topology of psychometric networks should not be interpreted in a strict mathematical sense, but rather as representing a skewed degree distribution, resembling the characteristics of a power-law distribution.

is likely to rapidly cause the activation of both neighboring and distant symptoms, leading to a cascade of symptom activation. Strong clustering additionally increases the likelihood of self-reinforcing loops, which are the main driver of phase-transitions in complex networks (Wichers et al., 2016). Assessing the tendency of clustering and degree of small-worldness may be informative about the liability for individuals to develop a disorder. The small-world property and scale-free degree distribution further implies that some symptoms have larger influence on the propagation of information through the network, than other symptoms. These are identified by centrality indices and have proven to have strong clinical relevance. In a network of depression symptoms, the most central symptoms (fatigue, concentration problems, loss of interest/pleasure and depressed mood) were found to be the strongest predictors of developing depression at a six-year follow-up (Boschloo et al., 2016). That is, individuals who scored higher on highly central symptoms at baseline were more likely to develop depression six years later. Targeting highly central symptoms in treatment programs may thus be advantageous in clinical practice, as reduction in these is more likely to alleviate the global system activity and reduce self-reinforcement among nodes.

Psychometric network models offer intuitive explanations of common findings in the literature. Comorbidity of disorders can be explained by “bridging” symptoms; symptoms that are part of networks for two different disorders and can propagate activity from one network to the other (Jordan et al., 2020). Another common finding is down-stream effects between symptoms (Beard et al., 2016), which can readily be explained by pairwise interactions in a network structure. One challenge of network models is that the large number of parameters increases the risk of overfitting to the sample. This issue was recently addressed in a meta-analysis, where Isvoranu and colleagues (2020a) applied a novel method, Meta-Analytic Gaussian Network Aggregation (MAGNA) on networks of PTSD symptoms. Results suggested that networks from single studies largely resembled the structures of a pooled network across studies, indicating no severe problems of overfitting in the given networks. Network models of psychometric components have several caveats, however. First, they assume no latent variables in the system. That is, all covariance between two components is ascribed to direct causal interaction between them. This is a significant problem, given that multiple items of psychopathology are likely to be, at least partly, caused by a common unobserved variable (Epskamp et al., 2017b). For instance, it seems unlikely that the two symptoms of schizophrenia, *apathy* and *asociality*, do not share any common source of variance, such as an underlying personality trait. In line with this critique is the notion that network models

assume no missing variables in the system, nor any overlapping components. That is, the model assumes no unmodelled sources of variance, which seems implausible in the context of mental disorders, where a myriad of factors has proven to play a role to various degrees, including biological, genetic, neurobiological, psychological, social, environmental, and socio-economic components, among others. It is highly unlikely that all relevant components are modeled in any network, and if they were, the model would most likely be too complex to be informative. Lastly, network models cannot account for measurement error, i.e., all observed values are assumed to be equal to the true value. However, as most psychometric assessments rely on questionnaires or severity ratings by psychiatrists, errors are likely to occur due to, for instance, differences in how questions are interpreted or the experience of the particular psychiatrist. Further, symptoms and cognitive abilities are often rated using a single item (question or task). Thus, values in psychometric data are likely to differ slightly from the true value of the object they are measuring and given the large number of variables in network models, measurement error will inevitably influence the estimated network structure.

1.3.3. Latent Variable Network Models

While psychometric network models have mainly been discussed in opposition to latent variable models, several scholars have recently argued that there is no clear dichotomy between the two approaches. Both frameworks provide means to assess the covariance structure of observed variables, where latent variable models focus on the shared variance between components while network models model the variance unique to pairs of components (Epskamp et al., 2017b). It is widely acknowledged that somatic disorders exhibit a broad spectrum of causal structures, where some can be described as a strict latent variable structure with a single common cause for all symptoms, and others are characterized by complex structures of multiple latent causes and dynamic networks of symptom interaction (Bringmann and Eronen, 2018). Hence, there is a whole range of possible covariance structures between the two extremes which could explain the observed co-occurrence of symptoms and other psychometrics in mental disorders, and different tools may be more appropriate in different situations.

Recently, a generalization of the GGM has been proposed that allows researchers to combine the latent variable and network frameworks in the estimation of covariance structures of psychometric variables (Epskamp et al., 2017b). This framework is generally motivated by four observations.

First, increasing empirical evidence indicates the presence of latent structures in symptom networks, violating assumptions of the network model. In a recent review on network models of symptoms in PTSD from different DSM categories, it was found that the most commonly identified edges across studies were those within the same DSM category (Li et al., 2020), suggesting that at least some of the variance between nodes can be ascribed to latent factors. In fact, clusters observed in GGMs may indicate the presence of shared variance between the nodes causing stronger connections within the cluster. Second, the assumption of local independence in the latent variable model seems to be frequently violated, either due to direct causal effects, reciprocal interactions, or conceptual overlap between variables (Epskamp et al., 2017b). That is, what the latent variable model ascribes to residual error may actually represent informative direct interactions between symptoms, where changes in one (e.g., fatigue) causes changes in another (e.g., poor concentration) regardless of the state of the latent factor (Epskamp et al., 2017b). Third, latent variable models need not be interpreted causally (Bringmann and Eronen, 2018). Latent variable models offer a technique for discovering patterns of shared variance among variables, and while latent variables may represent a common cause, they could also be interpreted as conceptually related to the indicators, i.e., a summation of the association between variables. A non-causal interpretation allows applying latent variable models even when the latent factor is not necessarily distinct from its indicators. Fourth, Epskamp and colleagues (2017b) described how the GGM can also be applied to common cause structures modelling the relationship between latent factors as pairwise partial correlations. This allows causal patterns where observed variables may not interact directly with each other, but their underlying constructs may influence each other causally (Bringmann and Eronen, 2018). Thus, the two frameworks each offer explanations complementary to the other, and in combination they allow researchers to disentangle covariance due to latent structures from covariance arising from direct interactions.

The generalization of the GGM is based on a multilevel modeling strategy with two components: *Latent Network Model (LNM)* and *Residual Network Model (RNM)*. The LNM models the latent variance structure of variables as a network (*Figure 4a*). The latent structure of symptoms is identified by estimating a factor model, distinguishing shared variance between symptoms that can be attributed to a predefined number of factors from residual error (i.e., co-variance between items that cannot be ascribed a latent factor). A GGM can then be fitted to the factor structure, where

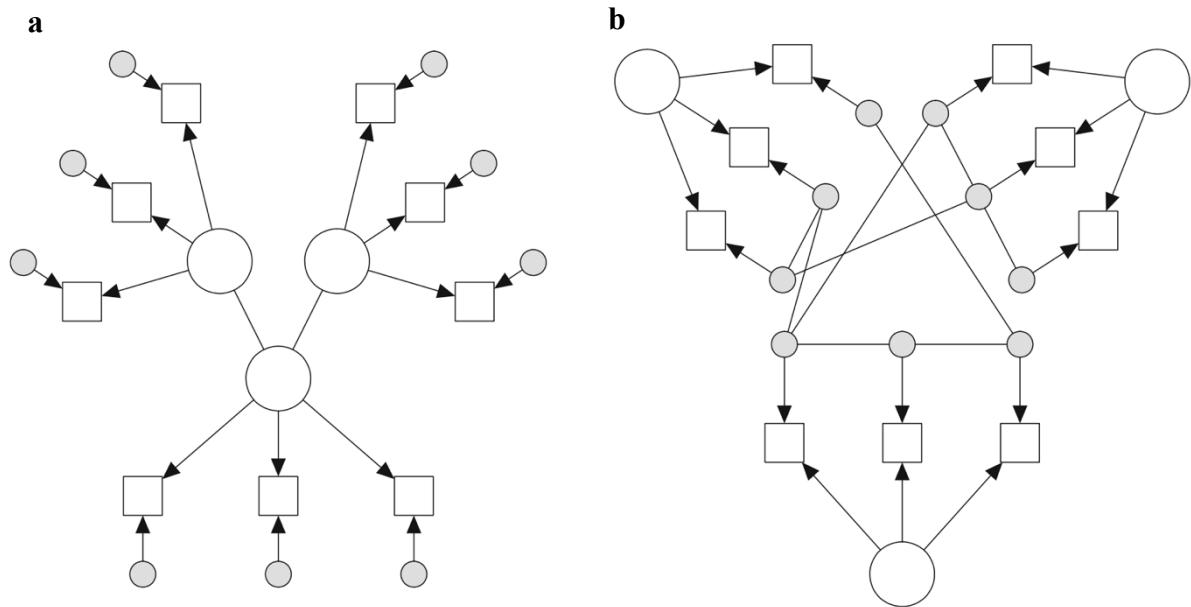


Figure 4. **a** latent network model. **b** residual network model. Circular nodes indicate latent variables. Square nodes indicate observed variables. Gray nodes indicate residuals. Directed edges represent factor loadings. Undirected edges indicate pairwise interactions (note that these are not mere covariances). Figure adapted from Epskamp et al. (2017).

nodes represent latent factors and edges represent partial correlations between these (Epskamp et al., 2017b). Thus, the LNM represents common sources of variance between symptoms as underlying symptom dimensions that form a network of pairwise interactions. Such interactions between latent factors may explain the co-occurrence of two symptoms, that cannot be attributed to direct interactions between them nor a shared common cause. Rather, two symptoms could co-occur because their corresponding underlying causal mechanisms (represented by the latent factor) are influencing each other directly, either in a unidirectional or reciprocal manner. Further, by modeling the covariance structure between latent factors as a GGM, graph theoretical methods can be applied to identify differences in connectivity patterns between symptom dimensions in distinct groups of patients, as well as dimensions with higher centrality in the latent network (Li et al., 2020).

Even when accounting for common underlying dimensions, we might still expect some degree of correlation between indicators. Such correlation is not modelled in standard factor analytic approaches, where excessive covariance between indicators is typically accounted for by combining these into subscales or global scores prior to factor analysis (Epskamp et al., 2017b). However,

these residual correlations may have valuable explanatory power of the causal relationships between items. The RNM models the residual variance of a factor model as a network (*Figure 4.B*). That is, a GGM is fitted to the variance that remains after conditioning on the latent factor structure, where nodes represent the residuals associated with each symptom and edges represent partial correlations between residuals (Epskamp et al., 2017b). Because partial correlations represent the covariance between two nodes after conditioning on all other nodes in the model, the RNM allows identification of direct relationships between symptoms (and other indicators) that cannot be attributed to a common cause, nor be explained by other symptoms in the network. The LNM and RNM thus provides significant advantages in the estimation of covariance structures between multiple variables, by circumventing critical assumptions of both models that are typically violated in empirical observations. The LNM allows the estimation of a network model even in cases where nodes are partly caused by unobserved or latent variables, while the RNM allows the estimation of factor structures without assuming local independence between indicators. Additionally, the RNM can improve the fit of confirmatory factor models in cases where all residuals correlate, by explicitly modeling these as pairwise interactions without changing the factor structure. Lastly, most psychometric variables implemented in network models are expected to exhibit substantial measurement error, as they are often scored using a single task or question. Hence, they cannot be assumed to be perfect indicators of those attributes, as assumed by the GGM. However, the LNM offers a way to account for this, by estimating the network structure of latent dimensions indicated by multiple variables (Epskamp et al., 2017b) The LNM and RNM frameworks thus allows the identification of more complex covariance structures in psychometric components and investigations of potential causal pathways of these, potentially encompassing both latent common causes and direct causal interactions between components.

1.4. The current study

Evidence collectively agree that schizophrenia is associated with significant phenotypic and genotypic heterogeneity that seems to arise from complex multi-factorial causal relationships. These findings imply the importance of complex models of disease liability and etiology, where downstream effects and causal pathways across biological, neural, cognitive and clinical dimensions can differ for individual components of these dimensions. The current study aimed to investigate the nature of the relationship between individual symptoms and cognitive functions associated with schizophrenia, and how each of these are related to genetic susceptibility, by modeling their

underlying covariance structure. Pairwise co-occurrence between components can arise from four events; 1) both are caused by a third variable, 2) one causes the other, 3) they are caused by two distinct variables of which one is the cause of the other, or 4) both causes a third variable. The fourth option is termed the collider effect in graph theory and refers to the induction of a spurious partial correlation between two variables, if they both cause of a third unmodelled variable (Pearl, 2000). This paper aimed to distinguish the first three types of covariance in 22 components encompassing measures of clinical symptoms, cognitive functions, and genetic risk variants, by comparing four models of covariance; a CFA, GGM, LNM and RNM. If all modelled components co-occur due to one or more common causes, we would expect the CFA model to exhibit best fit. If all components co-occur due to direct pairwise causal interactions, we expect the GGM to exhibit better fit. If components do not cause each other directly but arise from multiple unobserved components which interact directly, we would expect the LNM to exhibit better fit. Lastly, if covariance is partly explained by common underlying causes, and partly by direct interactions between components themselves, we expect the RNM to exhibit better fit.

Previous evidence from PTSD studies has showed that an LNM provided a better explanation of symptom covariance than a factor model (Li et al., 2020), indicating that dimensions of symptoms interact directly, potentially in a causal manner. Further, Wigman and colleagues (2015) demonstrated that symptom networks of psychosis disorders exhibited positive feedback loops, suggesting that downward spirals of pathological mental states may arise from symptoms directly enhancing each other. Such dynamics might be useful for unravelling the causal pathways of the observed associations between cognition, symptoms, and genomics in patients with schizophrenia. If the strong association between negative symptom severity and cognitive functions arises from a common underlying pathophysiology, as suggested by Engen and colleagues (2019), we would expect them to be independent in a GGM when conditioning on latent factors and all other models in the network. Further, if some of the covariance is explained by some of these components influencing each other directly, either positively or negatively, it would manifest as edges in the GGM, even after conditioning on latent factors. Some evidence suggests that improvement on social cognitive aspects had a larger impact on symptom reduction in patients than pharmacological treatment (Woodberry et al., 2016), indicating that some direct causal relationship may be expected. Scholars have further argued that impairments of auditory attention may have causal implications for the auditory-related symptoms in SCZ such as hallucinations (Seidman et al., 2017). If these two

alterations are completely independent when conditioning on a latent factor of shared variance, this would indicate that they exhibit strong associations due to a shared underlying pathology. Contrary, if an edge remains between them, even after conditioning on latent factors and all other modelled variables, this indicates that one may indeed have a direct causal effect on the other. Given the severe prevalence of attentional deficits in schizophrenia and their early pre-onset manifestation (Wang et al., 2018), it seems plausible that attention-related components will be strongly connected to some symptoms in a GGM, indicative of a causal relationship.

There are two ways genetic risk may influence symptom-cognition networks. First, it can act as a main effect, directly influencing some or all components, either positively or negatively. High genetic risk may for instance increase liability of poor working memory or impaired emotional expression. Second, it can act as a moderator, in which genetic risk profile influences the topology of the network, i.e., how components are connected and the strength of their connections. In this case, high genetic risk may for instance cause a stronger influence of impaired abstraction skills on emotion expression, indicated by a stronger edge between the two. As genetic risk components were included directly in the current models, results here focus on the first type of effect. Several scholars have pointed to the importance of investigating the degree to which variation in neurocognitive function is modulated by genetics, and the role this may play in symptom development (Wang et al., 2018; Seidman et al., 2017). While typical approaches rely on clear-cut diagnostic categories of case-control status, network models of covariance are more consistent with dominant psychosis liability theories which point to a spectrum of related phenotypes, where no single set of properties are necessary and sufficient, but liability can arise from a range of dynamic causal patterns (Isvoraru et al., 2020b). The current models may provide explanatory insight into the observed differences in how PGRS relates to the spectrum of positive and negative symptoms. Given evidence of a particular association between PGRS and the positive symptom spectrum (Isvoraru et al., 2020b), we might expect more and stronger edges between genetic components and positive symptoms than negative symptoms. Further, genetic variance may have a more indirect effect on negative symptom liability, implying a network structure where genetic components are connected to negative symptoms via other components. Given the observation that genetic risk is strongly associated with cognitive deficits (Germine et al., 2016), which in turn are strongly related to negative symptoms (Engen et al., 2019), we might expect connectivity patterns where genetic components are linked to negative symptoms via cognitive components. However, previous

network models have shown strong connectivity between positive and negative symptoms of psychosis (Isvoraru et al., 2020a; Rooijen et al., 2018), implying the possibility that genetic susceptibility to develop negative symptoms, at least in some cases, may be mediated by the effect on positive symptoms. Modelling the shared and unique variance among these components as a GGM, allows researchers to disentangle such dynamics in a parsimonious and detailed manner.

The current analysis consists of three parts. First, three subgroups of genetic risk profiles in the sample were derived via network-based stratification (NBS) based on 10.000 SNPs. This procedure grouped individuals according to the effect of their genetic variation profiles on molecular protein networks. This allowed implementation of a more heterogeneous representation of genetic risk in subsequent models (compared to PGRS), where distinct risk profiles can have different associations to clinical and cognitive components. Second, PCA and EFA were performed to assess how many underlying factors best describe the shared variance between observed components, and how individual components load on each factor. This was implemented to identify the most optimal factor structure to be applied in subsequent confirmatory models. Third, four models of covariance (CFA, GGM, LNM and RNM) were estimated and compared according to confirmatory out-of-sample fit. This allowed investigation of whether the covariance structure underlying observed components is better described in terms of underlying common causes (CFA), direct pairwise interactions (GGM), direct pairwise interactions of latent factors (LNM), or a combination of latent common causes and direct pairwise interactions between components (RNM). The procedure aimed to highlight potential shared and unique causal pathways between schizophrenia-related genetic, clinical and cognitive observables.

2. Methodology

2.1. Participants

Subjects were sampled from the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2016) and all subjects who were assessed on all clinical, cognitive, and genetic variables of interest were included. This yielded a final sample of 507 subjects of age 8 to 21 (mean=14.35, SD=3.45), of which 49,9% was female (*Table 1*). The sample comprises a general youth population of the Philadelphia area in the USA. All subjects included had received medical care from the Children's Hospital of Philadelphia. None were ascertained through psychiatric services.

Participants included in the PNC were recruited at random after stratification for sex, gender, and ethnicity. Inclusion criteria included ability to provide signed informed consent, English language proficiency, and physical and cognitive ability to participate in computerized clinical and neurocognitive assessment (Satterthwaite et al., 2016).

	N (%)	Age mean (SD)	Ethnicity* (%)	SIP mean (SD)	WRAT mean (SD)
Full sample	507 (100)	14.35 (3.45)	EA (100)	2.38 (3.36)	55.58 (8.04)
Females	253 (49,9)	14.41 (3.51)	EA (100)	2.16 (3.11)	55.1 (7.86)
Males	254 (50,1)	14.29 (3.39)	EA (100)	2.57 (3.61)	55.84 (8.19)

*EA = European American

Table 1. Demographic overview

2.2. Data

The PNC project is a large-scale study on child development funded by NIMH, which encompasses multi-modal neuroimaging, genetics, medical assessment, and extensive clinical and cognitive phenotyping. Data is publicly available from the database of Genotypes and Phenotypes (dbGaP). The current project included variables from three domains; prodromal symptoms of psychosis, neurocognition, and genotype.

2.2.1. Clinical symptoms

Clinical prodromal symptoms of psychosis were assessed with the Structural Interview for Prodromal Symptoms (SIP) as part of the Kiddie-Schedule for Affective Disorders and Schizophrenia (Kiddie-SADS) (Kaufman et al., 1997). Seven items were analyzed including 1) *trouble with focus and attention*, 2) *changes in speech, disorganized communication, tangential speech*, 3) *changes in the perception of self, others, or the world in general*, 4) *expression of emotion*, 5) *occupational functioning*, and 6) *avolition*. Each of these were scored on a 7-point Likert scale representing a global score of multiple sub-items associated with each symptom domain (score distributions can be found in appendix, *Figure A1*) All SIP items were assessed and rated by a trained clinician. In addition, the item *Psychosis* from the Kiddie-SADS Family Study Interview was included in the analysis. This item is scored on a 6-point scale counting the presence or absence of six binary (0,1) sub-items assessing experiences of hallucination- and delusions-like

character. Details on the interview questions used to assess these items can be found in appendix (*Table A1*). In total, seven indicators of clinical symptoms of psychosis were included in the study.

2.2.2. Neurocognition

Neurocognitive function was assessed with the Penn computerized neurocognitive battery (Penn CNB) (Moore et al., 2015) in a simpler and shorter version modified to the young population (Satterthwaite et al., 2016). All tasks for which the full sample was scored were included in the analysis, yielding 12 variables of cognitive functioning. *Social cognition* ability was assessed with the Penn Face Memory Test. In this task participants are asked to distinguish which of two presented faces are older, measuring ability to decode the age of faces. The task includes graded levels of difficulty, and is scored on a range (0,100) indicating percentage correct choices across all trials. *Facial memory* is based on the Penn Face Memory Test, measuring episodic memory for faces. In this task, participants are first presented with 20 images of faces, one at a time, and each for 1 second. Subsequently, in the recognition phase, participants are presented with 40 images of faces, one at a time, half of which appeared in the encoding phase, and half of which are novel images. The subject is to indicate for each image, whether they have seen the face before on a four-choice scale (from “definitely not” to “definitely yes”). The task is scored as number of correct choices across all trials. *Emotion recognition* was assessed with the Penn Emotion Identification Test, indicating ability to appropriately interpret facial expressions of emotion. Participants are presented with 40 faces, one at a time, and are to indicate for each face whether it expresses the emotion happiness, sadness, anger, fear or none. For each emotion four female and four male faces are presented. The task is scored as total correct responses across all trials. *Verbal memory* was measured with the Penn Word Memory Test, the procedure of which is identical to the Face Memory test using words instead of face images as stimuli. The task is scored as correct responses across all trials. *Verbal Reasoning* was assessed with the Penn Verbal Reasoning Test, measuring language-mediated cognition ability. Participants are to solve a series of analogy problems, derived from the Educational Testing Service factor-referenced test kit. The task is scored as correct responses for across all trials. *Motor Planning* was measured based on the Penn Motor Praxis Test, indicating sensorimotor ability. Participants are to move the mouse to click on a green box, sequentially appearing in unpredictable locations on the screen and with decreasing size for each trial. The task is scored as median response time (milliseconds) across all trials. *Abstraction* was assessed using the Penn Matrix Reasoning Test, indicating nonverbal reasoning ability. The

participant is to solve matrix reasoning problems, derived from the Raven's Progressive Matrices Test and the Matrix Reasoning subscale of the WAIS-III (Moore et al., 2014). The task is scored on range (0,100) representing the percentage of correct solutions across all trials. *Motor Speed* was measured with the Finger Tapping Test, in which the participant is to tap the space bar as many times as possible within a 10-second time window, using only the index finger (Gur et al., 2010). The task is administered for both hands and scored as the sum of the mean tap count across three trials for both dominant and non-dominant hand. *Visuospatial Learning and Memory* was assessed with the Visual Object Learning Test, the procedure of which is identical to the Word Memory Test, using 10 Euclidean shapes instead of 20 words as stimuli. The task is scored as number of correct responses across all trials. *Working Memory* was measured with the Letter N-Back test. Participants are sequentially presented with a letter and are to indicate whether it is identical to the letter preceding it (1-back condition) or to the letter presented two trials back (2-back condition) (Gur et al., 2010). The task is scored as number of correct responses across all 1-back and 2-back trials. *Attention* was assessed using the Penn Continuous Performance Test, measuring vigilance and visual attention independently of working memory. Vertical and horizontal lines are presented in 7-segment displays on the screen (with one second intervals), and participants are to respond when the lines are configured as numbers (first half) or letters (second half). Each half is 1.5 minutes, and within each 1 second response window the line is presented for 300 milliseconds. The task is scored as number of correct responses across all number- and letter trials. *Academic skills* were measured with the Wide Range Assessment Test, which involves a brief standardized reading test from the Wide Range Achievement Test (Wilkinson and Robertson, 2006). The test results are represented as a standard score in range (0,70). Score distributions for each variable are in appendix (*Figure A2*).

2.2.3. *Genotype*

The PNC sample was genotyped according to the CAG pipeline (Pinto et al., 2010) on the 550HH and 610Q single-nucleotide polymorphism (SNP) arrays from Illumina (Satterthwaite et al., 2016). SNPs are essentially mutations occurring at a single nucleotide on the genome (Lakna, 2019) and are typically identified from genome-wide association studies (GWAS) as genetic variants that distinguish a control population from a population with a specific disorder trait (Leiserson et al., 2013). The current study included 10.000 GWAS-derived SNPs scored on range (0, 2) representing allele counts for each SNP. SNPs were selected according to their importance in a whole genome-based calculation of polygenic risk score (PGRS) for schizophrenia. In short, PGRS summarizes

effects of trait-associated alleles across multiple genetic loci, weighted by the GWAS-estimated effect size (Isvoranu et al., 2020b) PGRS was calculated based on standard procedures with the PRSice-2 software (for details hereof please refer to Choi and O'Reilly, 2019).

While GWAS-derived PGRS scores have commonly been applied in the investigation of genotype-phenotype relationships, increasing evidence suggests that this approach may obscure important information on genetic variance in schizophrenia. Common SNPs explain minor increments in disease liability and even when aggregated, the PGRS accounts for only a fraction of the genetic effects in patients, even for disorders known to have high heritability (Germine et al., 2019; Leiserson et al., 2013). This problem is associated with significant genetic heterogeneity observed in patients, where few genetic variants are consistently linked to psychotic disorders (Isvoranu et al., 2020b). Hence, it is unlikely that particular constellations of risk variants will be characteristic of most patients, making the use of a single summary score problematic. This was supported in a recent network study that found very weak connections between PGRS and symptoms of psychosis in general (Isvoranu et al., 2020b). The authors suggested that identifying specific genetic segments related to individual symptoms may yield more informative biological structures. The current project aimed to implement more detailed measures of genetic risk, by applying network-based stratification (NBS) analysis integrating the GWAS-derived SNPs with molecular protein-protein interaction (PPI) networks. This approach is motivated by increasing evidence that many diseases arise not from individual mutations or genes, but from how these cause perturbations to biological molecular networks (Ratnakumar et al., 2020; Hofree et al., 2013). For instance, it has been demonstrated that while individual cancer tumors rarely have any gene mutations in common, the genes that are affected often reside on similar pathways affecting molecular networks in similar ways (Capriotti et al., 2019; Hofree et al., 2013). Considerable evidence shows that the protein-products of causal genes for a disease tend to form highly connected clusters in these networks often interacting directly with each other more than expected by chance and participating collectively in similar biological functions (Hormozdiari et al., 2015; Leiserson et al., 2013). Thus, mutations can be mapped onto PPI networks allowing the identification of genetic sub-groups based on the molecular network structures affected by the variants. This approach has proved able to identify meaningful homogeneous genetic subgroups with clinical relevance in cancer (Hofree et al., 2013) and recently autism (Kim et al., 2019). This project implemented NBS to stratify the sample into subgroups of functionally related genetic alterations. This implied mapping individual

SNPs onto their respective proteins in a PPI network, subsequently applying network propagation to identify downstream subnetworks affected by each SNP (Capriotti et al., 2018). Nonnegative matrix factorization was then implemented as community detection, yielding three distinct genetic subgroups in the current population (Cai et al., 2008). Each subject was scored on range (0,1) for each subgroup, indicating the correspondence between their individual mutation profile and the average mutation profile of that subgroup, where higher scores represent closer similarity.

Data preprocessing resulted in a complete dataset of 22 variables, of which 7 represent clinical measures, 12 indicate neurocognitive functioning, and 3 represent genetic variation profiles.

2.3. Analysis

2.3.1. Network-based stratification of genetic sub-profiles

For the purpose of stratification, all subjects in the full PNC dataset for whom the relevant SNP data was available was included ($N=4133$), yielding higher statistical power for robust identification of genetic sub-profiles. SNP allele counts (0, 1 or 2) were standardized to scale (0,1) to meet requirements of the *StratiPy* package. PPI network was obtained from the *STRING* database and contained 12.233 genes and associated protein interactions, based on known and predicted interaction data from humans (Szklarczyk et al., 2010). Nodes of the PPI network represent gene proteins while edges represent direct interactions between two nodes. Gene proteins in the PPI network were mapped to each of the SNPs in the current sample using the publicly available DisGeNET database, providing mappings between more than 1.200.000 genes and 370.000 variants associated with human diseases (Piñero et al., 2020). Network-based stratification of genetic sub-profiles was performed using the *StratiPy* python package following the procedure and code provided by the package developers (Kim et al., 2018). Two matrices were given as input. First, an $N \times P$ matrix, with allele counts for P SNPs across N subjects, defining the individual genetic variant profiles. Second, an $M \times M$ matrix, defining protein-protein interactions (PPI) in humans (the *STRING* network). The network-based stratification pipeline is exemplified in *Figure 5*. First, the variant profile of each subject is superimposed onto the PPI network independently. Next, network propagation is applied, iteratively spreading the influence of each SNP through the network via edges to neighboring nodes until reaching a convergence threshold (Cowen et al., 2017). The rate of diffusion through the network is determined by the propagation factor, a , where $a=0$ results in no diffusion and $a=1$ yields full diffusion. The current analysis was performed with $a=0.7$ and

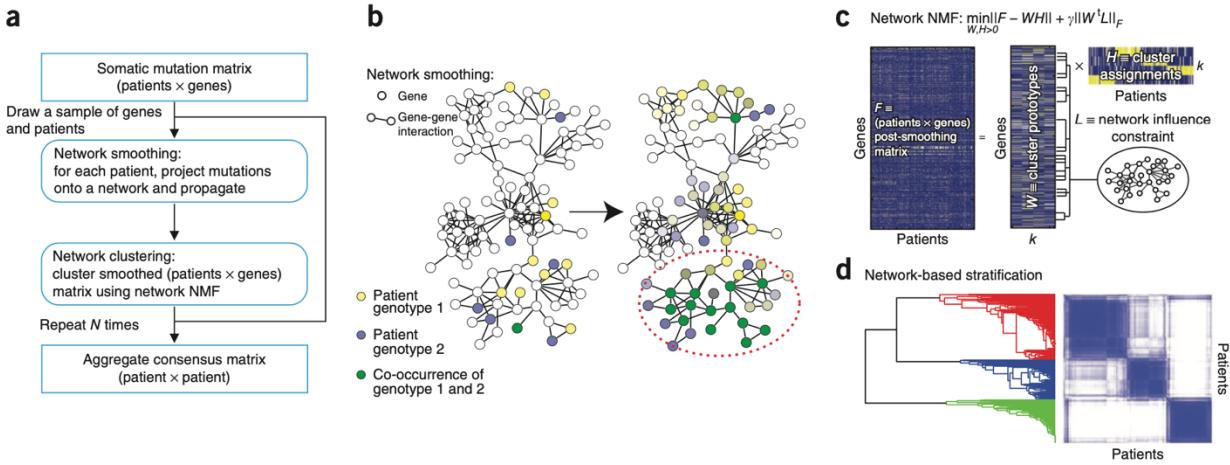


Figure 5. Overview of network-based stratification (NBS). **A** Flowchart of the approach. **B** Smoothing of patient somatic mutation profiles over a molecular interaction network. Mutated genes are shown in yellow (patient 1) and blue (patient 2) in the context of a gene interaction network. Following smoothing, the mutational activity of a gene is a continuous value reflected in the intensity of yellow or blue; genes with high scores in both patients appear in green. **C** Clustering mutation profiles using non-negative matrix factorization (NMF) regularized by a network. The input data matrix (F) is decomposed into the product of two matrices: one of subtype prototypes (W) and the other of assignments of each mutation profile to the prototype (H). The decomposition attempts to minimize the objective function shown, which includes a network influence constraint L on the subtype prototypes. The analysis is performed with k number of subtypes. **D** The final genetic subtypes are obtained from consensus assignments of each profile after 100 applications of the procedures in **B** and **C** to samples of the original data set. Darker blue color in the matrix represent higher co-clustering for pairs of subjects. Figure and text adapted from Hofree and colleagues (2013).

convergence threshold of 10e-3, both of which are default parameters. This resulted in a network-smoothed profile for each subject, where the value of each SNP indicated its network proximity to the associated gene on a continuous scale (0,1). Subsequently, network-smoothed patient profiles were stratified into subclusters using non-negative matrix factorization (NMF), which aims to identify a natural parts-based representation of the data allowing only additive combinations. The NBS method implemented in StratiPy applies a variant of NMF, Graph NMF (GNMF), which respect the network connectivity of the data. That is, decomposition takes into account the graph structure of the data space, aiming to find a representation space where data points connected in the graph are sufficiently close each other (Cai et al., 2008). The factorization procedure resulted in two non-negative matrices; a feature matrix, W , and a coefficients matrix, H . H has dimensions $S \times P$, representing the rank of each gene, P , for each subgroup, S . W has dimensions $N \times S$, representing the rank of each subject, N , for each subgroup, S , where the subject would be classified as a member

of the subgroup of which its rank is highest. To ensure robust clustering the factorization procedure was performed with bootstrapping in 100 permutations, each of which was run on a subset of 80% of the full sample for both subjects and genes, selected at random. This resulted in 100 W matrices. The subsequent analysis of this paper is based on the mean value for each subject across all 100 matrices for each subgroup, yielding three variables representing each subject's correspondence to three distinct genetic profiles. The entire NBS procedure was performed using default settings for the remaining parameters implemented in the StratiPy package (For further details please see Kim et al., 2018).

2.3.2. Model estimation

The analysis was performed in three parts. First, principal component analysis and confirmatory factor models were computed to determine appropriate factor structure of the data. Second, CFA, GGM, LNM and RNM models were estimated for two factor structures; the best fitting factor structure identified in the first step, and a three-factor structure defined according to the three categories of variables (clinical, cognitive, genetic). This yielded two CFA models, two LNM models, two RNM models and one GGM (as this model does not include factor structure). Lastly, all seven models were compared on out-of-sample fit indices and posterior model probability, to assess generalizability of the implied structure and sensitivity to the particular sample. All models were computed in the statistical software R (version 4.0.0) (R Core Team, 2020). Data was centered and scaled to reach model convergence, by subtracting the mean from each variable and dividing by the standard deviation. The three genetic variables obtained from NBS analysis were log-transformed prior to scaling to account for non-normality.

2.3.3. Confirmatory Factor Models (CFA)

Principal component analysis (PCA) was performed to explore the underlying factor structure of the data to be implemented in subsequent models. PCA aims to reduce the dimensionality of the data, by decomposing it into smaller components while preserving as much information as possible of the original data (Jaadi, 2021). The current PCA was performed with spectral decomposition, where components are identified based on covariance between variables. The resulting principal components represent linear combinations of the original variables that explain maximum amount of variance, mathematically expressed as eigenvectors with associated eigenvalues indicating how much information (explained variance) they contain (Jaadi, 2021). It is generally recommended that

components with eigenvalues above 1 are retained for further analysis (Hayton et al., 2004). PCA was performed using the R package *factorextra* (Kassambra and Mundt, 2017), and results suggested to include up to six components yielding 58% explained variance in total. However, a scree plot indicated that adding more than three components did not add noticeable explained variance. See appendix for eigenvalues and explained variance of each component (*Table A2*) and scree plot (*Figure A3*).

To further evaluate the optimal number of components in the dataset, we first performed Exploratory Factor Analysis (EFA) to investigate the factor loading structure for models with different number of factors, which were subsequently implemented in Confirmatory Factor Analysis (CFA) to inspect confirmatory fit. EFA estimates the underlying factor structure of a set of observed variables, identifying how much of the variance in each variable is related to each factor based on covariance between variables (Suhr, 2006). These are expressed as factor loadings and residual variance is modelled as measurement error. CFA is part of the general framework of Structural Equation Modeling (SEM) and addresses the confirmatory fit of a predefined factor loadings structure, testing the hypothesis that a causal relationship exists between the observed variable and the latent factor (Suhr, 2006). That is, the response vector y of P items, is assumed to be a causal linear effect of a set of M latent variables, η , and independent residuals, ε (Epskamp et al., 2017b):

$$\mathbf{y} = \boldsymbol{\Lambda}\boldsymbol{\eta} + \boldsymbol{\varepsilon}. \quad (1)$$

$\boldsymbol{\Lambda}$ represent a $P \times M$ matrix of factor loadings. With N samples of y , we can obtain the $N \times P$ matrix \mathbf{Y} where the i th row contains the realization y_i^T . The variance-covariance matrix, S , of \mathbf{Y} is then given by:

$$\mathbf{S} = \frac{1}{N-1} \mathbf{Y}^T \mathbf{Y}. \quad (2)$$

In CFA the model-implied variance-covariance structure, $\hat{\Sigma}$, is followingly defined as:

$$\hat{\Sigma} = \boldsymbol{\Lambda}\boldsymbol{\Psi}\boldsymbol{\Lambda}^T + \boldsymbol{\Theta}, \quad (3)$$

where ψ indicates variance of η and Θ represents variance of ε . $\hat{\Sigma}$ can then be estimated using maximum likelihood estimation (ML), and model fit is determined based on how well $\hat{\Sigma}$ approximates S . EFA was performed for a two-, three-, four- and five-factor model. EFA models were estimated using the *factanal()* R function with promax rotation and regression scores.

Subsequently, CFA models were estimated using the *lvm()* function of the *psychonetrics* R package (Epskamp et al., 2020b), where the factor structure, Λ , was defined as the factor loadings matrix from the corresponding EFA model (see the applied Λ for each of the four models in appendix, *table A3a*), and *variance* was used as identification parameter. Model fit was evaluated according to three statistical tests; root mean squared error approximation (RMSEA), Bayesian Information Criterion (BIC), and chi-square. RMSEA is an absolute fit index related to residuals in the model, assessing how far the hypothesized model is from a perfect model, where $\text{RMSEA} < 0.05$ is considered a good absolute fit (Kan et al., 2020). BIC is a relative model fit index, balancing model fit against model complexity where lower scores indicate better fit (Kan et al., 2020). Chi-square indicates difference between expected and observed covariance matrices. Lower chi-square values relative to number of degrees of freedom indicate better model fit (Kan et al., 2020). Results suggested that the three-factor and five-factor models had better fit (see fit indices in appendix, *Table A4*). As BIC values of these two models were close, these were transformed into posterior model probabilities to aid model selection. The posterior model probability, P_m , of each model, is given by:

$$P_m = \frac{\exp(BIC_m * -0.5)}{\sum(BIC_M)} \quad (4)$$

where m is the model and M is all models compared. Results indicated clearly that the five-factor model exhibited highest posterior probability (*Figure A4*).

The winning five-factor model was then compared to a three-factor model with loadings defined according to the three variable categories. That is, the seven clinical variables load on factor 1, the twelve cognitive variables load on factor 2, and the three genetic variables load on factor 3. Both models were then estimated on 50% of the data, and tested on the remaining 50% of the data, with Λ defined as the loading matrix obtained in estimation. Model comparison was performed according to absolute and relative fit indices and posterior model probability.

2.3.4. Gaussian Graphical Model (GGM)

The GGM is a pairwise Markov random field model, modelling pairwise partial correlation coefficients between the observed variables as a network, in which edges represent the weight of the

pairwise correlation between two variables, indicated by nodes, after controlling for all other variables. The network is defined as a symmetrical $p \times p$ weight matrix, Ω , where element ω_{jk} represents the edge weight between nodes j and k (Epskamp et al., 2017b):

$$\text{Cor} \left(y_j, y_k \mid \mathbf{y}^{-(j,k)} \right) = \omega_{jk} = \omega_{kj}. \quad (5)$$

The partial correlation coefficients are defined from the standardization of the precision matrix $\hat{\mathbf{K}}$, representing the inverse of the covariance matrix. That is, the k_{jk} elements of $\hat{\mathbf{K}}$ represents the partial correlation coefficients after conditioning on all other variables in range (0,1). Following, the GGM estimates the variance-covariance matrix $\hat{\Sigma}$ according to:

$$\hat{\Sigma} = \hat{\mathbf{K}}^{-1} = \Delta (\mathbf{I} - \Omega)^{-1} \Delta, \quad (6)$$

where Δ is a diagonal matrix whose elements, δ_{jj} is equal to $k_{jj}^{-\frac{1}{2}}$ and the weight matrix Ω has zeroes on the diagonal (Epskamp et al., 2017b). The GGM was estimated using the `ggm()` function of the *psychonetrics* package. Pairwise partial correlations of the variance-covariance matrix were estimated by optimizing the full-information maximum likelihood (FIML) fit function (Epskamp et al., 2020b), resulting in a saturated network, i.e. a fully connected network. To obtain a sparse network and control for inflation of false positives caused by the large number of parameters, step-down model search was applied to the network through pruning, fixing all non-significant edges to zero at significance threshold $\alpha=0.01$ and re-estimating the model (Epskamp et al., 2020b). Pruning was implemented with false discovery rate adjustment of multiple comparisons, controlling for the expected proportion of discoveries that are falsely rejected (Korthauer et al., 2019). Subsequently, stepwise model search was applied to find the optimal model based on minimization of the Bayesian Information Criterion (BIC) at significance threshold $\alpha=0.01$ (Epskamp et al., 2020b). The stepwise model search algorithm iteratively fits a proposed model, each time adding one of the non-significant edges (at significance threshold α) in the network. If the BIC of the new model is lower than the original model, the new model is retained as the “best” model, while higher BIC index results in removal of the edge. Thus, the procedure adds edges that improves the BIC of the model until it can no longer be improved. Simulation studies have found this model search procedure to perform better than other algorithms in retrieving the true network structure maintaining both high sensitivity and specificity (Epskamp et al., 2017a). The sparse GGM was first

estimated exploratively on 50% of the data. The resulting network structure of conditional dependencies, Ω , was extracted and fitted to the remaining 50% of the data to inspect confirmatory out-of-sample fit.

2.3.5. Latent Network Models (LNM)

The Latent Network Model is a generalization of the CFA framework where the factor structure is first estimated from the CFA decomposition in (3) and resulting variance-covariance matrix of latent variables is modelled as a GGM (Epskamp et al., 2017b):

$$\hat{\Sigma} = \Lambda \Delta_\Psi (\mathbf{I} - \Omega_\Psi)^{-1} \Delta_\Psi \Lambda^\top + \Theta. \quad (7)$$

Thus, partial correlation coefficients here represent edge weights between the latent factors. Two LNMs were estimated implementing the same five-factor and three-factor structure as for the CFA models. LNMs were computed using the *lnm()* function of the *psychonetrics* package. Pairwise correlations between latent variables were modeled as an undirected network (GGM) obtained with FIML estimation. Step-down model search was performed with pruning at significance threshold $\alpha=0.01$ with false discovery rate adjustment. Step-wise model search based on BIC minimization was performed at significance threshold $\alpha=0.01$ to identify the optimal model. This resulted in three matrices; Λ encodes the factor loadings, similar to the CFA models, Ω encodes the edge weights of latent factors, and Θ encodes the residual variance in each observed variable. The three- and five-factor LNMs were estimated on 50% of the data, and the resulting matrices were fitted in a confirmatory model on the remaining 50% of the data to compare out-of-sample fit.

2.3.6. Residual Network Models (RNM)

Residual network models are a generalization of the GGM allowing some of the covariance between variables to be explained by latent unobserved variables. Following decomposition of the variance-covariance matrix into a factor structure, the residuals, Θ , are modelled as a GGM. Thus, the variance-covariance matrix is defined as (Epskamp et al., 2017b):

$$\hat{\Sigma} = \Lambda (\mathbf{I} - \mathbf{B})^{-1} \Psi (\mathbf{I} - \mathbf{B})^{-1\top} \Lambda^\top + \Delta_\Theta (\mathbf{I} - \Omega_\Theta)^{-1} \Delta_\Theta. \quad (8)$$

Two RNMs were estimated implementing the previously described five-factor and three-factor latent structures. RNMs were computed using the *rnm()* function of the *psychonetrics* package. First the factor structure was estimated according to the CFA model (3), from which the residuals were modeled as a GGM by means of FIML estimation of conditional dependencies between the correlated errors (Epskamp et al., 2017b). Thus, the weighted edges in the resulting GGM can be understood as pairwise linear effects that are left after controlling for the latent structure. Models were pruned at $\alpha=0.01$ using false discovery rate adjustment, and subsequently optimized using stepwise model search with BIC minimization at significance threshold $\alpha=0.01$, similarly to previous models. Both models were estimated on 50% of the data, resulting in two matrices; Λ encodes the latent factor structure and Ω encodes edge weights of the residual network structure. These were then fitted to the remaining 50% of the data in a confirmatory model, allowing inspection of out-of-sample fit.

2.4. Model comparison

All models fitted to the test dataset were compared using the *comparison()* function of the *psychonetrics* package, which computes absolute and relative fit indices. Further, Bayesian posterior model probability was calculated for each of the models based on BIC fit indices, according to (4).

2.5. Visualization

All models were visualized using the *qgraph* R package (Epskamp et al., 2020a), which take a weight matrix as input. If the weight matrix is symmetric (as is the case for GGM structures) an undirected graph is plotted, while for asymmetric matrices (as is the case for factor structures) a directed graph is plotted. Variables are visualized as nodes and conditional dependencies or factor loadings between variables are visualized as *edges*. CFA and LNM models were visualized with the layout “tree”, the factor structure of the RNM was visualized using the layout “circle”, while the RNM network structure and the GGM were visualized with the “spring” layout. The “spring” layout uses the Fruchterman-Reingold algorithm (Fruchterman and Reingold, 1991), a forced-directed graph method aiming to minimize the number of overlapping nodes and crossing edges. While strongly connected nodes are generally positioned closer together, the algorithm additionally positions nodes so that edges have approximately the same length. Thus, the spatial arrangement in

the graph beyond general clustering structures cannot be interpreted (Jones et al., 2018). Thickness of the edges are determined by the edge weight, where stronger edges are thicker.

3. Results

3.1. Network based stratification

Network based stratification identified the correspondence between each individual's SNP profile and the pooled mutation profile for the three sub-profiles. Mean scores for each sub-profile across all subjects were 0.23 (SD=0.01), 0.07 (SD=0.09), and 0.09 (SD=0.03), respectively. N=444 subjects had highest score for profile 1, N=63 had highest score for profile 2, and no subjects had highest score for profile 3. This indicates that across all subjects, two general types of alterations could be identified on protein-protein interaction networks from genetic variants, where the vast majority of subjects (profile 1) exhibited similar alteration patterns. Thus, most of the genetic variance observed in the current sample appeared to affect similar functional pathways.

3.2. Three-factor versus five-factor model comparisons

All models were computed testing a data-derived five-factor latent structure (obtained from initial PCA and EFA) and a theory-derived three-factor latent structure. Comparison of out-of-sample fit indices of the two CFA models are in *Table 2*. Results indicated that the three-factor model had better relative fit than the five-factor model according to BIC index. However, while both models exhibited fairly good absolute fit, the five-factor model had slightly lower RMSEA.

Model	DF	BIC	RMSEA	ChiSq	ChiSq diff	DF diff	P value
Five-factor	188	13976.28	0.054	327.32			
Three-factor	206	13921.76	0.057	372.40	45.08	18	0.0004

Table 2. Confirmatory out-of-sample fit indices of five-factor CFA and three-factor CFA models

Comparison of out-of-sample test of LNM models are seen in *Table 3*. BIC indices indicated that the three-factor LNM had better fit than the five-factor LNM. Both models exhibited RMSEA values close to 0.05 indicating acceptable absolute fit, however with slightly lower RMSEA for the five-factor model.

Model	DF	BIC	RMSEA	ChiSq	ChiSq diff	DF diff	P value
Five-factor	188	13976.46	0.054	327.50			
Three-factor	206	13921.70	0.056	372.32	44.83	18	0.00044

Table 3. Confirmatory out-of-sample fit indices of five-factor LNM and three-factor LNM models

As the RNM analysis could not identify a model based on the defined five-factor latent structure, no comparison was made between RNM models.

3.3. Gaussian Graphical Model (GGM)

The GGM exhibited acceptable out-of-sample fit indicated by RMSEA of 0.061. The model showed three clear clusters in the network corresponding to the three variable categories (*Figure 6*). Most of the edges, including the strongest ones, were between two variables within the same cluster, indicating that components of the system are likely to interact directly with each other within measure domains. While the GGM suggested that symptoms, cognitive functions and genetic risk are generally independent from each other, a few negative cross-cluster connections were observed between the symptom *Attentional Deficits* and performance on the cognitive task *Visual Attention* and general *Academic Skills*. The negative correlation expresses that higher symptom scores is associated with lower cognitive performance scores. The GGM exhibited an almost flat degree distribution (appendix, *Figure A5*), with degrees distributed evenly across 2, 3, 4, 5 edges, and a bit lower for 6 edges, indicating no tendency of scale-free topology. The network had a mean edge weight of 0.049, and a mean clustering coefficient of 0.515 (see clustering coefficient of each node in appendix, *Figure A6*). Of the cognitive components, *Visual Attention* was the most central node in the system according to strength, and among the five most central according to expected influence. Of the clinical components *Avolition* was the most central node in the system according to both strength and expected influence (*Figure 10*). While the three genetic components were strongly connected to each other, they formed a cluster completely independent of the remaining components in the system (see adjacency matrix on which the graph is based in appendix, *Table A5*).

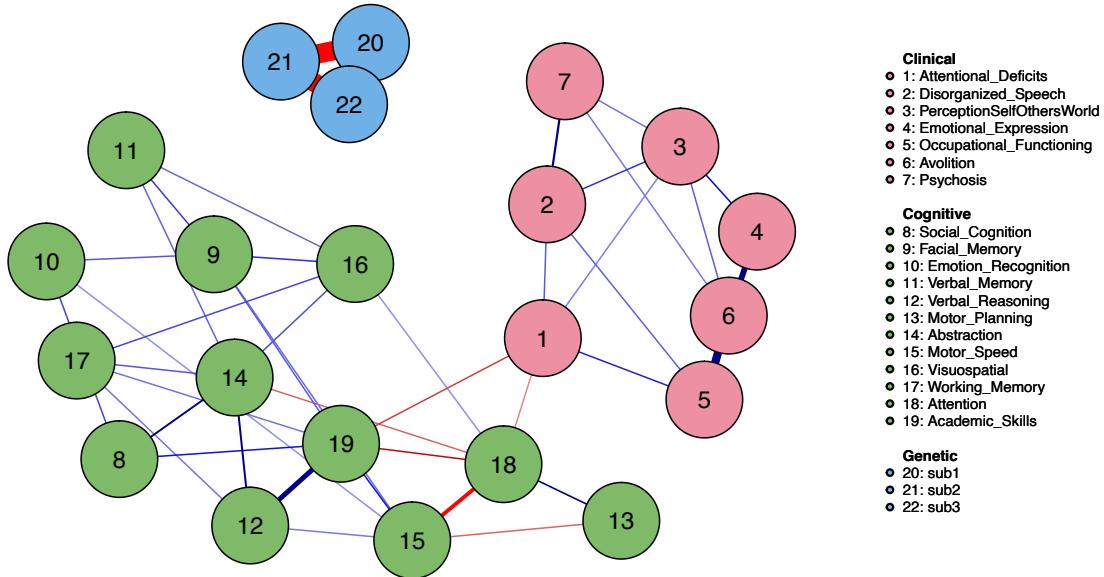


Figure 6. Gaussian Graphical Model (GGM). Nodes represent variables. Edges represent partial correlations between nodes. Thickness of edges correspond to the weight of the partial correlations. Blue edges indicate positive partial correlations, red edges indicate negative partial correlations.

3.4. CFA model

Results are reported for the three-factor CFA model which exhibited better fit. The model indicated that all variables loaded on the associated latent factor with varying degrees (*Figure 7*). Of the clinical components *Occupational Functioning* and *Avolition* loaded most strongly on the latent factor. Of the cognitive components *Verbal Ability* and *Academic Skills* loaded most strongly on the latent factor, while *Motor Functioning* and *Attention* loaded negatively on the latent factor. Genetic profile 1 loaded most strongly on the latent factor exhibiting a negative relationship, in contrast to the two remaining genetic profiles (see factor loadings of the CFA model in appendix, *Table A6*).

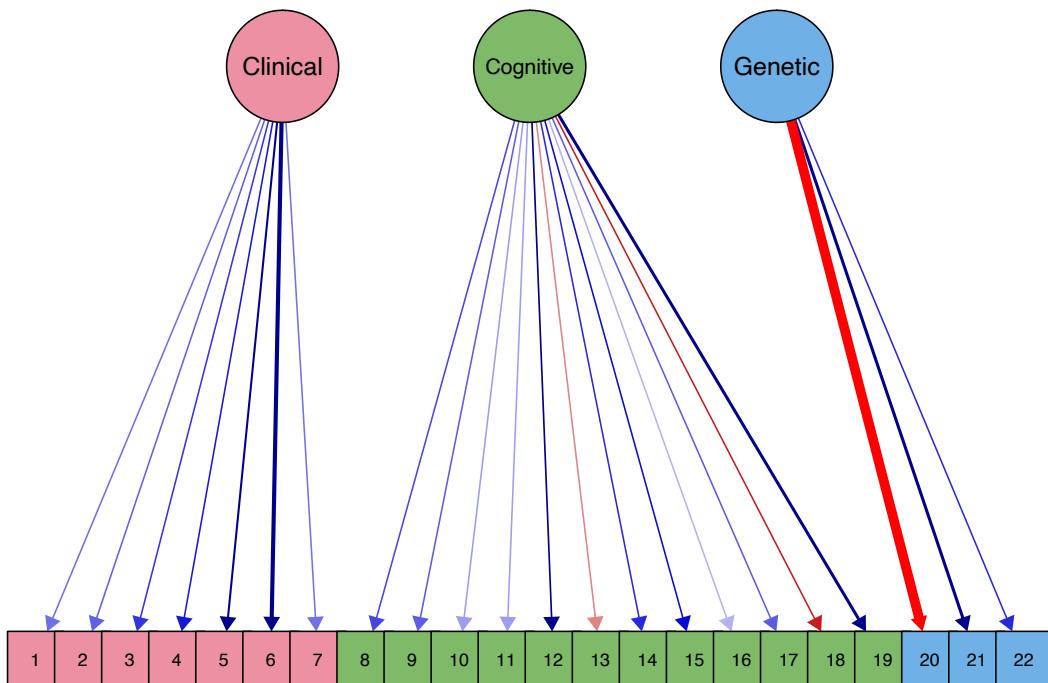


Figure 7. Confirmatory Factor Analysis (CFA). Circular nodes represent latent factors. Square nodes represent observed variables. Edges represent factor loadings. Thickness of edges correspond to the weight of the factor loading. Blue edges indicate positive partial correlations, red edges indicate negative partial correlations.

3.5. Latent Network Model (LNM)

The Latent Network Model exhibited acceptable absolute fit with RMSEA of 0.056 (*Figure 8*).

Motor planning and *attention deficits* loaded negatively on the respective factor, suggesting that the common source of variance exerts a distinct influence on these compared to the remaining cognitive functions. A similar pattern was observed for genetic profile 1, which loaded negatively on the latent factor in contrast to profile 2 and 3. Most importantly, the LNM identified no partial correlations between the three latent factors, suggesting that they are conditionally independent (see factor loadings, factor correlations, and residual errors in appendix, *Table A7-9*).

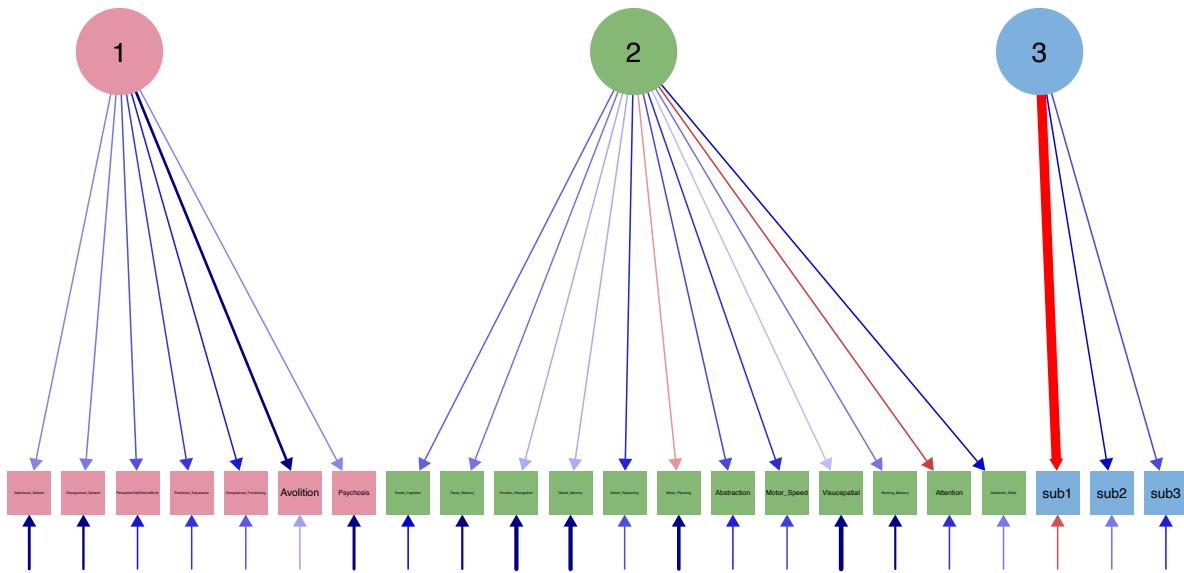


Figure 8. Latent Network Model (LNM). Circular nodes represent latent factors. Square nodes represent observed variables. Edges represent factor loadings. Thickness of edges correspond to the weight of the factor loading. Blue edges indicate positive partial correlations, red edges indicate negative partial correlations. Edges below squared nodes (short) represent residual errors, with thicker edges indicating larger errors.

3.6. Residual Network Model (RNM)

The RNM exhibited good absolute fit with RMSEA of 0.044. The model identified partial correlations among components not accounted for by a latent factor (*Figure 9*). Most of the edges occurred within domains and observed clusters generally represented either clinical, cognitive or genetic components. Cognitive components were separated in two clusters, one of which encompassed the functions *Motor Planning*, *Motor Speed* and *Attention*. The cognitive function *Verbal Ability* appeared conditionally independent of all other components in the network when accounting for a shared latent factor. *Academic Skills* was likewise conditionally independent of the remaining cognitive variables when taking into account the shared latent factor but remained connected to the clinical component *Attentional Deficits*. The symptom *Avolition* was isolated from all other components in the network after accounting for the shared latent factor. Residual partial correlation matrices of the RNM can be found in appendix (appendix, *Table A10*). Of the clinical

Results: Residual Network Model (RNM)

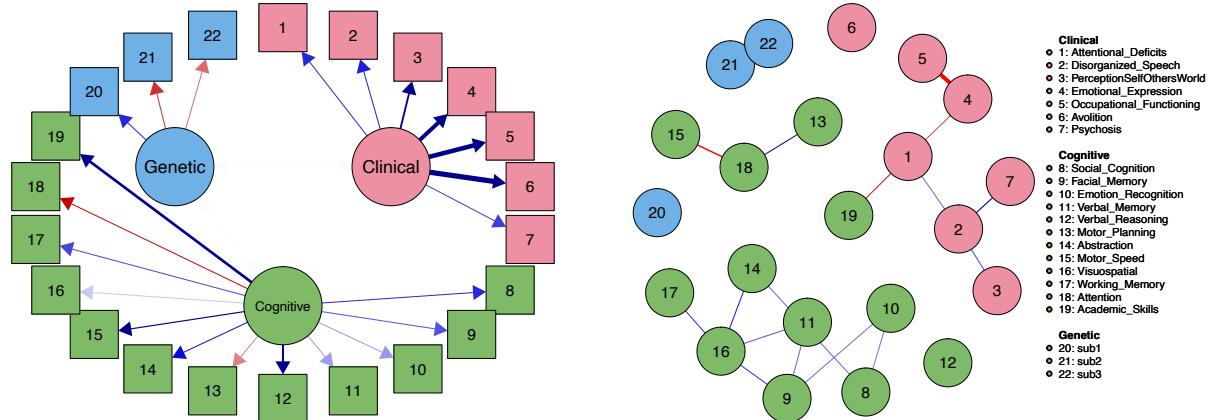


Figure 9. Residual Network Model (RNM). Left: factor structure. Right: residual network. Blue edges indicate positive partial correlations, red edges indicate negative partial correlations.

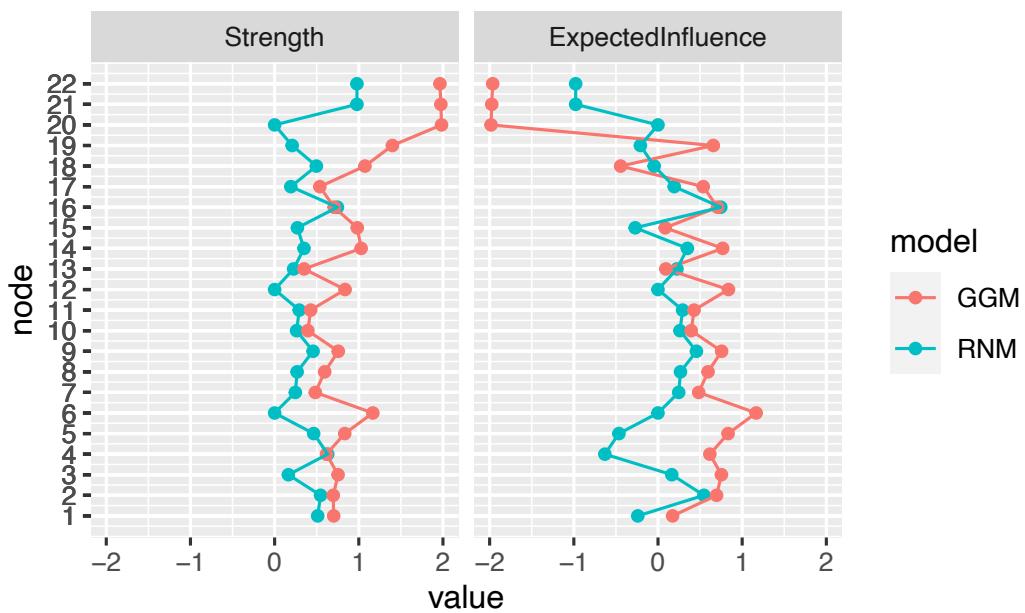


Figure 10. Centrality indices for GGM and RNM networks. X-axis indicates nodes. Y-axis indicate centrality index.

components *Emotional Expression* exhibited highest centrality according to strength, while *Disorganized Speech* exhibited highest expected influence on the system (*Figure 10*). The RNM exhibited a positive-skewed degree distribution, although fewer nodes had degree of 1 than 2 (appendix, *Figure A5*). The network had a mean edge weight of -0.002, indicating low connectivity. The fact that the mean connectivity was negative although the majority of edges were positive, indicates that negative edges were markedly stronger than positive edges in general. The RNM had a mean clustering coefficient of 0.668 (see individual clustering coefficients of each node in appendix, *Figure A6*). The most central of the cognitive components was *Visuospatial Learning and Memory* according to both strength and expected influence. Importantly, the RNM showed that many of the component pairs observed in the GGM, were rendered independent of each other after accounting for common sources of variances. For instance, the edge between *Attentional Deficits* (cognitive) and *Attention* (clinical) disappeared when conditioning on latent factors. Similarly, while the GGM found strong connections of *Verbal Ability* to several other cognitive domains, it appeared conditionally independent of all other cognitive variables when accounting for the shared variance in the RNM.

3.7. Model comparisons

Comparison of out-of-sample fit indices of the best performing three-factor CFA, LNM, RNM and a GGM indicated that the RNM had best relative fit of all models according to BIC, as well as best absolute fit according to RMSEA scores (*Table 4*). The RNM was the only model with RMSEA <0.05 considered good absolute fit. The CFA and LNM had very similar fit indices and both models exhibited moderate absolute fit. The GGM had poor absolute fit and performed worst of all models. Further comparison of posterior model probabilities supported the conclusion that the RNM was the more likely model given the data (*Figure 11*).

Model	DF	BIC	RMSEA	ChiSq	ChiSq diff	DF diff	P value
RNM	192	13911.02	0.044	284.20			
GGM	199	13975.47	0.061	387.38	103.18	7	<0.0001
CFA	206	13921.76	0.057	372.40	14.98	7	0.036
LNM	206	13921.70	0.056	372.34	0.063	0	<0.0001

Table 4. Comparison of fit indices for three-factor CFA, LNM and RNM, and GGM

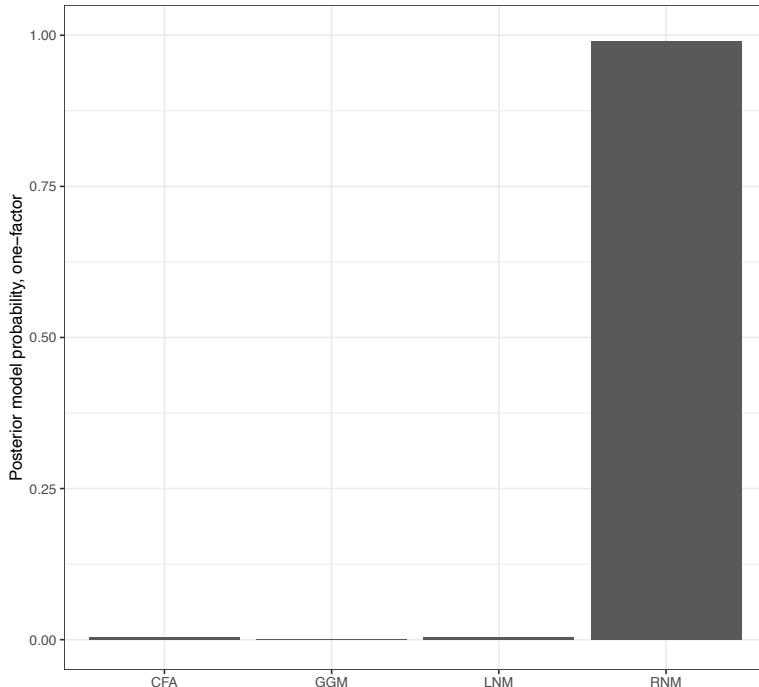


Figure 12. Posterior model probabilities of three-factor CFA, LNM and RNM, and GGM.

4. Discussion

The current study investigated the covariance structure of psychometric and genetic measures of schizophrenia, assessing the extent to which co-occurrence of items can be attributed to unobserved common sources of variance or to direct pairwise interactions between individual items. Comparing the fit of four models of covariance and inspecting the observed pairwise relationships between items in the best model, the study aimed to disentangle the complex causal pathways potentially driving or contributing to pathological development in schizophrenia. Results indicated that observed covariance between components arise in part from shared underlying factors, and partly from direct pairwise interactions. While genetic, clinical and cognitive components mainly organized in separate groups, attention-related mechanisms appeared to connect clinical and cognitive components. The following sections discuss the covariance structure and relationships among components suggested by the best model, addressing what these imply statistically and conceptually. Further, the clinical implications hereof are discussed and potential reasons for the suggested distinction between the three variable categories are addressed. Important limitations of

the analysis are highlighted, including generalizability of between-subject networks to individuals, statistical consequences of a limited sample in terms of size and population, the potential influence of age differences, violations of normality, potential limitations in the representation of genetic risk profiles, and the general robustness of the implemented NBS procedure. Subsequently, the general utility of network models in the case of schizophrenia is discussed, focusing on what the constituent elements of the network actually represent, the consequences and implications of the chosen network components, and the causal interpretations associated with different types of network structures. Lastly, further directions are discussed that may provide more details on the nature of the pathways observed in the current results, including temporal networks for causal inference, variability networks to assess differences and similarities between individuals, network-based early warning-signals as an index of pathological risk, and potential moderator effects of genetic variants and age.

Results showed that the RNM exhibited best out-of-sample fit, suggesting that psychometric measures of the disorder are best understood as arising from a combination of common latent causes, where multiple symptoms and cognitive deficits share underlying pathways, and from direct interactions between psychometric features. This suggests that symptoms and cognitive deficits cannot be treated as mere indicators of an underlying disease entity, but must, to a greater extent, be considered as constitutive elements of schizophrenia with potential causal roles in pathological development. The model indicated that cognitive components were mostly associated with other cognitive components, symptoms with symptoms, and genetic components with genetic components. While genetic components were completely isolated, the model suggested that cognition and clinical symptoms are associated through attention-related mechanisms which was directly associated with general academic ability and symptoms on the spectrum of both negative (*Emotional expression, Occupational functioning*) and positive (*Disorganized speech, Psychosis*) symptoms. Further, comparison of the RNM to the GGM showed that conditioning on latent sources of variance accounted for most of the covariance between pairs of items in the GGM, as most edges disappeared in the RNM. The topology of the RNM network indicated that the resulting interactions between items tend to organize in a small-world structure. Although the RNM generally exhibited weaker global connectivity than the GGM, it had a larger clustering coefficient characteristic of small-world topology, suggesting that information spreads efficiently among components in the systems. Under the assumption that edges are causal, this implies that if some

symptoms increase or decrease, this is likely to cause changes in other symptoms within the same cluster. When clusters are connected by a few central components, this will efficiently lead to perturbations of the entire network. Importantly, the current model suggested that cognitive dysfunction will efficiently spread among other cognitive abilities, and clinical symptoms to other symptoms. However, alterations in each of these will only affect the other in the presence of attentional deficits. The high clustering tendency in the model makes the network resilient to random perturbations such as the removal of individual nodes. That is, remediation of single symptoms, for instance, are unlikely to have large effects on the remaining items. Thus, results indicate that the network of psychometric features in schizophrenia may be optimally structured for causal cascades among symptoms and cognitive deficits, which might play an important role in the development of the disorder. Further, attention-related mechanisms appear to play a central role in these dynamics, comprising a unique link between both clinical and cognitive components, and symptoms of the negative and positive spectrum.

Results additionally showed that the latent factor structure of psychometric and genetic components was best represented by a three-factor model where items within the same response category (cognitive, clinical, or genetic) loaded on a common factor. This was supported both by exploratory factor analysis in which only a few cross-loadings were identified (appendix, *Figure A3a*), and by confirmatory factor analysis where a strict domain-specific factor structure performed best in out-of-sample tests. Thus, the model identified more shared variance between items of the same category than across categories. This could indicate that symptoms are more likely to share causal pathways with other symptoms than with cognitive functions or genetic effects, and vice versa. However, this could also be explained by semantic overlap between measures of the same assessment battery/scale. That is, some of the variance of individual measures may result from the nature of the specific paradigm used to assess these, where clinical items for instance are evaluated based on a structured verbal interview, while cognitive items are measured using practical tasks. This is supported by the observation that the cognitive item *Attentional Deficits* did not load on the same factor as the clinical item *Attention Problems*. Since the two represent the same general functioning, merely evaluated in two different ways, we would expect them to share underlying pathways and hence load on the same latent dimension. Thus, the resulting factor structure does not necessarily imply a strict causal explanation of the shared variance within response categories.

Modeling these structures, however, allows the assessment of relationships between variables that cannot be attributed to latent sources of variance, regardless of what these sources represent.

The RNM model indicated that most of the covariance between response items could be attributed to shared latent factors. However, even when accounting for these some of the residual variance qualified as direct pairwise interactions between items in a network structure. These generally organized in three clusters. One included all clinical items but *Avolition*, which was completely independent of all other items. The clinical cluster further included one cognitive item; *Academic Skills* representing wide range academic performance. This item was connected to the clinical items via the symptom of *Attentional Deficits*. *Attentional Deficits* further connected two subclusters of symptoms, and thus appear to play a central role in the potential causal pathways between symptoms and cognition. While *Academic skills* was independent of all other cognitive components, this node loaded most strongly on the latent cognitive factor. Thus, although the model suggested no direct interaction between this and other cognitive functions, these may be strongly associated through unobserved latent factors. Hence, it is likely that any influence on the remaining cognitive components will also affect that of *Academic Skills*, which in turn could influence clinical items through attention-related mechanisms. Despite low strength centrality of the clinical item *Attention*, indicating weak connections to other nodes, this item appeared to have a strong role in the structure of the network, by linking most of the remaining clinical items. That is, if components are causally influencing each other, this influence must pass through *Attention* to spread to peripheral items of where the change originated. This finding support previous evidence, suggesting that attention deficits play a central role in development and presentation of schizophrenia (Gold et al., 2018; Gur et al., 2007), and may serve as a an endophenotype of the disorder, mediating genotypic and phenotypic effects (Irani et al., 2012). Cognitive items organized in two clusters, where one generally represented motor functions and attention, and one represented memory-, abstraction-, and social-related cognition. Most cognitive items were found to interact positively, such that alterations in one increases the likelihood of alterations in another. Given the undirected network structure, direction of interaction between connected items cannot be interpreted. Surprisingly, the two cognitive items *Attention* and *Motor Speed* exhibited a negative interaction, implying that higher attention abilities are associated with poorer motor speed, or vice versa, which seems counterintuitive. One possible explanation for this observation may be that the edge is spuriously induced by a collider effect, i.e., they both have a causal effect on a third unmodelled variable.

Depressive symptoms (such as blunted affect) could potentially represent targets of such a collider effect, as they have shown to be strongly associated with attention- and motor-deficits (Tabarés-Seisdedos et al., 2003), and generally exhibit high comorbidity rates with symptoms of psychosis (Coentre et al., 2017). Alternatively, this could indicate a speed-accuracy tradeoff, as attention was measured according to correct responses while motor speed was assessed with reaction time.

Although the two measures were derived from two separate tasks, they may collectively represent an impulsivity trait, which has been found to be associated with the tendency to trade off accuracy for speed, or vice versa (Mulder et al., 2010). A particularly interesting finding is that some edges emerged in the RNM network which were not present in the GGM, for instance between *Emotional Expression – Occupational Functioning* and *Emotional Expression - Attentional Deficits*. This may result from the GGM forcing the covariance structure into a model of pairwise interactions, in cases where a significant portion of the shared variance arises from common latent sources. Pairs of nodes may thus be rendered conditionally independent when conditioning on other nodes (such as *Avolition* in this case), whose covariance in fact was largely explained by latent factors. Hence, these results highlight the importance of conditioning on latent variables when modelling psychometric networks, as the network structure can be largely misinterpreted if some of the covariance among items arises from common unmodelled sources.

The observation that direct interactions remain between some psychometric features of schizophrenia after accounting for common sources of variance, has important clinical implications both in terms of treatment and prevention. Such evidence suggests a causal role of symptoms and cognitive functions themselves in pathological development, where down-stream effects from one deficit to another can cause a cascade of deficits and symptoms. This implies that even if we can identify and treat underlying pathologies or genetic risk loci, pathological development may still arise from direct causal pathways between individual symptoms. Further, identifying the network structure of these relationships provides information about which symptoms, or other features, should be targeted in order to reduce severity of as many symptoms as possible. Prevention programs may target highly central symptoms or cognitive domains which have largest potential to causally influence other components in the network. Hence, both treatment and prevention strategies can exploit such down-stream effects and be designed according to the network structure in order to reduce global connectivity patterns and the risk of pathological self-reinforcing loops of symptom activation. Further, network structures of pairwise interactions can highlight differences in

causal pathways of individual symptoms which might improve treatment efforts. For instance, several studies have provided evidence that cognitive behavioral therapy has a positive effect on some symptoms of psychosis (Engen et al., 2019; Seidman et al., 2017), while other studies have reported no effect on symptom remission (Bell et al., 2006). Further, a network model on mechanisms of treatment in psychotherapy showed that different treatment measures (CBT and MCT) could be used to target different symptoms (Johnson and Hoffart, 2018). Evidence from symptom networks in PTSD similarly showed that individual symptoms were related differently to measures of behavior, neuroimaging and genetics. Hence, very few treatment strategies are likely to have similar effects, or any effect at all, on all symptoms. Investigating the network structure of symptoms and other disease-associated variables, might aid development of more efficient treatment strategies where symptoms can be targeted individually according to their causal relationship with other symptoms, cognitive domains, or other identified components.

The RNM identified no associations between the three measures of genetic variance and any clinical or cognitive indices. This is a surprising finding in light of the well-established heritability of schizophrenia, and previous network studies that identified a number of interaction relationships between PGRS and symptoms of psychosis (Isvoraru et al., 2020b). One explanation of this may be that the study was based on a general population sample of adolescents. Psychosis typically has its onset in late adolescence and the current clinical items represent prodromal symptoms. Hence, it is possible that psychometric symptoms have not yet manifested to a large enough degree to detect an association with genetic variance. Previous network studies have shown increased connectivity between psychosis-related components following disease onset (Rooijen et al., 2018), supporting this interpretation. Second, a general population sample will exhibit a very broad spectrum of symptom profiles, which could potentially weaken the predictive power of genetic variance (Isvoraru et al., 2020b). Despite such potential statistical challenges associated with using subclinical measures of psychosis, it is important to compute network models on samples like the PNC for two main reasons. Schizophrenia and other disorders on the psychosis-spectrum have been well established as developmental disorders (Seidman and Mirsky, 2017), and evidence suggests that patients exhibit subthreshold symptoms as early as 7-8 years prior to psychosis-onset (Schultze-Lutter et al., 2010). Further, severity and persistency of these subthreshold symptoms have predictive value of the risk of developing manifest psychosis episodes (Rosengard et al., 2019), and findings indicate that differences in the developmental courses of psychosis spectrum symptoms can

be detected early in premorbid youth samples (Calkins et al., 2017). Many youths exhibit early psychotic-like experiences but never develops a clinical disorder, while most of the youths who later develop not only psychosis, but also depression and anxiety, exhibit psychotic-like experiences early in development (Calkins et al., 2017). Hence, subclinical symptoms early in development contains crucial information about psychopathological risk and network models can help highlight how these may act in concert in different manners causing various trajectories of remediation or increased pathology. Second, the traditional case-control approach to mental disorders, that studies differences between a group of healthy control subjects and a group of patients, has been challenged in recent years as it fails to account for the significant heterogeneity in symptom profiles of patients (Wolfers et al., 2018). This approach assumes that both cases and controls are well-defined and clearly distinguishable groups, while most evidence shows that symptoms of schizophrenia occur on a spectrum across the population (Marquand et al., 2016). Further, since mental disorders are diagnosed based on symptoms, analyzing differences between cases and controls poses the risk of Berkson's bias. That is, when symptom networks are estimated on groups in the data defined based on a function of the analyzed variables (i.e., the symptoms), this corresponds to conditioning on a collider (De Ron et al., 2019). Hence, modeling symptom networks on a general population allows studying the disorder as a spectrum of symptom severity and avoid spurious edges induced by Berkson's bias. The weak connectivity patterns observed in current results may indicate that subthreshold symptoms and other disease-related components are only minimally causally related. However, this may also be explained by inadequate sample size. It is plausible that identifying partial correlations between symptoms and other components in a sample where many cases exhibit no or very weak symptoms, requires larger sample sizes. Further investigation is needed to determine which of the two explanations apply here. A potential solution to overcome Berkson's bias in network models without using a general population sample, may be to stratify subjects into groups based on genetic risk indices and compare network structures between groups. Costantini and colleagues (2019) recently developed a method, Fused Graphical LASSO, for the simultaneous estimation of networks in different groups, allowing quantification of differences and similarities in the connectivity patterns and system dynamics between networks. This will avoid modeling the very measures from which groups are defined. However, such an approach will not enable identification of differential effects of genetic variance on individual psychometric components.

4.1. Limitations and methodological considerations

A general limitation of network models estimated across subjects is that these may not generalize to networks of individuals. Given the established heterogeneity in symptom manifestation within schizophrenia, it is plausible that individuals will exhibit highly different network structures. It is also possible that heterogeneity manifest in connectivity strengths between symptoms and not in the general structure. It is currently unknown how much group-based networks overlap with networks at the individual level (van Rooijen et al., 2018). While between-subject networks (as the current model) investigate dynamics involving the stable component of individual differences across subjects, within-subject networks can be computed to assess the dynamics of individual differences within each subject (transient variability around the individual's mean) (Costantini et al., 2019). It is important for further studies to compare between-subjects to within-subject networks, to establish how group-level dynamics relate to within-subject dynamics. The current results represent an averaged symptom network and inferences on causal relationship on the basis hereof thus relate to general tendencies at group level. Interpretations on the intra-individual differences based on the current results should be made with caution. Further, in the case of schizophrenia where some clinical symptoms (such as hallucinations) are highly specific and severe, the extent to which networks based on a general population will generalize to a clinical population is questionable. Thus, the current results are informative regarding early premorbid developmental patterns on the psychosis spectrum, however, it is uncertain how well these dynamics describe a clinical group of patients with schizophrenia. Investigating how developmental pre-onset dynamics reflect post-onset dynamics between clinical and cognitive components is an important future prospect of psychometric network models. This could highlight potential differences in the causal pathways responsible for development of various symptoms and those responsible for maintaining pathological symptom patterns.

The network models of the current study are limited by a relatively small sample size. The high-dimensional nature of the GGM structure involves estimation of significant amounts of parameters which increases requirements for the sample size. The estimated weight matrix of a GGM contains $P(P-1)/2$ parameters, where P is the number of nodes (Epskamp et al., 2017a), yielding 231 parameters of the current models (253 parameters for the RNM including factor loadings). It has been argued that three subjects per parameter is a good rule of thumb (Fried and Cramer, 2017), however simulation studies on network models have indicated that an even larger ratio may be

required to ensure stability (Epskamp et al., 2018). Hence, the current sample of 517 subjects is likely too small to retain adequate power. In attempts to reduce the consequences of this networks were estimated using a conservative approach assuming a sparse network structure (attempts to account for the covariance structure with as few edges as possible relative to nodes), such that evidence of a partial correlation must be strong for an edge to be accepted. However, this is unlikely to account for the lack of power entirely, and in cases where the true data-generating network is indeed dense, this procedure will contaminate the resulting structure and interpretations. The consequences of this can be assessed with stability and robustness checks of the identified network structure, usually implemented with non-parametric bootstrapping addressing sampling variability in results, and case-dropping bootstrapping assessing sample size sensitivity (Epskamp et al., 2018). These methods, however, have not yet been implemented for *psychonetrics* objects (Epskamp et al., 2020b) and more work is needed to establish robustness of the current parameter estimates. Confirmatory out-of-sample model fit was computed to obtain some indication of generalizability, and results showed good absolute out-of-sample fit for the RNM ($\text{RMSEA} < 0.05$) (Kan et al., 2020), suggesting that the model retained acceptable robustness despite low sample size.

Further concerns arise from the ordinal nature of the clinical variables, which, due to the non-clinical sample, were highly positively skewed (most subjects scored 0) violating the assumption of Gaussian normality. It is possible that these variables did not contain adequate variance to detect stable pairwise correlations with other items. Likewise, the genetic variables violated this assumption slightly, despite log-transformation, which may have induced problems in estimation of the weight matrix. Using a larger sample size may alleviate the consequences of skewed ordinal variables. Additionally, ordinal variables challenge ML estimation, as this assumes normal distribution of observed variables. Further analysis may alleviate this problem by implementing weighted least square (WLS) estimation, which assumes a *latent* normal distribution underlying each observed variable and have proven to perform better than ML on ordinal variables (Li, 2016). This method, however, requires very large samples and could not be implemented in the current study.

It is important to note that the current result do not account for age differences. Cognitive function is highly associated with age (Keating, 2004), and onset of distinct clinical symptoms typically occur at different ages (Häfner, 2000). Given the large age span in the current sample, results are

limited in that they assume a constant covariance structure across age. This implies that identified factor loadings and partial correlations represent the average associations across all age groups. However, symptoms of psychosis, for instance, typically have late onset relative to other symptoms (such as depressive and negative symptoms (Häfner, 2000)), and strong connections between this node and other symptoms may be neutralized by the fact that this relationship cannot be detected in most of the sample. In this case results may falsely suggest no relationship, when in fact this observation results from the fact that *Psychosis* has not yet manifested in most individuals explained by their age. Further, some of the variation in cognitive performance may arise from age differences rather than actual deficits. In order to address the developmental differences in the identified dynamics, it is important for further studies to account for age effects. This may be implemented either by age-correcting variables prior to analysis, by modeling age directly in the network as a node, or by assessing the network structure individually for different age spans.

The isolation of genetic nodes observed in the present networks could indicate that no causal relationships can be identified between genetic variants and psychometric components in the current sample. However, it could also indicate that the implemented measures inadequately capture genetic risk profiles. There are several potential reasons for this. First, the NBS method requires a predefined number of subgroups into which subjects are stratified. The choice of three subtypes of genetic variation in the present study was rather arbitrary, as prior research on the integration of SNPs with PPI networks in schizophrenia is very limited. Some indication hereof come from Gilman and colleagues (2012), who developed the algorithm NETBAG+, which searches for homogenous clusters of genes affected by disease-associated genetic variations and identifies functional molecular networks associated with each cluster. Based on GWAS-derived single-nucleotide variants (SNVs) and copy number variants (CNVs) the study identified two cohesive gene clusters in patients with schizophrenia. While the NETBAG+ algorithm is not directly comparable to NBS, in that it is not based on PPI networks, this indicated that a small number of clusters may be expected in schizophrenia-related SNPs. Three was chosen to allow the possibility of slightly more heterogeneity in the current sample. The fact that no subjects were assigned to profile three (no subjects with highest value hereof) could indicate that genetic profiles generally divided in two types and that stratification into two sub-profiles might be sufficient. However, it is possible that an inappropriate number of subgroups may have polluted the results. A second reason for the potential inadequacy of the implemented genetic variables could be that NBS was based on

too few SNPs. While PGRS is typically calculated from hundreds of thousand SNPs (Lewis and Vassos, 2020), the current NBS procedure was based on only 10.000 SNPs which contributed most to the calculation of a PGRS. It is possible that these did not contain enough information to sufficiently distinguish subgroups of genetic variance, hence reducing the predictive value of resulting profiles. Further studies are needed to establish whether larger SNP samples can improve stratification into more robust and clinically relevant subgroups.

While the NBS procedure has shown stable identification of genetic subgroups based on PPI networks and genetic mutational profiles in cancer (Hofree et al., 2013), this is the first study to implement the method on schizophrenia-associated SNPs. One important difference between the two approaches is that the original work on cancer was based on binary mutation profiles containing digital signals (0 or 1), indicating whether a mutation is present or not on a given gene. Contrary, SNPs represent analog signals (0, 0.5 or 1). Digital systems have generally proven to yield higher accuracy and reproducibility and be more resilient to noise than analog signals (Hofree et al., 2013). It is therefore unknown whether the current approach can be expected to exhibit equally robust results. Lastly, methods relying on PPI networks are generally limited by the lack of information inherent in currently available networks. Protein interactions are not necessarily involved in all biological interactions (Hormozdiari et al., 2015) and important functional associations between genes may therefore be missing. In addition, available PPI networks contain false positive interactions and are largely incomplete with many missing edges (Leiserson et al., 2013) which reduces sensitivity of network analysis. Despite limitations of the NBS procedure there is significant evidence showing that the stratification of genetic profiles based on molecular interaction patterns can provide important information about the biological mechanisms mediating genetic risk in psychopathology, representing a promising method to account for the observed genotypic heterogeneity observed in patients with schizophrenia. Several studies have investigated the functional role of the molecular networks associated with each profile and provided insights into the distinct developmental trajectories of each in relation to clinical and cognitive outcomes. Results from the previously described NETBAG+ algorithm on schizophrenia-associated variants showed that genes in one cluster were functionally related to important neurodevelopmental processes, including cell migration, axon guidance, and neuron projection development, while genes in the second cluster were mainly involved in chromosomal organization (Gilman et al., 2012). Further, it has been reported that autism spectrum disorder, epilepsy and schizophrenia show significant

overlap in the molecular networks affected by disease-associated variants, despite highly different disorder manifestations (Hormozdiari et al., 2013). Hence, the assessment of genetic risk of various disorders may benefit greatly from focusing on the affected molecular networks and signaling pathways, rather than the genetic variations themselves, and some have argued that biological networks may serve as efficient targets of therapy (Hormozdiari et al., 2013). The NBS procedure have shown very good results in this regard, and further work should aim to establish out-of-sample generalizability of the currently identified sub-profiles and evaluate the general adequacy of the NBS procedure on SNP profiles in schizophrenia.

4.2. General discussion

4.2.1. Constituent elements of the networks

The current implementation of an RNM allowed the investigation of network dynamics between symptoms and cognitive deficits while circumventing the assumption of no latent variables. However, the RNM further relies strongly on the assumption of no missing variables in the model. Given the complexity of mental disorders it is highly implausible that all relevant causal factors are included in these models. However, a network including all implicated variables would rapidly render itself uninterpretable and uninformative. This constitutes a general challenge in the psychometric network approach, as researchers must define the boundaries of the system in terms of the chosen variables. The model can include virtually all factors hypothesized to be implicated in the etiology of schizophrenia, and what is included must be determined according to the research questions and interpretations made accordingly. Some networks may inspect how structural differences in the brain are related to symptoms, while others could explore the interaction patterns of socio-economic variables and symptoms. While network theory of mental disorders explains a mental disorder as interactions between constituent components of the system, the models we estimate cannot sufficiently describe such a system in its entirety. Network models provide insights into the complex interaction patterns of variables of *interest*, and the constituent elements in our models, and what they represent, define what sort of inferences can be made. There are several important considerations to be made in this regard. First, a major advantage of network models is that they allow investigations of *symptoms* rather than *syndromes*. However, symptoms included in the models tend to be based on the diagnostic categories defined in manuals as the DSM-IV or ICD-10, with which subjects have been assessed. This poses a major challenge, and the validity of diagnostic categories has been largely questioned in recent years (Fried and Cramer, 2017). For

depression, 1030 unique symptom profiles have been identified in 3703 diagnosed individuals (Fried and Nesse, 2015), and more than 636.000 symptom combinations qualify for a PTSD diagnosis (Galatzer-Levy and Bryant, 2013). Further, a significant portion of symptoms occur in multiple diagnoses (for example, GAD and MDD share four diagnostic symptoms (Zbozinek et al., 2012), PTSD symptoms overlap significantly with symptoms of MDD (Afzali et al., 2017), and schizophrenia and autism overlap substantially in social impairments (Morison et al., 2017)). Comorbidity of disorders is the rule rather than the exception (Caspi et al., 2018). Such findings indicate that what constitutes individual disorders is largely unresolved and defining network models on the basis hereof induces questionable preconceptions about the causal pathways underlying the disorders. Including symptoms and other components in the models beyond what is defined in the diagnostic categories may help alleviate this problem allowing for a broader representation of mental disorders. There are multiple ways to accomplish this depending on the research question. Including nodes beyond symptoms, such as cognitive measures or structural brain differences, is useful for identifying the extent to which different mechanisms (in this case computational processes and mental states) represent different expressions of the same pathways, strongly intertwined and operating in concert (cluster together), or whether they represent subsystems operating mainly independently but with the potential to influence each other through few causal pathways (form separate clusters connected by a few nodes). Another possibility is to include clinical symptoms beyond those defined by the diagnostic category in question. A good starting point in this regard, would be to model symptoms of disorders that exhibit high comorbidity with schizophrenia, allowing identification of potential *bridging symptoms* that are connected to symptoms of multiple disorders. The symptom *Avolition*, for example, might be a candidate symptom bridging schizophrenia and bipolar disorder, as this is a central symptom of both disorders (Strauss et al., 2016). *Avolition* may arise from other symptoms of bipolar disorder, e.g., *insomnia*, which in turn leads to other BD symptoms such as *Feelings of worthlessness*, but also symptoms of schizophrenia such as altered *Perception of self and others*, which in turn may trigger additional symptoms of schizophrenia. These symptoms of BD are further part of the symptomatology for depression (Tolentino et al., 2018), and may hence either arise from depression symptoms or cause further depressive development. Investigating symptom networks across disorders may provide insights into the mechanisms driving comorbidity moving beyond the theoretical boundaries imposed by the diagnostic categories, and rather model mental health as a unitary system of mental states where pathological activation patterns in different symptom clusters give rise to different

pathologies. Bridging nodes may also comprise cognitive dysfunctions, as these are prevalent and shared in many disorders. For instance *Attention deficits* and reduced *Executive Functioning* are central features of both schizophrenia and BD (Tabarés-Seisdedos et al., 2003).

Further, considerations must be made regarding what nodes in the model actually represent. For most disorders, multiple rating scales exist for assessing symptom severity, some of which are based on self-report and some which are based on structured clinical evaluation. Most scales score symptoms based on single items, and these are often based on diverse formulations or questions depending on the particular scale. For example, the Brief Psychiatric Rating Scale (BPRS) defines *Emotional withdrawal* as “Deficiency in relating to the interviewer and to the interviewer situation” (Overall and Gorham, 1962), while the Positive and Negative Syndrome Scale (PANNS) defines the same symptom as “Lack of interest in, involvement with, and affective commitment to life’s events” (Kay et al., 1987). These differences might induce different network structures, potentially resulting in largely diverse causal inferences. In particular for single-item symptom ratings, the identified network connections are likely to be sensitive to the particular assessment scales used. One potential way to accommodate this problem may be to include nodes that are based on multiple rating scales and measured by multiple items. This could reduce sensitivity to the particular measures used, ensuring more robust symptom representations in the models, and increase generalizability and comparability of different network studies. Further, averaging severity of each symptom across multiple assessment tools might reduce consequences of measurement error associated with individual psychometric rating scales. In line with this, researchers should always address instances of topological overlap among nodes in the model. If two nodes are in fact measures of the same construct, this can generate false causal claims between symptoms (Fried and Cramer, 2017). This can typically be identified if two nodes exhibit very similar connectivity patterns in the network and the removal of one does not change the structure of the remaining nodes, in which case one might beneficially combine them into one node. Redundancy of individual nodes can also be indicated by an exceptionally high clustering coefficient, which in some cases suggest that information in this node is fully captured by its neighboring nodes, and its removal will have no influence on the remaining system (Fried et al., 2016).

4.2.2. Hybrid models

The current results supported a model of schizophrenia where symptoms and cognitive deficits arise both from common causes and from direct interactions. Previous discussions in the psychometric network literature have hypothesized the presence of such hybrid models in mental disorders (Fried and Cramer, 2017). Such models could take different forms. One possibility is that symptoms are initially triggered by latent common cause, following which direct interactions in the symptom network are responsible for maintaining the presence of symptoms through self-reinforcing loops. This has been reasoned to be likely for disorders as PTSD and substance abuse, where a traumatic life event or dopaminergic abnormalities, respectively, may trigger symptoms initially.

Alternatively, a common cause may trigger only some symptoms, which in turn causes other symptoms to which they are associated. Such models are hypothesized as most likely in disorders as depression, where self-reinforcement and feedback loops in emotional- and mood states are well established (Fried and Cramer, 2017). If schizophrenia is indeed a hybrid model, as suggested in the present findings, it is of great importance to distinguish such common cause effects from direct causal effects of symptom co-occurrence, as the two imply fundamentally different predictions in regard to symptom onset and remediation. If, for instance, *problems with emotional expression* is causally related to *avolition*, then intervening on the former may alleviate the latter. However, if the two share a common cause such intervention will be unsuccessful, and symptom remediation can only result from intervention on the common cause. Further, it is plausible that the latent variables representing common causes organize in network systems themselves (e.g., disordered brain networks or genetic networks). Most likely, complex disorders as schizophrenia must be understood as multiple subsystems operating on different levels, including for example a genetic-biological system (Kottaram et al., 2019), a computational (cognitive) system (Godwin et al., 2017), an environmental system (Isvoranu et al., 2016) a psychological system (Isvoranu et al., 2020b), and potentially more. The clear formation of a cognitive cluster and a symptom cluster in the current results might indicate the presence of two largely separate developmental systems in schizophrenia, in which components mainly interact within-cluster, however, connected by a few individual components. Investigating each of such systems as a network, may help identify key components responsible for maintaining pathological behavior at each level. In addition, if components of multiple systems are included in one model, we may gain insights into how these systems influence each other with greater precision.

It is important to note that partial correlations in cross-sectional networks, like the current RNM, do not necessarily imply causal relationships, nor does it imply mere correlations. Two components can be highly correlated but not connected in the network, in cases where the correlation is accounted for by other components or a latent variable. Contrary, two nodes can be connected in the network, while in fact they are completely uncorrelated, in cases of a common effect (Epskamp et al., 2017b). More robust estimates of causal connections can be obtained from temporal network models on longitudinal data (discussed in subsequent sections), however, even in the case that a causal effect can be reliably established, network models provide no details on the biological or psychological processes comprising such effects. Hence, the observed network structure may be best implemented as a hypothesis-generating structure, highlighting potential causal pathways that can guide further investigations on the mechanistic processes underlying the observed connections.

4.3. Further directions

The present study suggested that the covariance between clinical indicators of schizophrenia and cognitive functions can be understood in part as arising from common underlying pathways and partly as a result of direct interactions between constituent components, where individual symptoms or cognitions themselves can have a central causal role in pathological development. Further, the structure of these relationships exhibited high tendencies of clustering, indicative of small-worldness, weakly supporting the conception of mental disorders as phase-transitions in a complex system. These observations suggest that further investigation of the network structure of these interactions, may provide novel insights into the evidently complex patterns underlying pathological development. However, in order to infer causality of the observed network structure, further investigations are needed. There are several advances to the GGM that can be implemented to allow inference on causality of the observed network structure and gain more detailed insight into the exact nature of such network dynamics in schizophrenia. These may provide explanatory insights to the questions raised by the current results.

4.3.1. Temporal Networks

The current analysis was based on cross-sectional data yielding undirected networks. While partial correlations indicate that two nodes are related to each other after accounting for all other nodes in the network, it cannot be determined whether this relationship is causal nor the direction of causality. Temporal networks can be computed with longitudinal data to empirically assess the

causal interaction structure over time in the system, providing information on the key dynamics giving rise to and maintaining a psychopathological network across individuals (Jordan et al., 2020). In such models, the network structure indicates which components predict changes in other components in future occasions, with edge weights corresponding to the strength of the predictive relationship (Jordan et al., 2020). The most widely used temporal model is the Graphical Vector Autoregression (GVAR) model, which estimates lagged relationships between variables in time-series data (Epskamp et al., 2018). That is, at timepoint t each node is regressed onto a lagged ($t-1$) version of all other nodes. While this does not imply causality in the strictest sense, GVAR models sufficiently provides estimates of Granger causality between pairs of components (Fried and Cramer, 2017), i.e., past values of X are informative about future values of Y, beyond the information inherent in past values of Y itself (Jordan et al., 2020). Following, pathological development in the network can arise from temporal self-reinforcement of symptoms, either in terms of autoregressive effects, where a node predicts future changes of itself, or cross-regressive effects between nodes. The GVAR model identifies the source and direction of such causal loops between symptoms and other components. Exploring this structure among early subclinical deficits can help unravel the causal role of individual cognitive aspects in the development of symptoms of psychosis. Most temporal network studies in psychopathology to date have relied on the assumption of no latent variables, however, the current results indicate that future research may benefit from distinguishing temporal dynamics in latent variables and residual interactions. An extension of the GVAR model has already been developed modeling lagged predictive relationships between latent variables identified in an LNM, termed latent-variable GVAR (lv-gvar) model (Epskamp, 2020). Similarly, GVAR models may be implemented on the RNM structure to identify the potential causal pathways underlying the interaction structure identified in the present paper. Take as example the observed relationship between *Attentional Deficits*, *Disorganized Speech*, *Psychosis* and *Perception of Self and Others*, where *Disorganized Speech* is linking the three other nodes. This structure could arise from several causal pathways, the identification of which has important clinical implications. First, *Attentional Deficits* may lead to *Disorganized Speech* which in turn influences *Perception of Self and Others* and indicators of *Psychosis* (here measured as perception of things that are not there). This model is supported by evidence that cognitive deficits tend to precede clinical symptoms by many years (Mollon and Reichenberg, 2018). In this case, clinical interventions may benefit from focusing on attention-related aspects of cognition in order to reduce symptoms of psychosis. Contrary, it is possible that *Disorganized Speech* is the main cause of all

three components to which it is connected, such that the three themselves have no direct influence on each other. This possibility is supported by evidence showing that a developmental trajectory of persistent disorganized communication from pre-onset to post-onset predicted transition to psychosis in a clinically high-risk sample (DeVylder et al., 2014), and suggests that prevention strategies may benefit from targeting language dysfunctions. Alternatively, *Psychosis* may cause *Disorganized Speech* which in turn leads to *Attention Deficits* and altered *Perception of Self and Others*. In this case, cognition-based treatment is unlikely to have any influence on psychosis severity. Clinical interventions may thus benefit largely from exploiting the temporal causal structure highlighted by GVAR models where directly intervening on individual symptoms can have downstream effects on other symptoms to which it is temporally connected.

4.3.2. *Variability networks*

As noted earlier, the models discussed here represent averaged networks across individuals, and must be interpreted at the group level. For instance, from the current results we may hypothesize that youths who have severe problems with *Disorganized speech* also tend to exhibit altered *Perception of self and others*. However, this may not be true for all individuals. Two advances to network models may be implemented to identify nomothetic pathways that generalize across individuals and idiographic structures that tend to vary between individuals. First, *variability networks* can be estimated from a regular GGM, identifying specific edges in the network that vary most between individuals as well as the most similar edges (Bringmann et al., 2013). Second, implementing *mixture-models* from the SEM framework on psychometric networks, which identifies sub-groups of subjects in the data, has been proposed as a promising way to study heterogeneity in symptom networks of mental disorders (Fried and Cramer, 2017). Such methods are important steps towards uncovering the observed clinical heterogeneity in schizophrenia and may allow for more personalized clinical assessment.

4.3.3. *Early Warning-Signals*

In addition to highlighting potential causal relationships between symptoms, temporal network dynamics provide novel tools to assess individual risk for pathological manifestation, independently of overall symptom severity. Complex network systems characterized by small-world topology have been shown to exhibited generic system dynamics directly preceding a phase-transition from one state to another (Wichers et al., 2016). These Early Warning-Signals (EWS) have been

demonstrated to predict critical transitions in a wide range of network systems, including the kinetic Ising model (Acharyya, 1997), cell signaling pathways (Bagowski and Ferrell, 2001), ecosystems (Scheffer et al., 2001) and the climate system (Lenton et al., 2008). EWS indicate a critical slowing down of the system and are quantified from the temporal dynamics in terms of increased temporal autocorrelation (node self-reinforcement), increased spatial correlation (global connectivity), and increased variance within components (fluctuations in individual measures) (Wichers et al., 2016). Such dynamics characterize a gradual increase in fragility of the system, such that the time required to recover from perturbations increases. At one point the system can reach a critical tipping point where recovery is no longer possible, and it will transition into a new stable state. Modeling the temporal dynamics of the PNC sample as youths develop would allow investigations of whether tendencies of critical slowing down can be observed in subjects who experience increased symptom severity, which may provide significant improvements to prevention and risk-reduction strategies. In networks of depression, Wichers and colleagues (2016) provided evidence that increasing EWS between symptoms preceded a clinically statistical transition in depression. In schizophrenia, it has been hypothesized that active periods of psychosis are characterized by increased spatial correlations (more densely connected networks) between symptoms (Rooijen et al., 2018). Further, clinical studies have suggested that successful treatment cases feature periods of instability comparable to EWS (Fried et al., 2017). Importantly, such temporal dynamics can explain differences in psychopathological development and risk independent of overall mean symptom severity (Jordan et al., 2020; Calkins et al., 2017).

4.3.4. Moderator effects

The current study investigated potential main effects of genetic profiles on other components in the network, modeling them directly as constituent components of the system. However, it is plausible that genetic variance act as moderators on the network structure, either increasing or decreasing the likelihood of some components to influence others. For instance, some individuals may be more likely than others to experience altered *Perception of self and others* following *Emotional expression* deficits, due to a general genetic susceptibility to altered social abilities. As such, some factors may lower the threshold of symptom propagation, while no direct main effect can be observed. In cases where the network structure in fact are under strong moderation by an unmodelled variable, the results will represent the interaction structure associated with the average value of the moderator (Haslbeck et al., 2019), which readily leads to false interpretations.

Conclusion

Moderator effects can be assessed with the Moderator Network Model (MMN) (Haslbeck et al., 2019), which estimates a GGM while allowing pairwise interactions to be moderated by one or multiple observed variables. Such moderator effects represent variables in the external field of the system, influencing the network from outside. Since genetic variants do not change over time (except from cases of epigenetic regulation), they are not expected to influence the temporal dynamics of the system causing symptom maintenance. Rather, genetics operate in a dispositional manner and may thus be profitably assessed as external effects on the temporal symptom dynamics. Based on previous findings described here, it may be hypothesized that higher genetic risk for schizophrenia is associated with more densely connected networks. Alternatively, it could be hypothesized that genetic risk increases the strength of association between cognitive dysfunctions and symptoms, such that one is more likely to have effects on the other. Given the established heritability of schizophrenia, and the observed lack of associations between genetic variance and symptoms or cognition in present results, it is important for further studies to address the potential moderating effects of genetic variants on symptom networks of schizophrenia. Further, age might comprise an important moderator on the network structure, given that cognitive functions and many symptoms are strongly associated with age.

5. Conclusion

The current project investigated the complex relationship between genetic variants, clinical symptoms, and cognitive alterations associated with pathological development of schizophrenia, by assessing the underlying covariance structure of these components. Results indicated that co-occurrence of the observed variables was best described as partly arising from common latent sources of variance and partly from direct pairwise interactions. This suggest that clinical symptoms and cognitive deficits may play an active role in the development of schizophrenia, where some deficits may increase the likelihood of additional alterations, or even cause them directly. The present model identified no shared latent factors between items of the three categories, suggesting that these arise from distinct causal pathways. Likewise, most direct interactions were observed within category, such that cognitive components mainly interacted with other cognitive functions, and symptoms with symptoms. To the extent that clinical symptoms and cognitive alterations influence each other, this was suggested to be explained by attention-related mechanisms. Genetic risk profiles did not exhibit any influence on cognitive or clinical components in the network. There are several limitations to the present results challenging the robustness of model structure, as well as

Conclusion

generalizability of the observed relationships to a clinical sample and to individual subjects. Hence, inferences based on the current results are best implemented to generate hypotheses about potential causal pathways, that can be further investigated using methods discussed here. However, the finding that the RNM exhibited best fit do indicate that we cannot assume that symptoms of schizophrenia only arise from underlying pathologies. Symptoms and cognitive alterations appear to exhibit unique covariance that cannot be attributed to latent constructs, highlighting the importance of investigating direct interactions between psychometric components, when aiming to explain the causal pathways underlying pathological development of schizophrenia.

Scripts available on GitHub:

<https://github.com/LineKruse/CovarianceStructureOfPsychometricFeaturesInSchizophrenia>

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Appendix

Figure A1. Score distributions of clinical variables.

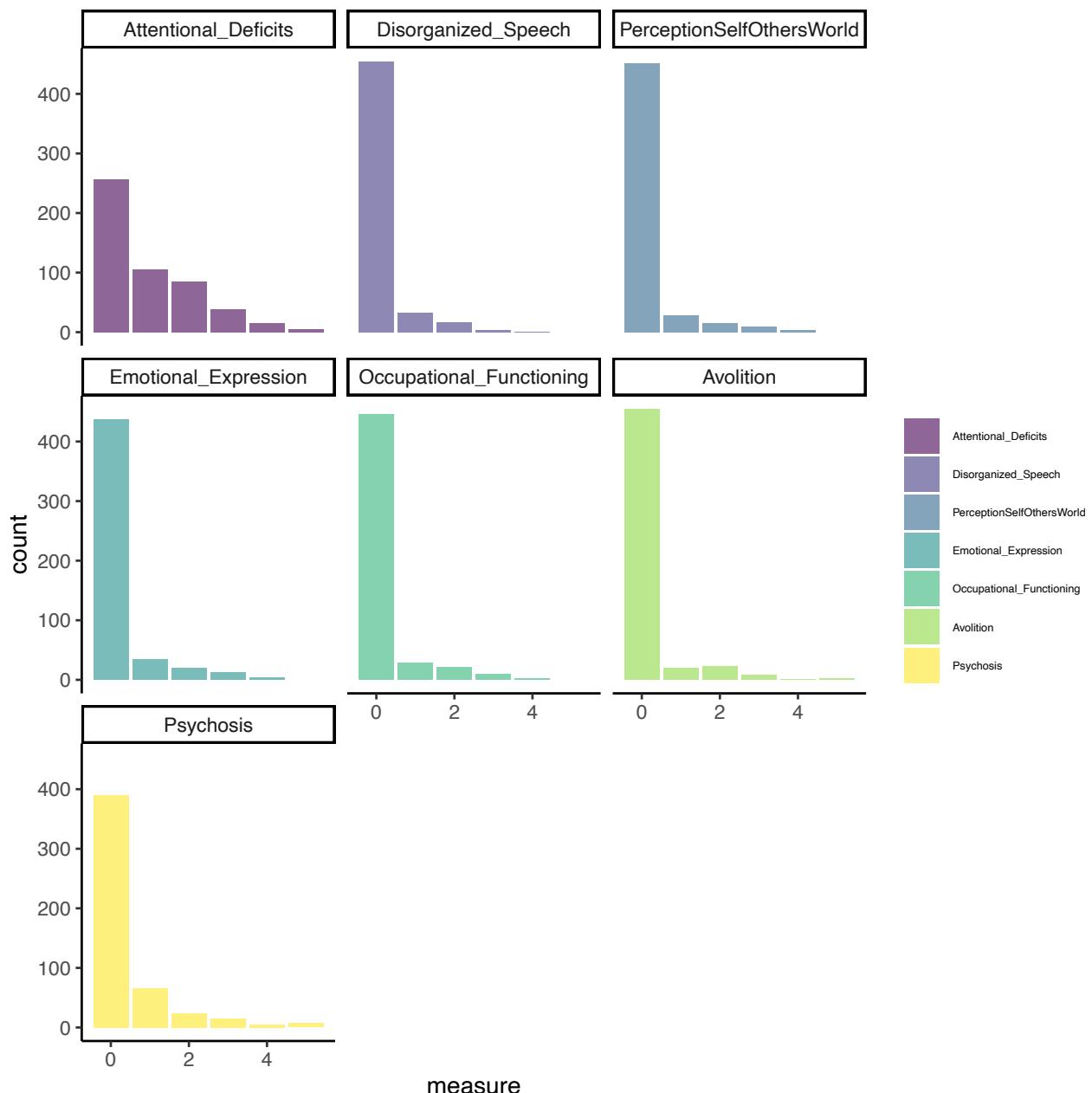


Table A1. Overview of clinical items

Name	SIP/Kiddie-SADS Item	Rating scale
Attentional Deficits	SIP item. Trouble with focus and attention (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Disorganized communication	SIP item. Changes in speech, disorganized communication, tangential speech (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Perception Self, Others, World	SIP item. Changes in perception of self, others, or the world in general (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Emotional Expression	SIP item. Expression of emotion deficits (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Occupational functioning	SIP item. Occupational functioning (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Avolition	SIP item. Avolition (severity scale)	0=absent 1=questionably present 2=mild 3=moderate 4=moderately severe 5=severe 6=extreme
Psychosis	Kiddie-SADS Family Study Interview Psychosis item. Aggregated score based on binary items (0=No, 1=Yes): <ul style="list-style-type: none"> - Have you ever heard voices when no one was there? (0,1) - Have there ever been anything unusual about how things smelled or looked or felt? (0,1) 	1=1 item present 2=2 items present 3=3 items present 4=4 items present 5=5 items present 6=6 items present

	<ul style="list-style-type: none">- Have you ever seen visions or seen things which other people could not see? (0,1)- Have you ever smelled strange odors other people could not smell? (0,1)- Have you ever had strange feelings in your body like things were crawling on you or someone touching you and nothing or no one was there? (0,1)- Have you ever believed in things and later found out that were not true, like people being out to get you, or talking about you behind your back, or controlling what you do or think? (0,1)	
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Figure A2. Score distributions of cognitive variables

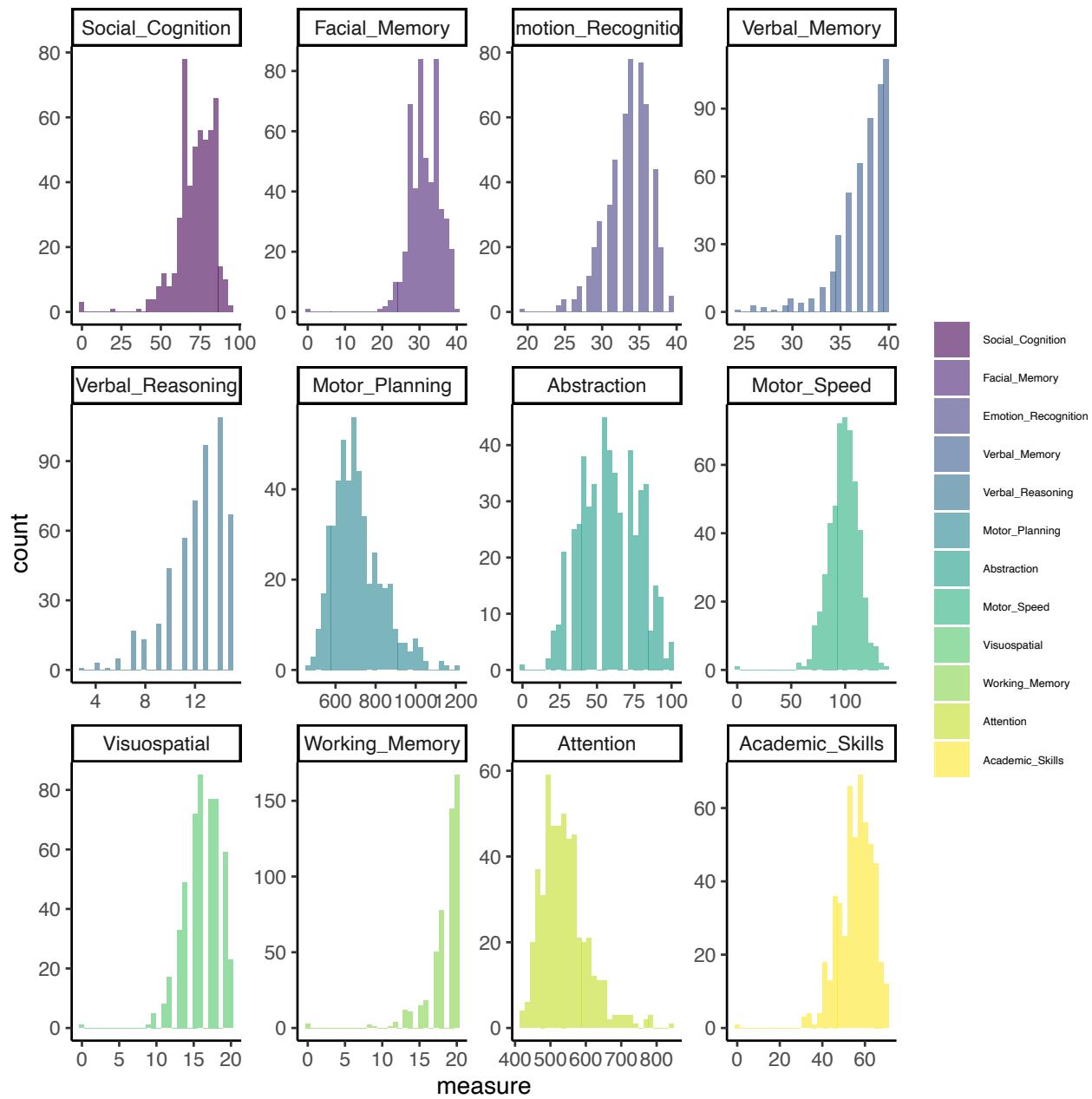


Table A2. PCA results

Component	Eigenvalue	Explained variance (%)	Cumulative variance (%)
Dim. 1	3.70	16.8	16.8
Dim. 2	3.03	13.8	30.6
Dim. 3	2.36	10.7	41.3
Dim. 4	1.32	6.0	47.3
Dim. 5	1.16	5.3	52.6
Dim. 6	1.05	4.8	57.4
Dim. 7	0.97	4.4	61.8
Dim. 8	0.88	4.0	65.8
Dim. 9	0.84	3.8	69.6
Dim. 10	0.77	3.5	73.1
Dim. 11	0.70	3.2	76.3
Dim. 12	0.69	3.1	79.4
Dim. 13	0.65	2.9	82.4
Dim. 14	0.61	2.8	85.1
Dim. 15	0.59	2.7	87.8
Dim. 16	0.57	2.6	90.4
Dim. 17	0.55	2.5	92.9
Dim. 18	0.46	2.1	95.0
Dim. 19	0.45	2.0	97.0
Dim. 20	0.37	1.7	98.7
Dim. 21	0.28	1.3	99.9
Dim. 22	0.00	0.00	100.0

Figure A3. PCA results.

Scree plot visualizing cumulative explained variance of components.

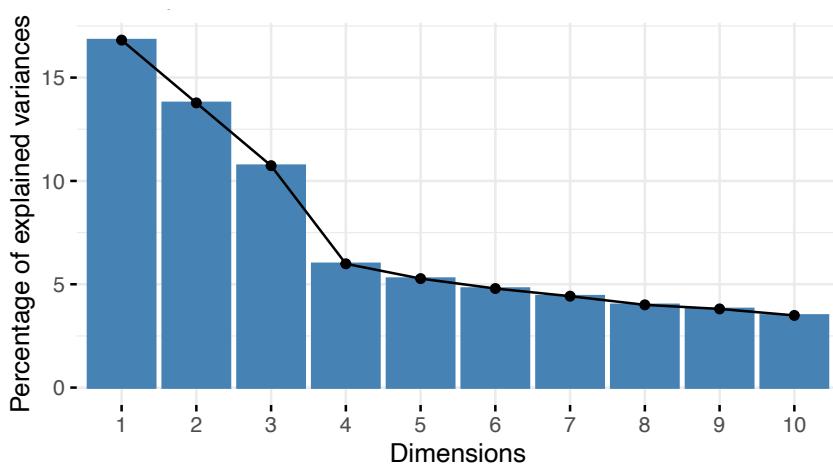


Table A3. Factor loadings matrices

a. EFA derived factor loading matrices

	Two-factor		Three-factor			Four-factor				Five-factor				
	F1	F2	F1	F2	F3	F1	F2	F3	F4	F1	F2	F3	F4	F5
1	0	0	1	0	0	1	1	0	0	0	1	0	0	0
2	0	0	0	0	0	0	1	0	0	0	1	0	0	0
3	1	0	0	1	0	0	1	0	0	0	1	0	0	0
4	0	0	0	0	0	0	1	0	0	0	1	0	0	0
5	0	0	0	0	0	0	1	0	0	0	1	0	0	0
6	0	0	0	0	0	0	1	0	0	0	1	0	0	0
7	0	0	0	0	0	0	1	0	0	0	1	0	0	0
8	0	0	1	0	0	1	0	0	0	1	0	0	1	0
9	0	0	1	0	0	1	0	0	0	1	0	0	1	0
10	0	0	1	0	0	1	0	0	0	1	0	0	0	0
11	0	0	1	0	0	1	0	0	0	0	0	0	1	0
12	0	0	1	0	0	1	0	0	0	1	0	0	1	0
13	0	0	1	0	0	1	0	0	0	1	0	0	1	0
14	0	1	1	0	0	1	0	0	0	1	0	0	1	0
15	0	0	1	0	0	1	0	0	0	1	0	0	0	0
16	0	0	1	0	0	1	0	0	0	1	0	0	1	0
17	0	0	1	0	0	1	0	0	0	1	0	0	1	0
18	1	1	1	0	0	1	0	0	0	1	0	0	1	0
19	0	0	1	0	0	1	0	0	0	1	0	0	1	0
20	1	1	0	1	1	0	0	1	1	0	0	1	0	1
21	1	1	0	1	1	0	0	1	1	0	0	1	0	1
22	0	1	0	0	1	0	0	0	1	0	0	0	0	1

b. Theory-based three-factor loading matrix

	Three-factor		
	F1	F2	F3
1	1	0	0
2	1	0	0
3	1	0	0
4	1	0	0
5	1	0	0
6	1	0	0
7	1	0	0
8	1	1	0
9	0	1	0
10	0	1	0
11	0	1	0
12	0	1	0
13	0	1	0

14	0	1	0
15	0	1	0
16	0	1	0
17	0	1	0
18	0	1	0
19	0	1	0
20	0	0	1
21	0	0	1
22	0	0	1

Table A4. CFA model comparison - Fit indices

Model	DF	BIC	RMSEA	Chisq	Chisq Diff	DF Diff	p-value
cfa_5f	188	27263.41	0.048	408.72			
cfa_4f	200	32098.80	0.22	5318.85	4910.13	12	<0.0001
cfa_3f	209	27943.88	0.098	1219.99	4098.86	9	<0.0001
cfa_2f	221	28896.27	0.13	2247.12	1027.14	12	<0.0001

Figure A4. CFA model comparison – Posterior Model Probability

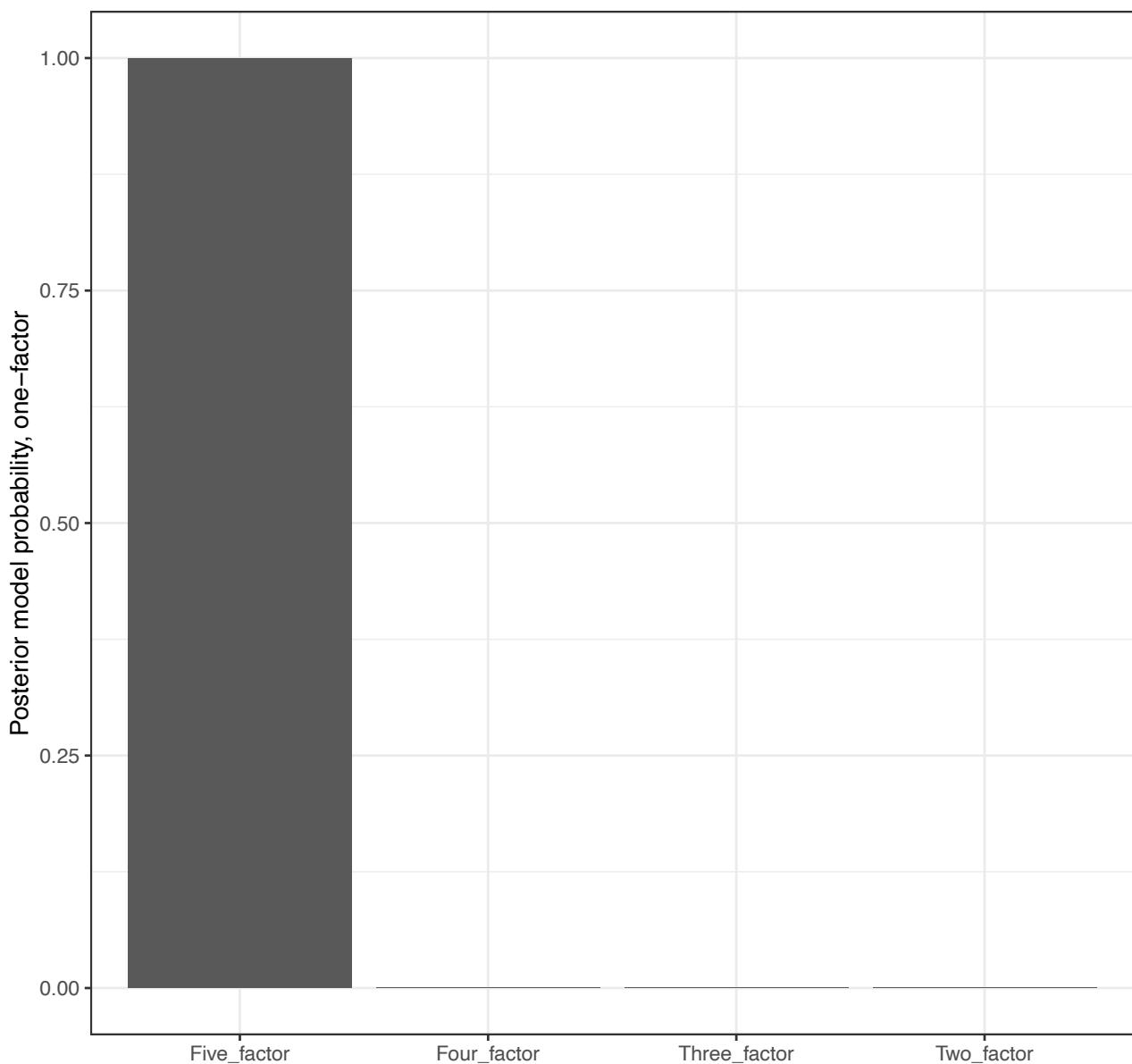


Figure A5. Network degree distributions
Left=GGM, Right=RNM.

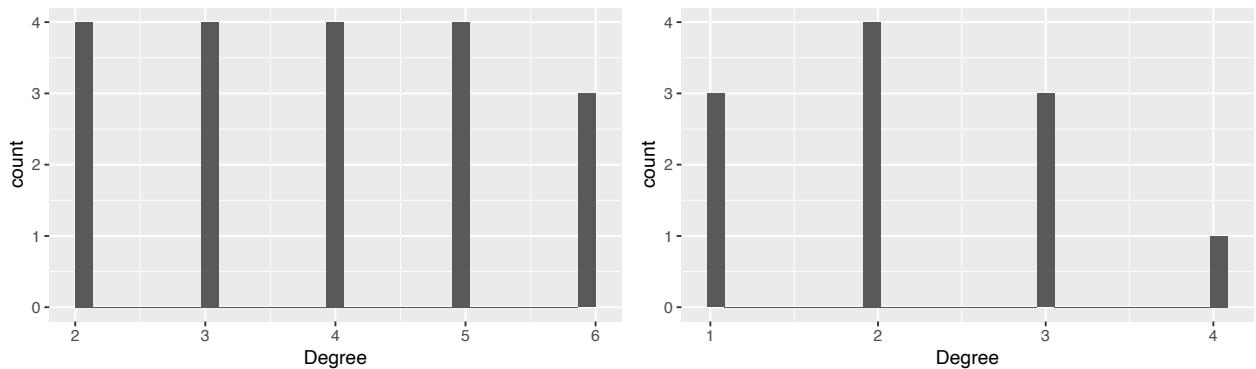


Figure A6. Node clustering coefficients

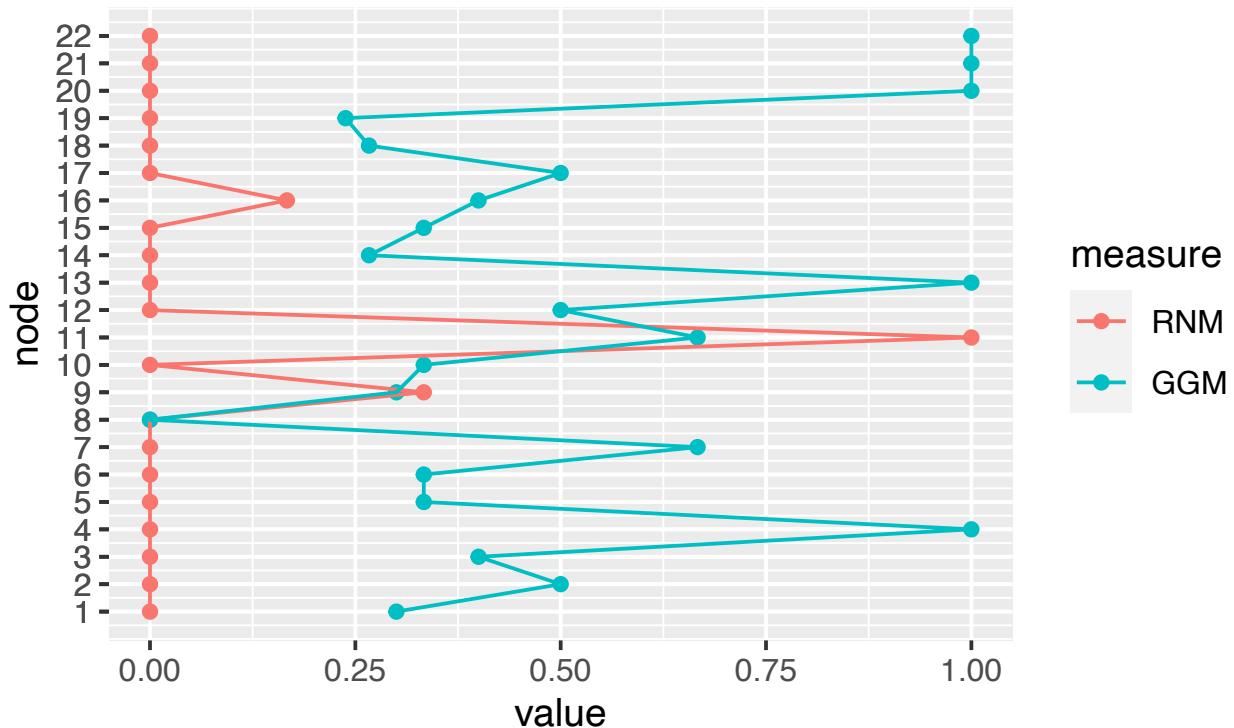


Table A5. GGM adjacency matrix

Cell values represent partial correlation coefficients and corresponds to the edge weights in the graph.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	0.0	0.14	0.11	0.0	0.19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.10	-0.16	0.0	0.0	0.0	0.0
2	0.12	0.0	0.18	0.0	0.14	0.0	0.25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
3	0.11	0.18	0.0	0.21	0.0	0.14	0.12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.21	0.0	0.0	0.40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	0.19	0.14	0.0	0.0	0.0	0.51	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6	0.0	0.0	0.14	0.40	0.51	0.0	0.12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
7	0.0	0.25	0.12	0.0	0.0	0.12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.17	0.0	0.0	0.0	0.23	0.0	0.0	0.0	0.0	0.20	0.0	0.0	0.0	0.0
9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.17	0.0	0.0	0.0	0.13	0.18	0.0	0.0	0.14	0.0	0.0	0.0	0.0
10	0.0	0.0	0.0	0.0	0.0	0.0	0.16	0.14	0.0	0.0	0.0	0.0	0.0	0.0	0.09	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.17	0.0	0.0	0.0	0.0	0.13	0.0	0.13	0.0	0.0	0.0	0.0	0.0	0.0	0.0
12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.24	0.11	0.0	0.12	0.0	0.37	0.0	0.0	0.0	0.0
13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.13	0.0	0.0	0.0	0.0	0.0	-0.13	0.0	0.0	0.22	0.0	0.0	0.0	0.0	0.0
14	0.0	0.0	0.0	0.0	0.0	0.23	0.0	0.0	0.13	0.24	0.0	0.0	0.0	0.15	0.14	-0.13	0.0	0.0	0.0	0.0	0.0	0.0
15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.13	0.13	0.0	0.11	-0.13	0.0	0.0	0.0	0.0	-0.32	0.20	0.0	0.0	0.0	0.0
16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.18	0.0	0.13	0.0	0.0	0.15	0.0	0.0	0.16	0.09	0.0	0.0	0.0	0.0	0.0
17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.12	0.0	0.14	0.0	0.16	0.0	0.0	0.12	0.0	0.0	0.0	0.0
18	-0.10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.22	-0.13	-0.32	0.09	0.0	0.0	-0.21	0.0	0.0	0.0	0.0
19	-0.16	0.0	0.0	0.0	0.0	0.0	0.20	0.14	0.0	0.0	0.37	0.0	0.0	0.20	0.0	0.12	-0.21	0.0	0.0	0.0	0.0	0.0
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.99	0.0	-0.97
21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.99	0.0	-0.97	0.0
22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.08	-0.97	0.0	0.0	0.0

Table A6. CFA three-factor model - factor loadings matrix
Confirmatory model.

	F1	F2	F3
1	0.35	0.0	0.0
2	0.41	0.0	0.0
3	0.53	0.0	0.0
4	0.61	0.0	0.0
5	0.70	0.0	0.0
6	0.85	0.0	0.0
7	0.0	0.0	0.0
8	0.0	0.48	0.0
9	0.0	0.42	0.0
10	0.0	0.26	0.0
11	0.0	0.25	0.0
12	0.0	0.76	0.0
13	0.0	-0.32	0.0
14	0.0	0.56	0.0
15	0.0	0.64	0.0
16	0.0	0.20	0.0
17	0.0	0.43	0.0
18	0.0	-0.59	0.0
19	0.0	0.77	0.0
20	0.0	0.0	0.0
21	0.0	0.0	0.0
22	0.0	0.0	0.0

Table A7. LNM factor loadings
Confirmatory model.

	F1	F2	F3
1	0.38	0.0	0.0
2	0.41	0.0	0.0
3	0.53	0.0	0.0
4	0.61	0.0	0.0
5	0.70	0.0	0.0
6	0.85	0.0	0.0
7	0.37	0.0	0.0
8	0.0	0.48	0.0
9	0.0	0.43	0.0
10	0.0	0.25	0.0
11	0.0	0.25	0.0
12	0.0	0.76	0.0
13	0.0	-0.32	0.0
14	0.0	0.56	0.0
15	0.0	0.64	0.0
16	0.0	0.20	0.0
17	0.0	0.43	0.0
18	0.0	-0.60	0.0
19	0.0	0.77	0.0
20	0.0	0.0	-1.24
21	0.0	0.0	0.77
22	0.0	0.0	0.55

Table A8. LNM factor partial correlations
Confirmatory model.

	F1	F2	F3
F1	1	0	0
F2	0	1	0
F3	0	0	1

Table A9. LNM residuals
Confirmatory model.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
0.86	0.83	0.71	0.63	0.51	0.28	0.86	0.76	0.82	0.93	0.93	0.54	0.90	0.68	0.58	0.96	0.81	0.64	0.41	-0.53	0.41	0.70

Table A10. RNM residuals

Confirmatory model.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	0.0	0.14	0.0	-0.17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.21	0.0	0.0	0.0	
2	0.14	0.0	0.16	0.0	0.0	0.0	0.25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
3	0.0	0.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	
4	0.0	0.0	0.0	0.0	-0.46	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	0.0	0.0	0.0	-0.46	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6	0.0	0.0	0.0	0.40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
7	0.0	0.25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.13	0.0	0.0	0.0	0.14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.13	0.14	0.0	0.0	0.0	0.19	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10	0.0	0.0	0.0	0.0	0.0	0.0	0.13	0.13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.14	0.0	0.0	0.0	0.0	0.0	0.0	0.16	0.0	0.0	0.0	0.0	0.0	0.0	0.0
12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.23	0.0	0.0	0.0	0.0	0.0
14	0.0	0.0	0.0	0.0	0.0	0.0	0.14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.21	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.27	0.0	0.0	0.0	0.0	0.0
16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.19	0.0	0.16	0.0	0.0	0.21	0.0	0.0	0.19	0.0	0.0	0.0	0.0	0.0	0.0
17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.19	0.0	0.0	0.0	0.0	0.0	0.0	0.0
18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.23	0.0	-0.27	0.0	0.0	0.0	0.0	0.0	0.0	0.0
19	-0.21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.97
21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.97
22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-0.98	0.0	0.0	0.0	0.0