Understanding Schizophrenia:
A Bayesian Symptom Network Approach

Khan Buchwald

A thesis submitted to
Auckland University of Technology
in fulfilment of the requirements for the degree of
Doctor of Philosophy

2025

School of Clinical Sciences, Faculty of Health and Environmental Science

Abstract

Schizophrenia is one of the most debilitating mental health conditions, marked by moderate to severe cognitive and functional impairments. With an increase in research on the aetiology, symptoms, and prognosis, researchers are close to developing robust social, biological, and cognitive conceptualisations of schizophrenia. A recent model of health is the network theory of mental disorders (NTMD), where symptoms of a mental disorder are modelled in a complex system. Here, symptoms cause or are dependent on the expression of other symptoms, named symptom networks (SN). The research in this thesis aims to review the SN research of schizophrenia, conduct an SN that evaluates the role of cognition, among other variables, and provide evidence for the NTMD.

The first study in this thesis is a systematic review of SNs, which aims to identify major themes across studies and identify gaps in the literature. The findings in the systematic review highlight that cognition and functioning were central nodes across the included studies. Hallucinations and/or delusions were not central in most of the networks. This finding aligns with other evidence that proposes that schizophrenia is a disorder of cognition.

Following the results of the systematic review, the second study aims to identify the role of cognition, sociodemographic, psychopathology, and quality of life (QOL) variables from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study using a Bayesian network (BN) framework. Findings indicate that processing speed significantly predicts all other cognitive processes and QOL, highlighting processing speed as a core cognitive impairment in schizophrenia.

The third and final study aims to determine whether latent variable models (LVMs) and SNs can be integrated to improve model fit. It was found that the integrated model significantly improves the fit of an LVM alone when using the Positive and Negative Syndrome Scale (PANSS) from the CATIE study and the Scale of Psychosis-Risk Symptoms (SOPS) from the North American Prodromal Longitudinal Study 3 (NAPLS3) study. The results provide partial support for the complexity principle of the NTMD, which states that complex relationships between symptoms represent mental disorders.

The collection of these three studies fills a gap in research using SNs to understand schizophrenia. By focusing on systems of symptoms, this thesis provides evidence for an alternative modelling approach to schizophrenia where complex interactions of symptoms are represented using SNs. Two integrative proposals extend from the results of this thesis: that processing speed is the prime cognitive impairment in schizophrenia and that the SN methodology may also have applications for use in clinical profiles for people living with mental illness in general.

Table of Contents

List of Figures

List of Tables

List of Appendices

List of Commonly Used Abbreviations

AIC	Akaike Information Criterion
AUTEC	Auckland University of Technology Ethics Committee
BIC	Bayesian Information Criterion
BN	Bayesian Network
BPRS	Brief Psychotic Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDSS	Calgary Depression Scale for Schizophrenia
CFI	Comparative Fit Index
DAG	Directed Acyclic Graph
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBIC	Extended Bayesian Information Criteria
GGM	Gaussian Graphical Model
GLASSO	Graphical Least Absolute Shrinkage and Selection Operator
HC	Healthy Controls
ICD	International Classification of Diseases
IQ	Intelligence Quotient
LVM	Latent Variable Model
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
NAPLS	North American Prodrome Longitudinal Study
NTMD	Network Theory of Mental Disorders
PANSS	Positive and Negative Syndrome Scale
PDS	People Diagnosed with Schizophrenia
PLS	People Living with Schizophrenia
PMRF	Pairwise Markov Random Field
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	Quality of Life
RMSEA	Root Mean Square Error of Approximation
SCM	Structural Causal Model
SEM	Structural Equation Model
SN	Symptom Network
SOPS	Scale of Psychosis-Risk Symptoms
TLI	Tucker-Lewis Index

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor used artificial intelligence tools or generative artificial intelligence tools (unless it is clearly stated, and referenced, along with the purpose of use), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signature: Khan Buchwald Date: 24/06/2025

Co-authorship Contribution Within This Thesis

This thesis provides scholarly material where the majority of the work to arrive at the final manuscripts and thesis is from the student, I, Khan Buchwald. This includes the three manuscripts included in this thesis, of which I am the first author. All four supervisors and I contributed to each manuscript, and we sought advice from other experts during the development of the manuscripts. Each supervisor assisted with a specific contribution to the research. In the supervision team, we have two supervisors with strong statistical and computer science expertise and two with a strong background in clinical psychology and methodology. Despite these fields of expertise, the supervisors provided advice on the manuscripts as a whole, and there was advice from the clinical psychology experts on the methodology and statistical approach, and advice from the statistics and computer science experts on the clinical rationale and inferences of the results. The contributions to each manuscript are recorded below.

The development of Chapter 4: Centrality Statistics of Symptom Networks of Schizophrenia: A Systematic Review was composed and developed by me, with assistance from the supervision team, Mrs Kim Arrowsmith, and Andrew South. In terms of my own input, I led the development of the selection criteria and protocol, led the literature search, trained the coauthor Kim Arrowsmith in the screening and full-text review, conducted the screening the full-text review, solely completed the data extraction, wrote the original and revised drafts, and wrote the final manuscript included in the publication. Associate Professor Margaret Sandham contributed the most of all supervisors and collaborators in developing the protocol, data collection, data analysis, and feedback on the written and revised drafts. Professor Richard Siegert, Professor Emeritus Ajit Narayanan, and Senior Lecturer Matthieu Vignes provided conceptual advice, reviewed the protocol, and provided feedback on the written and revised drafts. Andrew South provided assistance in the development of the search strategy, and Kim Arrowsmith provided support in the screening and full-text review stages of the research.

For the development of Chapter 5: Directed Symptom Networks of Cognitive Impairment of the Schizophrenia Syndrome: Insights from the CATIE Study, I was the primary investigator, and the supervision team provided nearly equal support. I had the majority contribution of each of the following: data collection, data processing, statistical analysis, writing of the original draft and following drafts, and writing the final manuscript. Associate Professor Margaret Sandham provided the direction, conceptualisation, and revisions on this manuscript at each stage and assisted with ensuring this manuscript was fit to be submitted for publication. Professor Richard Siegert assisted with the direction, conceptualisation, feedback on written drafts, and ensured it was fit for submission. Senior Lecturer Matthieu Vignes and Professor Emeritus Ajit Narayanan reviewed the statistical method, ensured it was robust, and commented on the written drafts.

For the development of the final study, Chapter 6: Evidence for the Network Theory of Mental Disorders in People at Ultra High Risk of and Diagnosed With Schizophrenia, again, I was the majority contributor, and there were some near-equal contributions. We also invited Associate Professor Matt Williams to review the final draft before submission, and his feedback assisted in the revision of the manuscript prior to submission. For this study, I conceptualised the study, collected the data, prepared the data for analysis, conducted the statistical analysis, wrote the original draft and revised the following drafts until submission. Professor Richard Siegert provided the rationale and monitored the manuscript from analysis to submission, ensuring it was robust for publication. Senior lecturer Mattieu Vignes provided considerable statistical and conceptual support in developing this research and support in the manuscript drafts. Associate Professor Margaret Sandham provided feedback on the manuscripts at each stage of the process, and Professor Emeritus Ajit Narayanan provided very useful methodological critique to assist with the robustness of the research and provided feedback on written drafts. Overall, I contributed at least 84% to each manuscript from the beginning of the research to the published or submitted draft. The exact contribution to each piece of research is provided below.

STUDENT AND SUPERVISOR APPROVALS

By signing, you are confirming that the co-author contributions stated in the table(s) below are accurate.

Student Name	Khan Buchwald	**Signature**	Khan Buchwald	**Date**	20/06/2025
Supervisor Name	Richard J. Siegert	**Signature**		**Date**	24/06/2025

Chapter Number:	**4**
Manuscript Title:	**Centrality Statistics of Symptom Networks of Schizophrenia: A Systematic Review**
Publication Status:	**Published**
Reference if published:	**Buchwald, K., Narayanan, A., Siegert, R. J., Vignes, M., Arrowsmith, K., & Sandham, M. (2024). Centrality statistics of symptom networks of schizophrenia: A systematic review. Psychological Medicine, 54(6), 1061-1073. https://doi.org/10.1017/S003329172300363X**

AUTHOR SURNAME: (order as per manuscript)	**CONTRIBUTION** (May copy from the guidelines above)
Khan Buchwald	**85% including conceptualisation, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualisation, writing-original draft, and writing-review and editing.** Khan Buchwald
Professor Ajit Narayanan	**3% including conceptualisation, investigation, methodology, supervision, validation, visualisation, and writing-review and editing.**
Professor Richard J. Siegert	**3% including conceptualisation, funding acquisition, investigation, methodology, resources, software, supervision, validation, visualisation, and writing-review and editing.**
Dr Matthieu Vignes	**3% including conceptualisation, investigation, methodology, supervision, validation, visualisation, and writing-review and editing.** Matthieu Vignes

Mrs Kim Arrowsmith	**2% including data curation, software, and writing-review and editing.**
Dr Margaret Sandham	**4% conceptualisation, data curation, funding acquisition, investigation, methodology, resources, software, supervision, validation, visualisation, and writing-review and editing.** Margaret Sandham

STUDENT AND SUPERVISOR APPROVALS

By signing you are confirming that the co-author contributions stated in the table(s) below are accurate.

Student Name	Khan Buchwald	**Signature**	Khan Buchwald	**Date**	20/06/2025
Supervisor Name	Richard J. Siegert	**Signature**		**Date**	24/06/2025

Chapter Number:	**5**
Manuscript Title:	**A Symptom Network Approach to Schizophrenia in the CATIE study: Processing Speed as the Central Cognitive Impairment**
Publication Status:	**Submitted for publication**
Reference if published:	**Buchwald, K., Siegert, R. J., Vignes, M., Narayanan, A., & Sandham, M. (2025). A symptom network approach to schizophrenia in the CATIE study: Processing speed as the central cognitive impairment. BJPsych Open.**
AUTHOR SURNAME: **(order as per manuscript)**	**CONTRIBUTION** **(May copy from the guidelines above)**
Khan Buchwald	**88% including conceptualisation, data curation, formal analysis, investigation, methodology, project administration, software, visualisation, writing-original draft, and writing-review and editing.** Khan Buchwald
Professor Richard J. Siegert	**3% including conceptualisation, data curation, methodology, project administration, supervision, and writing-review and editing.**

Dr Matthieu Vignes	**3% including conceptualisation, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, and writing-review and editing.** Matthieu Vignes
Professor Ajit Narayanan	**3% including conceptualisation, data curation, methodology, project administration, supervision, and writing-review and editing.**
Dr Margaret Sandham	**3% including conceptualisation, data curation, methodology, project administration, supervision, and writing-review and editing.** Margaret Sandham

STUDENT AND SUPERVISOR APPROVALS

By signing you are confirming that the co-author contributions stated in the table(s) below are accurate.

Student Name	Khan Buchwald	**Signature**	Khan Buchwald	**Date**	20/06/2025
Supervisor Name	Richard J. Siegert	**Signature**		**Date**	24/06/2025

Chapter Number:	**6**
Manuscript Title:	**Evidence for the Network Theory of Mental Disorders in People at Ultra High Risk of and Diagnosed With Schizophrenia**
Publication Status:	**Submitted for publication**
Reference if published:	**Buchwald, K., Vignes, M., Sandham, M., Narayanan, A., Williams, M., & Siegert, R. J. (2025). Evidence for the network theory of mental disorders in people at ultra high risk of and diagnosed with schizophrenia. Collabra: Psychology.**
AUTHOR SURNAME: **(order as per manuscript)**	**CONTRIBUTION** **(May copy from the guidelines above)**

Khan Buchwald	**84% including conceptualisation, data curation, formal analysis, investigation, methodology, project administration, software, validation, visualisation, writing-original draft, and writing-review and editing.** Khan Buchwald
Dr Matthieu Vignes	**4% including conceptualisation, formal analysis, investigation, methodology, supervision, validation, and writing-review and editing.** Matthieu Vignes
Dr Margaret Sandham	**3% including conceptualisation, data curation, supervision, validation, and writing-review and editing.** Margaret Sandham
Professor Ajit Narayanan	**3% including conceptualisation, data curation, investigation, methodology, supervision, validation, and writing-review and editing.**
Dr Matt Williams	**2% including methodology and writing-review and editing.** Matt Williams
Professor Richard J. Siegert	**4% including data curation, methodology, supervision, and writing-review and editing.**

Acknowledgements

First and foremost, I would like to express my sincere gratitude and continuing indebtedness to my supervision team. You provided me with unwavering support and assistance, and an opportunity to learn and grow throughout my PhD. Professor Richard Siegert and Professor Emeritus Ajit Narayanan from the Auckland University of Technology, Senior Lecturer Matthieu Vignes and Associate Professor Margaret Sandham from Massey University, your professional support enabled me to transform what once was a dream into something I will be thankful for throughout my journey. Thank you for your continued support, professional advice, acceptance, critique, collaboration, mentorship, and the opportunity that has changed my life forever.

Dr Alexander Stevens II, it took about a second to decide to inquire about my PhD. Easily missed, that second transformed into a meaningful relationship in which you and I began to explore the content and administration of my PhD. I would like to personally thank you for your interest in my PhD and academic journey and for the potential study we could pursue in the future.

Debra Lampshire, thank you for your insightful discussion, which helped me very early in my PhD. You filled me with meaningful perspectives on schizophrenia that I integrated into my PhD. From my adolescence, I have known your achievements and wished I could one day meet you. I look forward to hearing from you about your challenge to me as a person living with schizophrenia and the meaning you have brought into many people's lives.

To my co-authors, Dr Matt Williams and Kim Arrowsmith, your invaluable contribution helped shape the research in a time of need. Your professional advice developed and refined the research to ensure high-quality outputs. Thank you. To Andrew South, I would like to recognise your assistance in developing a systematic review protocol, which assisted with the design of this research and provided the structural support for the ensuing publication. Thank you. I want to express my gratitude to Charles Grinter, who challenged each study's ethics to ensure it meets the rigorous scrutiny of the Auckland University of Technology Ethics Committee (AUTEC). Thank you. Lastly, thank you, both Professor Yung and Professor Berk, for the early work we did on developing ideas for dynamic models for people at ultra-high risk of schizophrenia. I hope our paths meet again and we can do fascinating work together.

The large language model ChatGPT (OpenAI, 2025) was queried for resources and to identify conceptual and structural aspects of this thesis to improve its robustness (whether conclusions are robust, the conceptualisation and integration of hypotheses and results, thesis structure, chapter structure, titles, cover letters for manuscript submissions, as a search engine for searching for research, effect size guidelines, APA 7 formatting, and historical information hard

to locate through search engines). No written information was copied from any large language model, nor was information from a large language model paraphrased.

Ethics Approval

Ethical approval was obtained for work on the data from the North American Prodromal Longitudinal Study 3 (NAPLS3) on the 20^{th} of April 2023 (ref. 22/388 Dynamic Symptom Networks of Schizophrenia: American data Set)) and the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) on the 12^{th} of July 2023 (ref. 23/387 Static Symptom Networks of Schizophrenia) from the AUTEC. Letters confirming ethical approval for these studies can be found in Appendix A1 and Appendix A2. Both studies previously received ethical approval, and the reanalysis of the datasets was approved by AUTEC up to the 19^{th} of April 2026 and the 12^{th} of July 2026 for the NAPLS3 and CATIE dataset, respectively. As the AUTEC advised, ethical approval for the systematic review was not required.

Chapter 1 Introduction

> Some decisions that might not have been the most rational. Times I didn't follow the norm, thought differently. But I can see there's a connection between not following normal thinking and doing creative thinking. I wouldn't have had good scientific ideas if I had thought more normally. (Hegarty, 2005, April 8)

Given my own lived experience of schizophrenia, this quote from Professor John Nash, the only publicly known person with schizophrenia to receive a Nobel prize, appropriately embodies the relationship I have between the mental health disorder schizophrenia and someone who pursues research using alternative statistical and conceptual models.

1.1 Positioning myself as a researcher

This section describes my position as a doctoral researcher. In 2010, I was diagnosed with schizophrenia, a label for particular, brave experiences of a new world. In 2010, my psychiatrist wrote to my former university about my ability to study in a quote: "he is therefore unable to study and although I hope that at some point he may be able to return to his studies this is not likely to be for many months, if at all" (D. Manovitch, personal communication, June 3, 2010). My mother also experiences schizophrenia. As the son of a mother living with severe and debilitating schizophrenia and with lived experience of schizophrenia, my experiences have shaped my ambition and drive to understand the schizophrenia syndrome, and education is the method I have used to achieve this. Following a near-complete symptomatic recovery and 12 years of education in psychology, mental health, schizophrenia, and statistics, the connection with the original condition and some of my experiences can be elusive and retrospective at times.

My previous experiences with delusions and my experiences as a son of a parent diagnosed with schizophrenia highlight an abyss that some people living with schizophrenia (PLS) live in. An abyss which people cannot escape, so deep and dark that the person is unaware of the abyss they live in. Despite a plethora of research, a means to reverse schizophrenia, or the abyss, permanently in people who experience symptoms and functional impairment after the first episode, people with a chronic condition, seems to be more a matter of hope than something that is translational, given the current research. With my previous experiences with mental illness, the support I received during my journey, my background as a statistician, and my education in psychology, my primary goal in education is to alleviate the poor outcomes of schizophrenia so that the prognosis I experienced can be transferable to others. This thesis serves as a stepping stone to achieving this goal.

The drive to produce something ground-breaking for schizophrenia also reflects my pain in the understanding of the incremental progress of schizophrenia since the discovery of the efficacy of chlorpromazine in the 1950s (Seeman, 2021). Despite being incremental, I have an understanding that schizophrenia is a well-documented and well-researched area of investigation (Weinberger & Harrison, 2011). The list of research topics on schizophrenia is extensive, and outcomes of schizophrenia have improved markedly over the decades. Many PLS may lead a meaningful life, contribute to society, and experience general feelings of well-being and quality of life (QOL). Approximately 60% of people have symptom and functional remission from the first episode of schizophrenia (Lally et al., 2017). However, a proportion of PLS patients remain treatment-resistant or experience severe symptoms (Correll & Howes, 2021), long hospitalisation (Ajnakina et al., 2020), poor functioning (Yang et al., 2021), lack of employment and education (Holm et al., 2021), worse QOL (Dong et al., 2019), lower life expectancy (Peritogiannis et al., 2022), and higher rates of suicide compared to healthy controls (HC) (Peritogiannis et al., 2022). These poor outcomes have given me the drive to research, a drive that is rooted in personal experiences and the relationship with my mother, who has lived treatment-resistant for the majority of her life. A Master in Applied Statistics degree, being a PhD candidate, and having a drive for research have set me on a journey to use robust, but not mainstream, approaches to the study of schizophrenia.

The research presented herein can be considered a reflection of efforts to develop and utilise new methods and inferences for evaluating both established and emerging theories and conceptualisations of schizophrenia. The epistemological stance taken, a complex systems approach to schizophrenia, is not mainstream yet, and part of my intention was to push the boundaries of current research as it applies to PLS. My mother, my peers, and I with schizophrenia challenge notions of normality, and this thesis is perhaps a reflection of this. This method was chosen selectively to pursue reframing schizophrenia as a complex phenomenon alongside other evidence-based conceptualisations of schizophrenia. In this thesis, this often translates into unavoidable arguments for the network theory of mental disorders (NTMD). Utilising SNs was intended to provide something different, novel, meaningful, and substantial, as opposed to an argument for a new doctrine in research.

Henceforth, the works contained herein set out an approach to schizophrenia that transitions from primarily traditional methodologies and conceptualisations of schizophrenia to an alternative view of schizophrenia, a complex understanding of this heterogeneous syndrome. This approach is selected to improve future outcomes of schizophrenia by being innovative in the design and implementation of this thesis, by a person with schizophrenia, for people with schizophrenia. For this purpose, the remaining introduction to this thesis provides a brief overview of schizophrenia, symptom networks (SNs), and their applicability to schizophrenia, as well as the rationale for each manuscript included. Following this in the introduction, an outline of the thesis organisation is presented, along with the aims and objectives of this thesis, before proceeding to the next chapter on the schizophrenia syndrome.

1.2 Overview of schizophrenia

Schizophrenia is classified as a mental disorder, usually diagnosed in early adulthood, and can lead to decades of impairments in psychological, functional, social, occupational, and QOL domains (American Psychiatric Association, 2022; Charlson et al., 2018). Schizophrenia is one of the most debilitating mental health conditions, as acute schizophrenia has the highest disability weights of all conditions in the Global Burden of Disease study (Charlson et al., 2018). PLS have approximately 15-20 years lower life expectancy, primarily due to natural causes, but also because of unnatural causes such as suicide (Peritogiannis et al., 2022). Many PLS commit suicide due to its debilitating nature, and PLS with good insight may commit suicide due to the understanding of the suffering, stress, shame, and stigma associated with the illness (Peritogiannis et al., 2022). Despite these negative statistics, a substantial body of evidence describes the nature of the syndrome, which may soon lead to enduring improvements for PLS.

There have been many advances in the understanding of schizophrenia since the discovery of the efficacy of first-generation antipsychotic medication in 1952 (Seeman, 2021), and the deinstitutionalisation of PLS and community integration. These more recent advances include early intervention, the development of robust conceptual models or paradigms of schizophrenia, advances in neuroimaging and genomics technologies and the assessment of schizophrenia (Weinberger & Harrison, 2011). These advances have allowed for a more detailed theoretical understanding of the schizophrenia syndrome. Current research includes the development of newer atypical antipsychotics (Kane & Correll, 2010), research on the prevention of some people at ultra-high risk of schizophrenia from acquiring schizophrenia (Mei et al., 2021), and research on cognitive remediation therapies for treating cognitive and functional impairments of schizophrenia (Lejeune et al., 2021). Future developments might include cognitive-enhancing medications (McCutcheon et al., 2023), treatments of negative symptoms (Shukla et al., 2024), gene editing (Khalesi & Khalesi, 2024), and precision medicine (Manchia et al., 2020). Despite these advances in the understanding and treatment of schizophrenia, these advances may not yet be realised in terms of reversing or preventing schizophrenia, or do not have a large effect on symptom domains other than hallucinations or delusions, as described in Chapter 2.

Despite the advancement in the understanding of schizophrenia, the first-line treatment of schizophrenia applies advances in older models of health: the prescription of antipsychotics and community care (Shrivastava & Johnston, 2010), although advances in other treatments, such as cognitive remediation and early intervention, are recommended to be used in routine treatment (Cella et al., 2017; Cheng & Schepp, 2016; Vita et al., 2021). Future advancements may transform the treatment and outcomes of schizophrenia and lead to breakthrough improvements for PLS. Other advances include conceptual or modelling, which are non-specific to schizophrenia. These broader developments can be attributed to advancing technology, conceptual models, and modelling techniques (Correll et al., 2022; Cortes-Briones et al., 2022; Cuthbert & Morris, 2021). A new modelling technique may advance the understanding of the phenomena of mental illness and schizophrenia, specifically SNs, which contrasts with other models of health.

1.3 Overview of symptom networks and their applicability to schizophrenia

SNs are new modelling techniques that are increasingly used to advance the understanding of mental illness (Berta et al., 2022). SNs are graphical models of symptoms and provide a novel paradigm or explanatory framework of mental health conditions based on the complex relationships between symptoms underlying a disorder, such as schizophrenia (Borsboom, 2017). SNs have seen a significant increase in interest since their first application in 2010 (Berta et al., 2022; Cramer et al., 2010). This method has provided a promising alternative to traditional views of mental health by proposing models that capture the complex interplay between symptoms as components of a larger system. Symptoms here are not expressions of an illness that point to a likely disease; symptoms may individually or jointly cause other symptoms. SNs of mental disorders differ from other paradigms as the joint expression of all symptoms represents a condition or phenomenon, given the properties of the network (Guyon et al., 2017). SNs not only offer a novel way to model complex experiences of schizophrenia, but schizophrenia can represent the attractor of the network properties (Borsboom, 2017; Guyon et al., 2017). That is, the structure and properties of the network may represent the mental disorder schizophrenia (Borsboom, 2017; Guyon et al., 2017), an inference not proposed when examining the individual parts of the network, such as examining hallucinations or delusions individually. A Bayesian network (BN) is a particular modelling framework that encodes conditional probability relationships into a directed acyclic graph (DAG), as detailed in Chapter 3. In this thesis, SNs' graphical network model of symptoms and BNs represent a methodology which may not be limited to modelling symptoms. These terms independently describe components of Bayesian symptom networks. The SN and BN frameworks allow research to make unique inferences for schizophrenia, and schizophrenia may uniquely be well-suited for SN models.

Previous theoretical orientations have labelled schizophrenia as a disease entity or syndrome, yet no biomarker of schizophrenia has been identified to date (Fišar, 2023). Concordantly, diagnosis relies on the reporting of clinical manifestations of the syndrome rather than through biomedical indicators (Isvoranu et al., 2018). Before the SN approach to mental disorders (Borsboom, 2017; Borsboom & Cramer, 2013), the biomedical view of schizophrenia regarded signs and symptoms as indicators of disease, placing little importance on the structure and relationships between these signs and symptoms (Isvoranu et al., 2018). Given that the symptoms of schizophrenia are not unique to schizophrenia, that they are a collection of symptoms found in other conditions (Barch et al., 2022), the properties arising from the dependency between a constellation of symptoms in schizophrenia may be regarded as key in the understanding and representation of the syndrome. In this framework, symptoms such as hallucinations, delusions, alogia, and asociality may be dependent on or cause each other, rather than the proposal that these symptoms serve as signs and symptoms of an underlying condition. Furthermore, schizophrenia is a heterogeneous syndrome with diverse presentations, aetiology, and outcomes (Isvoranu et al., 2018). Therefore, a complex systems approach may be well-suited to model the complexity of schizophrenia, to understand the variation in symptomatic presentation, and to make predictions based on network properties (Isvoranu et al., 2018). The inferences made when applying a complex system to model schizophrenia may also have unique value in understanding, preventing, or treating schizophrenia (Isvoranu et al., 2018). Given this brief overview of schizophrenia, SNs, and the applicability of SNs to schizophrenia, the following section of this introduction focuses on an overview of the rationale of each study manuscript included in this thesis as part of the Doctor of Philosophy degree.

1.4 Overview of each study

Because of the applicability of SNs to model schizophrenia, several SN studies of schizophrenia have already been published (Isvoranu et al., 2018; Isvoranu et al., 2020; Isvoranu et al., 2016); however, it is also unclear whether the literature on SNs of schizophrenia has congruent findings and is complete. Given this, I conducted a systematic literature review to identify the most important variables in the networks across studies (Buchwald et al., 2024). Furthermore, this research included information on the methodologies of the various studies to determine what additional research is needed for further studies in this thesis. This systematic review has been published in the journal Psychological Medicine (Buchwald et al., 2024).

Within the systematic review, cognition was identified to be the central component of schizophrenia. Other research suggests cognition or cognitive impairment has a strong predictive validity in determining functional outcomes (Kahn & Keefe, 2013). The evidence for the primacy of cognition has led to the hypothesis that schizophrenia is primarily a disorder of cognition (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). Although there is a body of research on SN of schizophrenia, and despite arguments for the primacy of cognition, there is no research identifying the structure and relationship of cognitive functions, demographics, QOL, and clinical covariates in a directed network (Buchwald et al., 2024). Hence, following the systematic review, in Chapter 5, I investigated the directed relationships between scores on cognitive assessments and other variables to identify critical areas that may be targeted to potentially improve outcomes for PLS. This manuscript has been submitted to BJPsych Open and is currently awaiting the handling editor's decision.

In addition to these novel research areas, Borsboom (2017) proposed the NTMD, which proposed four principles or assumptions that enable a comprehensive theoretical model of mental disorders to account for the complex relationship between symptoms. Yet none of these principles has been assessed empirically for their validity. Additionally, in the literature review and other publications, other studies on SN have been conducted in opposition to other models of health, such as the latent variable model (LVM) and disease model (Bringmann & Eronen, 2018; Buchwald et al., 2024). Despite this, some researchers have proposed that LVMs and SN models are compatible with each other (Bringmann & Eronen, 2018; Epskamp et al., 2017) and suggest that these theoretical frameworks can be complementary and statistically integrated into one model (Bringmann & Eronen, 2018; Epskamp et al., 2017). No study identified in the systematic review conducted an integration between an LVM and an SN model for PLS (Buchwald et al., 2024). Hence, the third study presented here aimed to determine whether a network model with latent variables would fit better than a network or LVM alone in modelling relationships between items on the Positive and Negative Syndrome Scale (PANSS) and the Scale of Psychosis Risk Symptoms (SOPS) assessment in people diagnosed with schizophrenia (PDS). I submitted this research to the journal Collabra: Psychology. These three manuscripts comprise the body of the thesis, along with other key chapters. An outline of the thesis structure is provided below.

1.5 Thesis outline, aims, and objectives

This thesis follows the format-two structure of a PhD by publication at Auckland University of Technology, allowing the research to evolve through a series of interconnected studies that build progressively on earlier findings over the course of the PhD. All references included in this thesis are in APA 7 format (American Psychological Association, 2020). In this thesis, I describe the clinical research on PLS in Chapter 2, including its presentation, prevalence, aetiology, course, prognosis, cognitive impairments, cultural aspects, treatments, and theoretical orientations. In Chapter 3, I first examine how SNs serve as a paradigm of mental health, followed by a brief overview of pairwise Markov random fields (PMRFs), the essentials of BNs, and finally, Structural Causal Models (SCMs). I also discuss some inference techniques that are available when applying a SN. A more detailed overview of PMRF, an alternative statistical approach, is documented in Appendix B. Following these literature review chapters, Chapter 4 presents the systematic review published in Psychological Medicine (Buchwald et al., 2024). Chapter 5 contains the manuscript of an SN of cognition, QOL, demographics and clinical covariates. I present the last manuscript in Chapter 6, which assesses the complexity principle of the NTMD (Borsboom, 2017). BNs are the statistical method applied in the second

(Chapter 5) and third (Chapter 6) studies included in this thesis. In Chapter 7, I integrate the findings and inferences from the three manuscripts, highlight the relevance of processing speed and cognition for PLS, identify a novel application of SN, and end with a summative conclusion. Given the structure of this thesis, the following aims and objectives, which evolved over the course of the research, are proposed:

1. To provide an overview of schizophrenia and the SN approach.
2. To identify which domain of health is most central across SN studies of schizophrenia.
3. To identify critical gaps in the literature on SNs of schizophrenia.
4. To reconstruct a BN on cognitive, clinical, QOL, and demographic characteristics of schizophrenia to make inferences about the relationship between cognition and other variables.
5. To test the complexity principle theorised by Borsboom (2017),
6. Given the existing literature and the research conducted, this thesis aims to explore the primacy of cognition in schizophrenia and propose a new application of SNs using BNs.

Chapter 2 Literature Review. The Schizophrenia Syndrome

2.1 Overview

Schizophrenia is a heterogeneous syndrome marked by symptoms including cognitive impairment, reality distortion, psychomotor poverty, and disorganisation (American Psychiatric Association, 2022; World Health Organization, 2019). Schizophrenia is one of the more severe psychological disorders due to the chronicity and functional impairment that is often associated with its diagnosis (Borsboom, 2017; Jauhar et al., 2022). Although recovery from schizophrenia has improved considerably over the years (Taylor & Jauhar, 2019), PLS generally have poorer outcomes than most other mental health conditions, as schizophrenia is associated with a reduction in functional capacity in multiple domains of life (Vita & Barlati, 2018). According to Charlson et al. (2018), acute schizophrenia carries the highest disability weight of all disorders in the Global Burden of Disease study. Similarly, whether people have acute symptoms or not, schizophrenia ranks 15th highest as a cause of disability from all disorders in the Global Burden of Disease study, as reported by Moreno-Kustner et al. (2018). Overall, people with schizophrenia have a reduced life expectancy of 10 to 20 years due to natural causes, such as medical conditions and unnatural causes, such as suicide (Laursen et al., 2012; Lee et al., 2018; Peritogiannis et al., 2022). Despite the research on schizophrenia increasing steadily over time, many salient aspects of schizophrenia, such as the exact causal mechanisms underpinning schizophrenia, remain elusive (Kiraz & Demir, 2021; Weinberger & Harrison, 2011). With the steady increase in research in the last five decades with the introduction of new technologies, historically, early conceptualisations of schizophrenia, such as schizophrenia being a dementing condition, and later conceptualisations, such as schizophrenia being primarily defined by positive (hallucinations and delusions) and negative (alogia, anhedonia, blunted affect, asociality, amotivation) symptoms, have changed in recent decades (Kiraz & Demir, 2021; Taylor & Jauhar, 2019).

2.2 History and development

Early conceptualisations of schizophrenia postulated that schizophrenia was a dementing condition and was given the term *dementia praecox* (premature dementia) by Emil Kraepelin in 1893 (Kraepelin, 1913). Schizophrenia was then conceptualised as marked by a slow and steady decline in cognition (Kahn, 2020). At the time, the label dementia praecox was part of an attempt to create a diagnostic entity for schizophrenia (Katschnig, 2018). According to Kahn (2020), Kraepelin placed less focus on psychotic symptoms of schizophrenia, the symptoms that later became core criteria for the diagnosis of schizophrenia (American Psychiatric Association, 2022; World Health Organization, 2019), as documented in Section 2.3.3 in this thesis. Although the identification of schizophrenia as a diagnostic entity can be traced to Kraepelin, it was not long before other researchers, such as Eugen Bleuler, challenged the notion that schizophrenia was a dementing condition and in 1908 (Bleuler, 1908), Bleuler suggested that the name of the condition be changed to *schizophrenia* (Katschnig, 2018). Schizophrenia, which currently remains the formal term for this condition, can be translated from Greek to *split mind* to emphasise the incoherence of associations that could be observed in people with schizophrenia (Gaebel & Kerst, 2019; Katschnig, 2018). Hence, more emphasis was placed on thought disorder symptoms, which are evident through aberrant language, as defined in Section 2.3.1. Nevertheless, early theories of symptoms (defined in Section 2.2) can be dated back to Kraepelin and Bleuler's pioneering investigations (Mosolov & Yaltonskaya, 2022).

In terms of symptomatology, early accounts tended not to regard hallucinations and delusions as core symptoms of the disorder until later, when Kurt Schneider argued that hallucinations and delusions should be considered *first-rank symptoms* of schizophrenia in 1939 (Katschnig, 2018). The definition of first-rank symptoms led to the adoption of criteria, including hallucinations and delusions, in diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) for a diagnosis of schizophrenia (American Psychiatric Association, 2013). In addition to the diagnosis and symptom structure of schizophrenia, several movements focused on the validity of schizophrenia as a disease entity. The proposal of antipsychiatry movements criticised how mental illnesses were defined, including schizophrenia (Laing & Esterson, 1964). The work of R.D. Laing suggested that schizophrenia was internal conflict, a product of schizophrenogenic parents (Laing & Esterson, 1964). However, the biological basis of schizophrenia and mental disorders in general is now more established and therefore notions of mental illness are more difficult to debunk (Szasz, 2011). Contemporary research tends to suggest that schizophrenia is marked primarily by cognitive impairment (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022).

The development of assessments to measure the qualities of people with schizophrenia has been useful in identifying clinical traits associated with the disorder, ranging from symptoms to cognition to QOL. New developments in technologies and computing, assessments, and statistics have had a profound effect on the ability to research the complexities of schizophrenia. Functional magnetic resonance imaging, for example, has led to the resurgence of conceptualising schizophrenia as characterised by a split mind, due to the finding of disconnected brain regions (Bleuler, 1908; Friston & Frith, 1995). Advances in genetics have led to the discovery that schizophrenia is highly polygenic (Smeland et al., 2020). Lastly, innovative statistical and mathematical modelling techniques have led to advances in the theory and understanding of schizophrenia (Valton et al., 2017). For example, recent models that view symptoms as a complex system, rather than focusing on individual signs and symptoms of a disease, enable researchers to investigate the complexities and comorbidities of mental disorders, as well as improve predictions of outcomes (Borsboom, 2017; Briganti et al., 2023).

2.3 Symptomatology and diagnosis

2.3.1 Symptomatology

The symptom profile of schizophrenia is unique to the disorder, but no one symptom is pathognomonic to schizophrenia (Barch et al., 2022). This means all the symptoms of schizophrenia can occur in other conditions and are not unique to the syndrome (Barch et al., 2022). Because no symptom is pathognomonic to schizophrenia, using specific symptoms as markers of schizophrenia results in problems of specificity and sensitivity in classifying schizophrenia. It is the collection of specific symptoms and classification guidelines that allow for a differential diagnosis of the schizophrenia syndrome, however. Additionally, some symptoms of schizophrenia are more common than others. PLS generally experience hallucinations and delusions, which are excesses to normal experience (positive symptoms). A hallucination can be defined as "a sensory experience that resembles veridical perception without having a corresponding sensory stimulation from the external environment" (Montagnese et al., 2021, p. 237). Similarly, a delusion can be defined as a "false belief that is held with certainty and which cannot be corrected", where logic is insufficient to change a person's belief (Feyaerts et al., 2021, p. 2). Delusions must be beliefs not experienced by the same-culture peers (Galbraith, 2021). Hence, this rules out conspiracy theories or religious beliefs as delusions so long as these beliefs align with socio-cultural norms (Galbraith, 2021). Other symptoms reflect deficits in experiences or reduction in normal function (negative symptoms). Correll and Schooler (2020) identify five primary negative symptoms: (a) alogia, reduction in the number of words spoken; (b) anhedonia, reduced experience of anticipatory pleasure; (c) asociality, reduced social interaction; (d) avolition, a lack of motivation leading to less goal-directed behaviour; and (e) blunted affect, diminished facial or vocal expressions. Negative symptoms may be regarded as *signs* (i.e., observable, objective) of schizophrenia, whereas positive symptoms may be regarded as *symptoms* (i.e., subjective, reported but not directly observable) of schizophrenia. Schizophrenia and depressive disorders are often comorbid in a diagnosis of schizophrenia, partially because the symptom anhedonia is a shared symptom of both conditions, although there may be some phenomenological differences (Lambert et al., 2018).

Depression is particularly common in PLS, and depending on whether people are in the acute stages of the illness or remission, the prevalence of depression differs (Upthegrove et al., 2017). According to Upthegrove et al. (2017), up to 60% of people in the acute stages of the illness, those experiencing positive symptoms, have depression. In contrast, about 20% of people with chronic schizophrenia and 50% of people after the first episode experience depression (Upthegrove et al., 2017). Other research suggests that negative symptoms are associated with depressive symptoms, but only in females (an der Heiden et al., 2016). Overall, approximately 80% of PLS experience a significant depressive episode once or more during the early phases of schizophrenia (Upthegrove et al., 2017). The symptom anhedonia is shared with depressive disorders, but it is the presence of various symptoms, such as positive, negative, and thought disorder symptoms, that characterise the schizophrenia syndrome.

PLS may also experience thought disorder symptoms, which are inferred from aberrant communication and language. Investigations of rating scales have identified up to 18 thought disorder symptoms, and according to Roche et al. (2015), thought disorder symptoms may represent multiple pathologies. Some thought disorder symptoms identified by Roche et al. (2015) include loosening of associations, pressure of speech, tangentiality, derailment, incoherence, and circumstantiality. The study of thought disorders assumes that thought organisation can be inferred from speech, although some researchers argue that these are language disorders rather than disturbances in thought processes (Hart & Lewine, 2017). Although mild impairments in speech occur in HC, a thought disorder should be regarded as multidimensional and multifaceted due to its complexity (Hart & Lewine, 2017). Thought disorder symptoms also have a stronger link to etiological processes than positive and negative symptoms in PLS (Hart & Lewine, 2017). Key positive, negative, and thought disorder symptoms can be found in Figure 1.

PLS may experience a wide range of symptoms, and two PLS may be diagnosed with schizophrenia and not share any symptoms based on the DSM-5 criteria (American Psychiatric Association, 2022). Moreover, given criteria A in the DSM-5-Text Revision for the diagnosis of schizophrenia (see Section 2.3.3), nine people can all have schizophrenia, each with different symptom profiles (American Psychiatric Association, 2022). Despite the small number of symptom profiles of schizophrenia in the DSM-5, there is considerable heterogeneity and diversity in the presentation, aetiology, history, and outcomes of PLS. Because of this heterogeneity of schizophrenia, schizophrenia is better regarded as a syndrome, or a collection of diseases, rather than a unitary disease entity (Carpenter, 2007).

The rationale for conceptualising schizophrenia as a syndrome becomes apparent when its symptoms are reduced to more specific phenomena. For example, in their lifetime, 64-80% of PLS experience auditory hallucinations, 23-31% experience visual hallucinations, 9-19% experience tactile hallucinations, and 6-10% experience olfactory hallucinations (McCarthy-Jones et al., 2017). Furthermore, although most people experience hallucinations in one sensory modality, approximately a third experience hallucinations in two modalities (McCarthy-Jones et al., 2017). Moreover, hallucinations are specified further as musical hallucinations, acousmas, (sounds such as rattling, humming, laughing), command hallucinations (instructing the person to carry out a task), autoscopic hallucinations (hallucination of the image of one's own body or face), for example (Aleman & Larøi, 2008; Anzellotti et al., 2011). In particular, there are possibly six types of autoscopic hallucinations (Anzellotti et al., 2011). The diversity in the symptomatology of hallucinations also applies to delusions, which also have many subtypes. There is no consensus in the literature on whether specific symptoms have multiple dependencies on each other when considered within a complex systems approach, particularly for specific subcategories of symptoms. Because of the diversity and breadth of symptoms experienced by PLS, research on schizophrenia has attempted to group symptoms of schizophrenia into meaningful categories, such as those introduced in the DSM-IV (American Psychiatric Association, 1994) and DSM-5 (American Psychiatric Association, 2013).

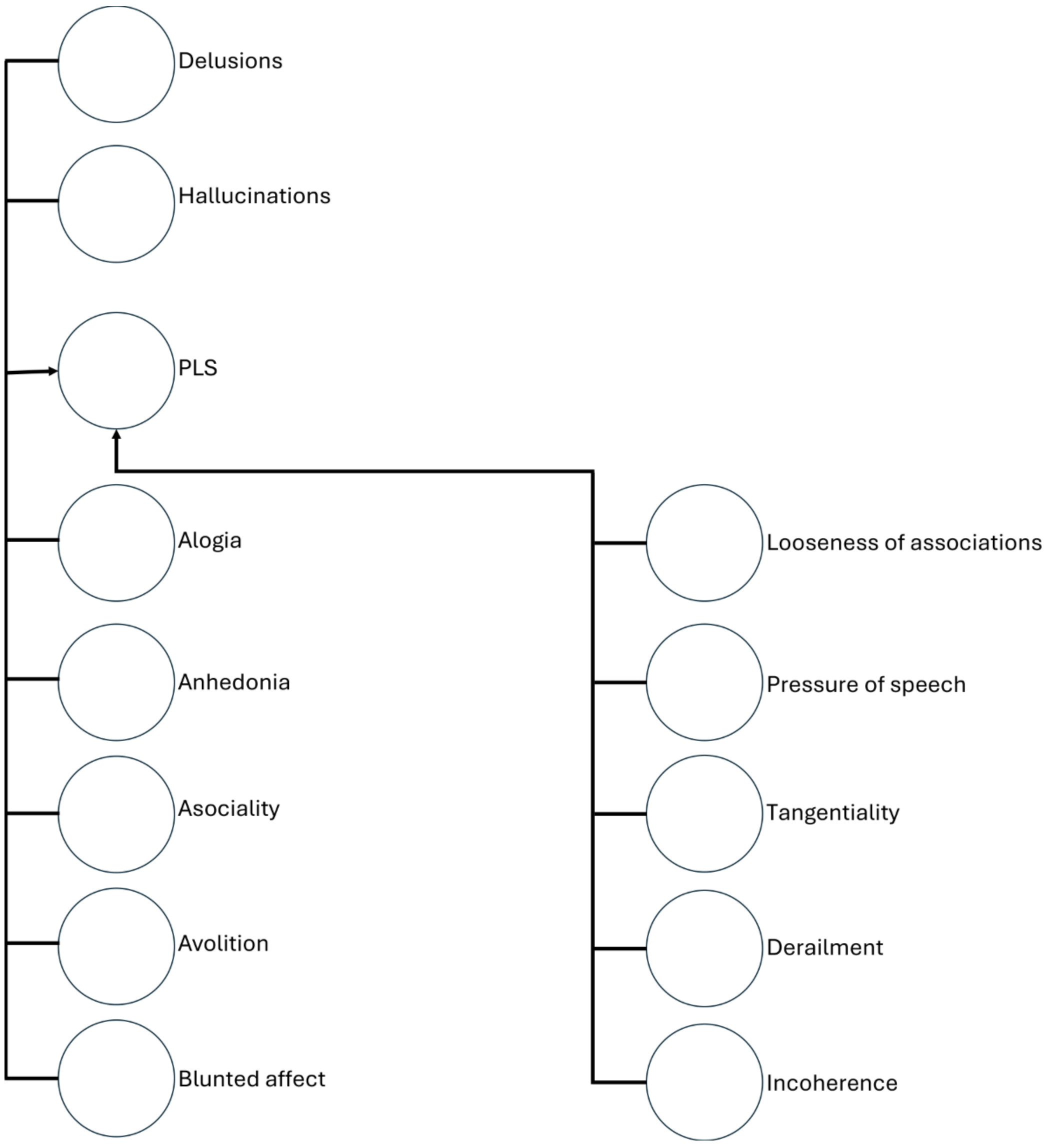

Figure 1. Symptoms of Schizophrenia.

2.3.2 Symptom groupings

To unify experiences of the schizophrenia syndrome, numerous symptom groupings have been proposed. One natural way to view symptoms is to cluster them into groups that share similar features, although other methods can examine the interconnections between symptoms using a complex systems approach. This section will review classification approaches to schizophrenia, and the systems approach will be addressed in Section 2.10.7 and Chapter 3. One such classification of symptoms was by Andreasen and Olsen (1982), who grouped symptoms into positive symptoms (Hallucinations, delusions, positive formal thought disorder, and bizarre behaviour), negative symptoms (Alogia, anhedonia, affective flattening, avolition, and attentional impairment) and mixed schizophrenia (prominence of both positive and negative schizophrenia or a lack of both positive and negative schizophrenia). Other researchers, such as Liddle et al. (1989), classified the symptoms of the schizophrenia syndrome into three groups based on the statistical method: factor analysis. According to Liddle et al. (1989), these were: reality distortion (Hallucinations and delusions), psychomotor poverty (Alogia, flat affect, decreased spontaneous movement, paucity of expressive gestures, affective non-responsivity, lack of vocal inflection) and the disorganised syndrome (inappropriate affect, poverty of content of speech, tangentiality, derailment, pressure of speech, distractibility). Figure 2 presents an example of symptom grouping, as described by Liddle et al. (1989). In contemporary research, the symptoms of schizophrenia may be generally categorised into positive, negative, and disorganised symptoms.

In addition to these dimensions of schizophrenia, some authors identify that impaired cognition should be added as another symptom dimension of schizophrenia (Bell et al., 1994; Buchanan & Carpenter, 1994). Some authors treat cognition as a symptom dimension in an attempt to compare its relationships with other symptom dimensions (Klingberg et al., 2006). Cognitive symptoms appear to have a stronger correlation with negative symptoms than disorganised symptoms and almost no correlation with the severity of positive symptoms (Klingberg et al., 2006; O'Leary et al., 2000). The symptom groupings may also differ in their onset time or trajectory over the illness. Impaired cognition, for example, has a different onset time and course than positive symptoms (Heilbronner et al., 2016; Napal et al., 2012), with evidence suggesting that cognitive impairment may originate in infancy or early childhood (Keefe & Harvey, 2012; Mollon & Reichenberg, 2018). Conversely, positive symptoms mark the onset of a psychotic disorder as part of the DSM-5, Text Revision (DSM-5-TR) definition of psychotic disorders, which may lead to a diagnosis of schizophrenia, depending on the length of time a person is symptomatic (American Psychiatric Association, 2022). More information on the course of symptoms can be found in Section 2.6.4.

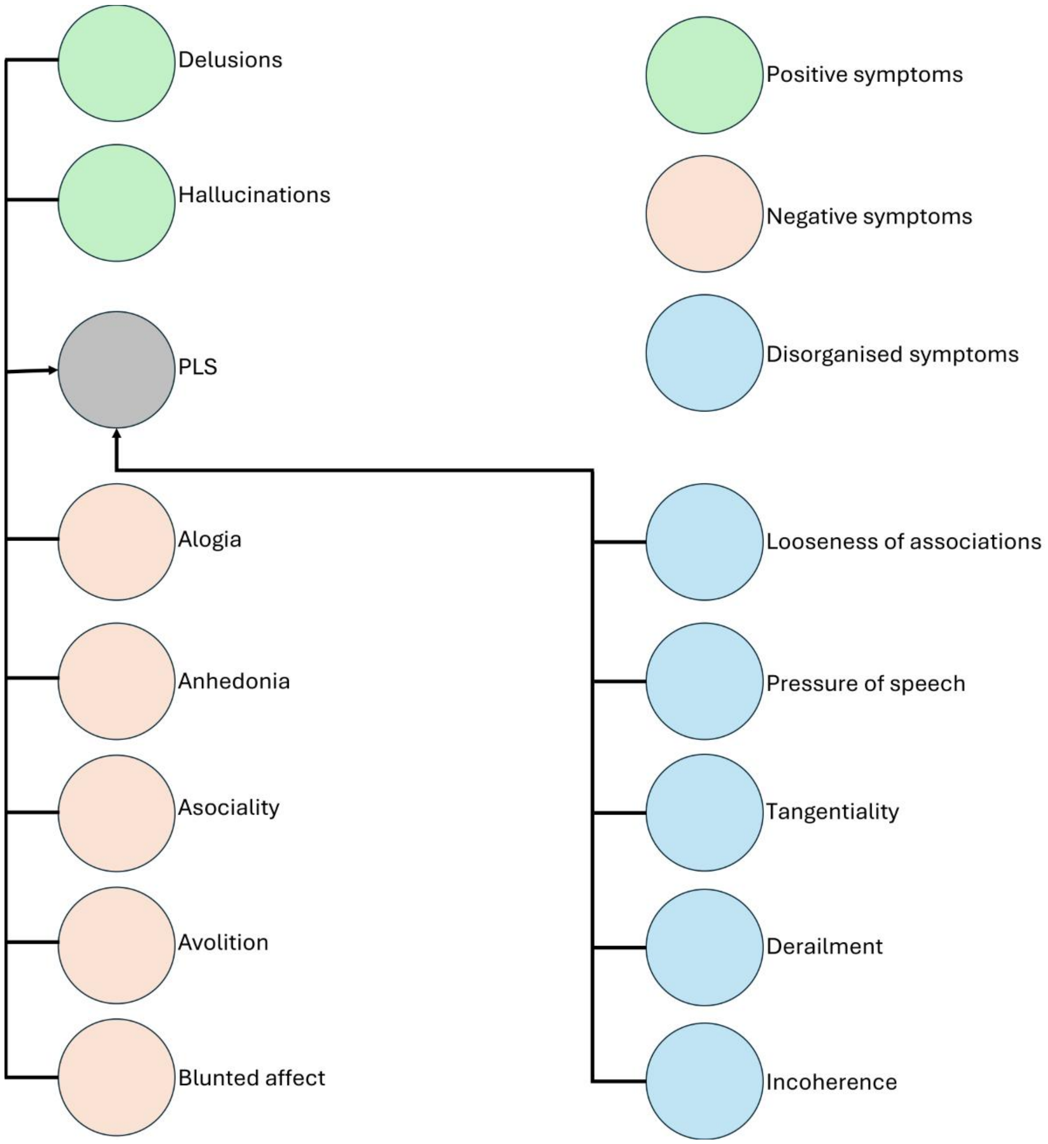

Figure 2. Symptom Groupings of Schizophrenia.

2.3.3 Diagnosis

Currently, positive symptoms, negative symptoms, and disorganised symptoms are typically regarded as the three major symptom classifications in schizophrenia, as supported in the DSM-5-TR (American Psychiatric Association, 2022) and the International Classification of Diseases 11th Edition (ICD-11; World Health Organization, 2019). Cognition was not, however, introduced into the DSM-5, as the Work Group on the Classification of Psychotic Disorders agreed that although it had good prognostic value, it would complicate the differential diagnosis of schizophrenia (Biedermann & Fleischhacker, 2016; McCutcheon et al., 2023; Reddy et al., 2014). Cognitive impairment was, however, included as a symptom qualifier in the ICD-11 (Gaebel et al., 2020). Figure 3 provides symptom grouping and includes key DSM-5-TR diagnostic criteria (American Psychiatric Association, 2022).

According to the DSM-5-TR (American Psychiatric Association, 2022, p. 114), a diagnosis of schizophrenia can be made if criterion A is satisfied: “Two (or more) of the following, each present for a significant proportion of time during 1 month (or less if successfully treated) at least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganised speech (e.g., frequent derailment or incoherence).
4. Grossly disorganised or catatonic behaviour.
5. Negative symptoms (i.e. diminished emotional expression or avolition).”

Other criteria include the length of the illness, which should be at least six months since the onset of symptoms, with one month of symptoms meeting the above criteria, and other conditions such as bipolar, depression, schizoaffective disorder, substance use intoxication, withdrawal, or dependence, another medical condition, and in some cases, autism ruled out as part of the diagnosis (American Psychiatric Association, 2022). The person must also have a disturbance in functioning in one or more major areas, including interpersonal relations or self-care, to make a diagnosis of schizophrenia (American Psychiatric Association, 2022).

In terms of the ICD-11, to be diagnosed with schizophrenia, people must experience a disturbance in multiple modalities, including thinking (delusions, thought disorganisation), perception (hallucinations), self-experiences (an experience that one’s feelings, impulses, thoughts or behaviour are under the control of an external force), cognition (attention, verbal memory, social cognition), affect (blunted affect), and behaviour (behaviour that appears unpredictable, bizarre or purposeless, or inappropriate emotional responses that interfere with the organisation of behaviour), according to the World Health Organization (2019). Here, persistent delusions, persistent hallucinations, a thought disorder, and experiences of passivity, influence, or control are considered core symptoms (World Health Organization, 2019). In addition to this, people must have had symptoms for at least one month to receive a diagnosis, the symptoms must not be a manifestation of another health condition, and the symptoms must not be an effect of a substance or medication, including substance withdrawal (World Health Organization, 2019).

Although schizophrenia represents a unique diagnosis, other psychotic conditions can be diagnosed that are related to schizophrenia and share similar symptoms. Suppose a person has experienced one or more of delusions, hallucinations, or disorganised speech and grossly disorganised behaviour for at least one day but less than one month, with a full return to premorbid functioning. In that case, that person may be diagnosed with brief psychotic disorder, as opposed to schizophrenia in the DSM-5 (American Psychiatric Association, 2022). Note that at least one of the symptoms must have been delusions, hallucinations, or disorganised speech

(American Psychiatric Association, 2022). Similar criteria are found for a diagnosis of schizophreniform disorder, compared with schizophrenia, as two or more symptoms from criterion A must be present, with one of these symptoms being delusions, hallucinations, or disorganised speech (American Psychiatric Association, 2022). Furthermore, for schizophreniform disorder, the symptoms must be present for less than six months (American Psychiatric Association, 2022). Additionally, schizoaffective disorder is another psychotic disorder and includes criterion A of schizophrenia but also consists of a major depressive episode, manic episode, or mixed episode concurrent with symptoms from criterion A of schizophrenia (American Psychiatric Association, 2022). For schizoaffective disorder, the person must have "delusions or hallucinations for 2 or more weeks in the absence of major mood episode (depressive or manic) during the lifetime duration of the illness", and symptoms for a mood episode must be present for a substantial proportion of the total duration of the active and residual periods of the illness (American Psychiatric Association, 2022, p. 121). In this thesis, the diagnoses schizophrenia, schizophreniform, brief psychotic disorder, and schizoaffective disorder are collectively referred to as schizophrenia or within the context of PLS or people PDS. Other disorders, such as delusional disorder, psychotic disorder due to another medication condition, substance/medication induced psychotic disorder, unspecified schizophrenia spectrum and other psychotic disorder, other specified schizophrenia spectrum, and other psychotic disorder, are not termed schizophrenia or included in the term PLS or PDS in this thesis.

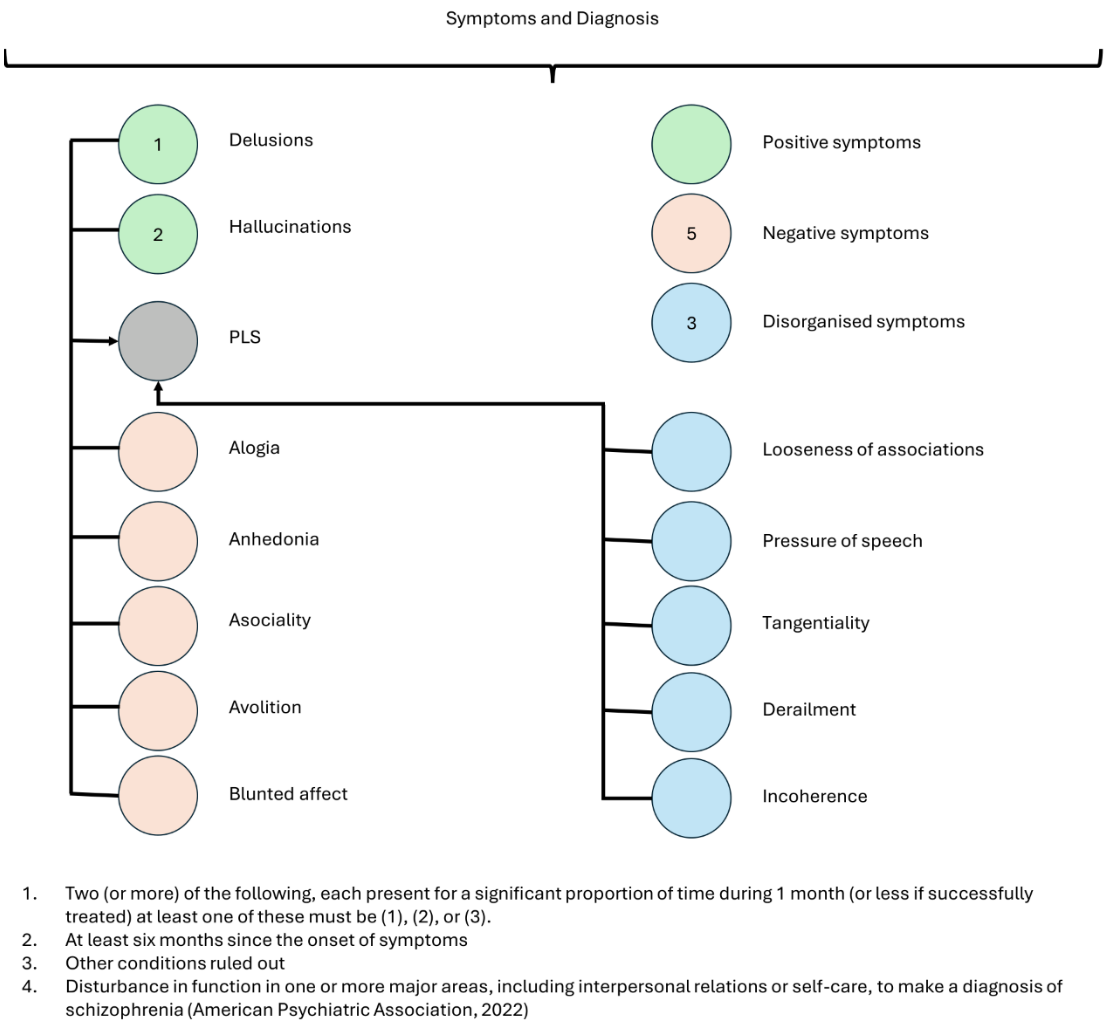

Figure 3. Symptom Groupings and DSM-5 Diagnostic Criteria of Schizophrenia.

2.4 Prevalence

2.4.1 Global and national estimates

The lifetime prevalence of schizophrenia is estimated to be 0.73% (Moreno-Kustner et al., 2018), which means 0.73% of the population will be diagnosed with schizophrenia at some point in their life. One study found an age-standardised point prevalence of 0.28%, indicating that .28% of the global population was diagnosed with schizophrenia in 2016, given countries that had recorded prevalence estimates in the global burden of disease study (Charlson et al., 2018). Although prevalence estimates are approximately similar across countries, minor differences are also found by country of origin (Siegert, 2000). According to Charlson et al. (2018), Taiwan and China had the largest age-standardised point prevalence of schizophrenia in 2016 compared to other countries considered (0.44% and 0.42%, respectively). Interestingly, New Zealand had a higher age-standardised point prevalence (.31) compared to the worldwide age-standardised point prevalence in 2016 (.28). The lowest estimate for age-standardised point prevalence worldwide in 2016 was in Afghanistan (.16). However, less data were available in low and middle-income countries in this study (Charlson et al., 2018).

2.4.2 Gender

According to Ochoa et al. (2012), there are no gender differences in the lifetime prevalence of schizophrenia between genders; however, men may have a higher incidence of schizophrenia. Some authors have found that the incidence of schizophrenia is greater among men than women, and this difference may be due to genetic vulnerability, the protective factor of estrogens, greater substance abuse among men, and diagnostic criteria (Ochoa et al., 2012; Sommer et al., 2020). Furthermore, Ochoa et al. (2012) identify that men have an earlier onset (between ages 18 and 25) than women (between ages 25 and 35), which may contribute to incidence estimates.

2.4.3 Age

Another consideration is prevalence by age group. The highest global mean point prevalence rate is at age 40, with a decline in older age groups (Charlson et al., 2018). This means that the highest proportion of PLS were age 40, compared to other ages, at the time of the study. According to Clemmensen et al. (2012), a minority of PLS had the onset before age 18 (4.7% of all PLS), and the onset of schizophrenia before age 13 (child onset) is extremely rare (1 in 30,000 children). More research is needed on childhood-onset schizophrenia using standardised assessments (Clemmensen et al., 2012; Driver et al., 2020). Childhood-onset schizophrenia is associated with a very poor prognosis, a worse prognosis than early-onset schizophrenia or adult-onset schizophrenia (Clemmensen et al., 2012).

2.5 Aetiology

2.5.1 Heritability and twin studies

In a meta-analysis of twin studies, heritability estimates of schizophrenia tend to identify that genetics accounts for the majority of the variation in the cause of schizophrenia (81%), with 95% confidence intervals for these estimates ranging from 73% to 90% (Sullivan et al., 2003). According to one meta-analysis, people who have one proband diagnosed with schizophrenia have an increase in odds of 7.7 that they will be diagnosed with schizophrenia, and those with two probands have an increase in odds of 11.1, compared to those with no probands with schizophrenia (Lo et al., 2020). The risk of schizophrenia also depends on the degree of relatedness with the proband. In the study by Gottesman et al. (2010), if both parents were admitted to a hospital for schizophrenia, 29.3% of the children were later diagnosed with schizophrenia. Moreover, in families where one parent was admitted for schizophrenia, 7% of the offspring were diagnosed with schizophrenia, compared to 0.86% where neither parent was admitted for schizophrenia. In monozygotic twins, if one twin is diagnosed with schizophrenia, there is more than a 50% chance the other twin will be diagnosed with schizophrenia at some point (Janoutová et al., 2016). Earlier estimates are available from Gottesman (1991), who identified that in dizygotic twins with one twin with schizophrenia, 17% of the remaining twins were diagnosed with schizophrenia. Furthermore, in people with a sibling currently diagnosed with schizophrenia, 9% of the undiagnosed siblings were diagnosed with schizophrenia at some point in their lives (Gottesman, 1991). Recent information on familial risk is needed. Schizophrenia is highly heritable and is regarded as a polygenic condition, which means more than one gene is related to the expression of schizophrenia (Smeland et al., 2020).

2.5.2 Biological causes

Many genetic studies have been conducted on schizophrenia, and it is estimated that 1000s of genes could be associated with the risk of acquiring schizophrenia, where most genes have a very small effect size (Smeland et al., 2020). Gene variants that feature in the causal pathway of schizophrenia have been well-established in the literature, and although genome-wide association studies have been useful for schizophrenia, they do not identify the biological mechanism by which genes translate into the clinical phenomena of schizophrenia (Tamminga et al., 2017). Because of this, endophenotype studies have received more interest over the years (Weinberger & Harrison, 2011), and some major genes have been associated with biochemical processes with moderate effect sizes in schizophrenia.

The focus on dopamine dysfunction as a cause of schizophrenia has developed from the dopamine hypothesis, which was identified when antipsychotic medication was first found to be successful at reducing positive symptoms of schizophrenia (Howes et al., 2017). The importance of dopamine in the expression of positive symptoms of schizophrenia has been well-researched (McCutcheon et al., 2019). The unifying dopamine hypothesis of schizophrenia suggests that altered transmission of nerve signals and striatal dopamine dysregulation result from the interaction of environmental, genetic, and neurodevelopmental risk factors, which lead to the onset of schizophrenia (Fišar, 2023; Howes & Kapur, 2009). Another dopamine theory of the cause of schizophrenia, the integrated sociodevelopmental-cognitive model, suggests that neurodevelopment, caused by genes and adversity during childhood, sensitises the dopamine system and leads to excess presynaptic dopamine synthesis and release (Fišar, 2023; Howes & Murray, 2014). Although the dopamine hypothesis has received considerable attention over the years, researchers now turn to other neurotransmitters to identify the cause and maintenance of schizophrenia.

Both glutamate and dopamine have been implicated in the pathoaetiology of schizophrenia more so than other neurochemicals (Howes et al., 2015). A particular focus has been given to glutamate in recent years, primarily because dopamine hyperactivity is a partial consequence of glutamate dysregulation in the prefrontal cortex in schizophrenia and because the relationship between glutamate is central to cognition in schizophrenia (Howes et al., 2015; Stahl, 2018). Evidence suggests glutamate receptor dysfunction may have a higher association with impairments in cognition and negative symptoms than dopamine dysregulation (Howes et al., 2015). Glutamate dysfunction is currently regarded as being associated with the structural changes in the brain in PLS (Plitman et al., 2014). The current understanding suggests that rather than a deficit in glutamate neurotransmission, the primary involvement is in N-methyl-D-aspartate receptor dysfunction (Howes et al., 2015).

Glutamate dysfunction has also been proposed to be in the causal pathway of schizophrenia. Increased glutamate and N-methyl-D-aspartate hypofunction tends to have toxic effects on humans and can lead to structural abnormalities in schizophrenia, treatment-naïve PLS, and people at ultra-high risk of schizophrenia (Plitman et al., 2014). One theory of the etiological basis of schizophrenia, the epigenetic hypothesis, identifies that genetic and epigenetic susceptibility to schizophrenia is responsible for the causes of schizophrenia (Fišar, 2023). This theory hypothesises that reduced glutamate hypofunction leads to insufficient gamma-aminobutyric acid release on cortical pyramidal neurons (Fišar, 2023). An alternative hypothesis has been proposed, known as the unitary pathophysiological hypothesis. This hypothesis posits that early brain insults can lead to the abnormal development of specific neural circuits, ultimately resulting in cognitive and psychosocial dysfunction (Fišar, 2023). This theory proposes that early neurodevelopmental changes in response to glutamatergic neuronal loss during pregnancy, as well as late neurodevelopmental changes in N-methyl-D-aspartate receptor hypofunction, excessive synaptic pruning, and neurodegenerative processes resulting from glutamate excitotoxicity, may cause the development of schizophrenia in late adolescence (Fišar, 2023). Glutamate has been implicated in numerous other hypotheses for the cause of schizophrenia, with neurodevelopment being at the forefront of these hypotheses (Fišar, 2023).

2.5.3 Developmental causes

A strong line of research has identified that prenatal, perinatal, and postnatal factors are the primary causal factors of schizophrenia (Murray et al., 2017). This forms the neurodevelopmental hypothesis of schizophrenia (Murray et al., 2017). Development in childhood and adolescence is also implicated in schizophrenia under this hypothesis (Murray et al., 2017). Part of the neurodevelopmental approach to schizophrenia identifies that neurodevelopmental functions go awry, and this leads to the onset of schizophrenia (Murray et al., 2017). Hence, genetics, the environment, and aberrant development together increase the risk of schizophrenia (Murray et al., 2017).

People with schizophrenia have an increased number of adverse events during childhood (Davies et al., 2020). After excluding studies based solely on recall or retrospective questionnaires, a systematic review and meta-analysis by Davies et al. (2020) found that over 30 prenatal and perinatal risk factors and five prenatal and perinatal protective factors were implicated. These include pregnancy and birth factors such as the age of the mother at the child's birth, fewer antenatal care visits, winter birth, famine and nutritional deficiencies during pregnancy, and infections of the mother, such as herpes type 2 or toxoplasmosis (Davies et al., 2020). Events during birth include, but are not limited to, obstetric complications, hypoxia, ruptured membranes, polyhydramnios, and blood loss during pregnancy (Davies et al., 2020). Many of these factors had an odds ratio higher than 1.5 (Davies et al., 2020). Low birth weight is associated with an increased risk of schizophrenia, whereas higher birth weight is associated with a decreased risk of schizophrenia (Davies et al., 2020). Lastly, premature birth and congenital malformations were associated with an increased risk of schizophrenia (Davies et al., 2020). For the most part, these findings are in agreement with the systematic review by Laurens et al. (2015) and Radua et al. (2018), who both conducted a review of prenatal and perinatal risk factors of schizophrenia.

The neurodevelopmental hypothesis extends to events in childhood. These events are considered environmental or epigenetic (Popovic et al., 2019). According to Popovic et al. (2019), these environmental risk factors may be associated with DNA hypomethylation and over-activation of the stress response. This over-activation of the stress response may increase cortisol levels and dopamine, and may be related to the development of psychotic symptoms (Kraan et al., 2015). In a meta-analysis by Varese et al. (2012), sexual abuse, physical abuse, emotional abuse, bullying, neglect, and parental death were associated with an increased risk of developing schizophrenia in children under the age of 18. Some studies indicate that childhood trauma is related to more severe positive symptoms in people with schizophrenia, according to a systematic review and meta-analysis (Bailey et al., 2018). Although childhood trauma is associated with an increased risk of schizophrenia, one meta-analysis found a lower prevalence of recent life events in people at ultra-high-risk of schizophrenia and did not find an association between recent life events and transition to schizophrenia in people at ultra-high risk (Kraan et al., 2015).

2.5.4 Environmental causes

In addition to the developmental risk factors described in the sections above, there are other risks associated with schizophrenia that may interact with genes to increase the risk of a diagnosis of schizophrenia. The association between genes and the environment can be identified by comparing the concordance rates of monozygotic twins, dizygotic twins, siblings who are not twins, siblings reared together, and siblings reared apart. Interestingly, there is a greater risk for schizophrenia if the child of a mother with schizophrenia is reared in adoptive settings, whether this is a foster home or an institution (Gejman et al., 2011). Further, offspring of mothers without a diagnosis of schizophrenia, raised with adoptive parents who had schizophrenia, did not increase the risk of the child acquiring schizophrenia (Gejman et al., 2010). The increased risk of a child whose mother had schizophrenia raised in an adoption setting may be due to a dysfunctional adoptive family environment in which the child was raised (Fosse et al., 2016). This is evidence that both a dysfunctional environment for the child and the separation of children from their parents may be environmental risk factors for schizophrenia.

A significant amount of evidence has accumulated for the social causes of schizophrenia. For example, it has long been established that migration is associated with an increased risk of schizophrenia (Cantor-Graae & Selten, 2005; Henssler et al., 2020), and the risk of acquiring schizophrenia is higher in refugee migrants compared to nonrefugee migrants (Brandt et al., 2019). Other considerations include whether people are at greater risk of schizophrenia in rural compared with urban environments. In developed countries, people have a greater risk of schizophrenia if they were raised in an urban environment, and this risk increases with the level of urbanicity (Castillejos et al., 2018). Urbanicity may be associated with an increased risk of schizophrenia in people with genetic liability because of social fragmentation, poor cohesion, isolation, social stress, and less perceived safety (Van Os, 2004). Lastly, in terms of social-environmental causes, there is considerable evidence that bullying or social adversity is associated with an increased risk of schizophrenia. Bullying confers a moderate increase in the risk of schizophrenia, with an odds ratio of 2.1, compared to individuals who were not exposed to bullying (Cunningham et al., 2016). The authors note that the risk of acquiring schizophrenia increases as the severity and frequency of bullying increase, indicating a dose-response relationship between bullying and the risk of schizophrenia (Cunningham et al., 2016). These social considerations have a moderate effect on the risk of someone acquiring schizophrenia. However, other biological and environmental risk factors have a much larger association with the risk of someone acquiring schizophrenia. Figure 4 presents key risk factors of schizophrenia grouped by prenatal, perinatal, and postnatal/environmental factors.

Environmental risk factors such as substance abuse, which operate immediately on the biology of a person with schizophrenia or a person at risk of schizophrenia, may be considered the most influential environmental risk factors of schizophrenia. The evidence suggests that substance abuse, particularly at younger ages, increases the risk of schizophrenia considerably compared to those who abstain or delay the use of substances (Kiburi et al., 2021). One meta-analysis identified an increased risk of schizophrenia for the heaviest cannabis users, with an odds ratio of 3.9 compared with non-users, with the median use of cannabis odds being 1.9 compared to non-users (Marconi et al., 2016). Additionally, earlier use of cannabis is associated with both an increased risk of schizophrenia and an earlier onset of schizophrenia (Kiburi et al., 2021; Large et al., 2011). Other substances may also increase the risk of schizophrenia. One study found that the risk of schizophrenia increases most with a methamphetamine-related diagnosis, followed by cannabis, cocaine, alcohol, and then opioids, compared to a control group of no drug use (Callaghan et al., 2012). Evidence indicates that methamphetamine use at younger ages and more prolonged use increases the chance of diagnosis of schizophrenia (Callaghan et al., 2012).

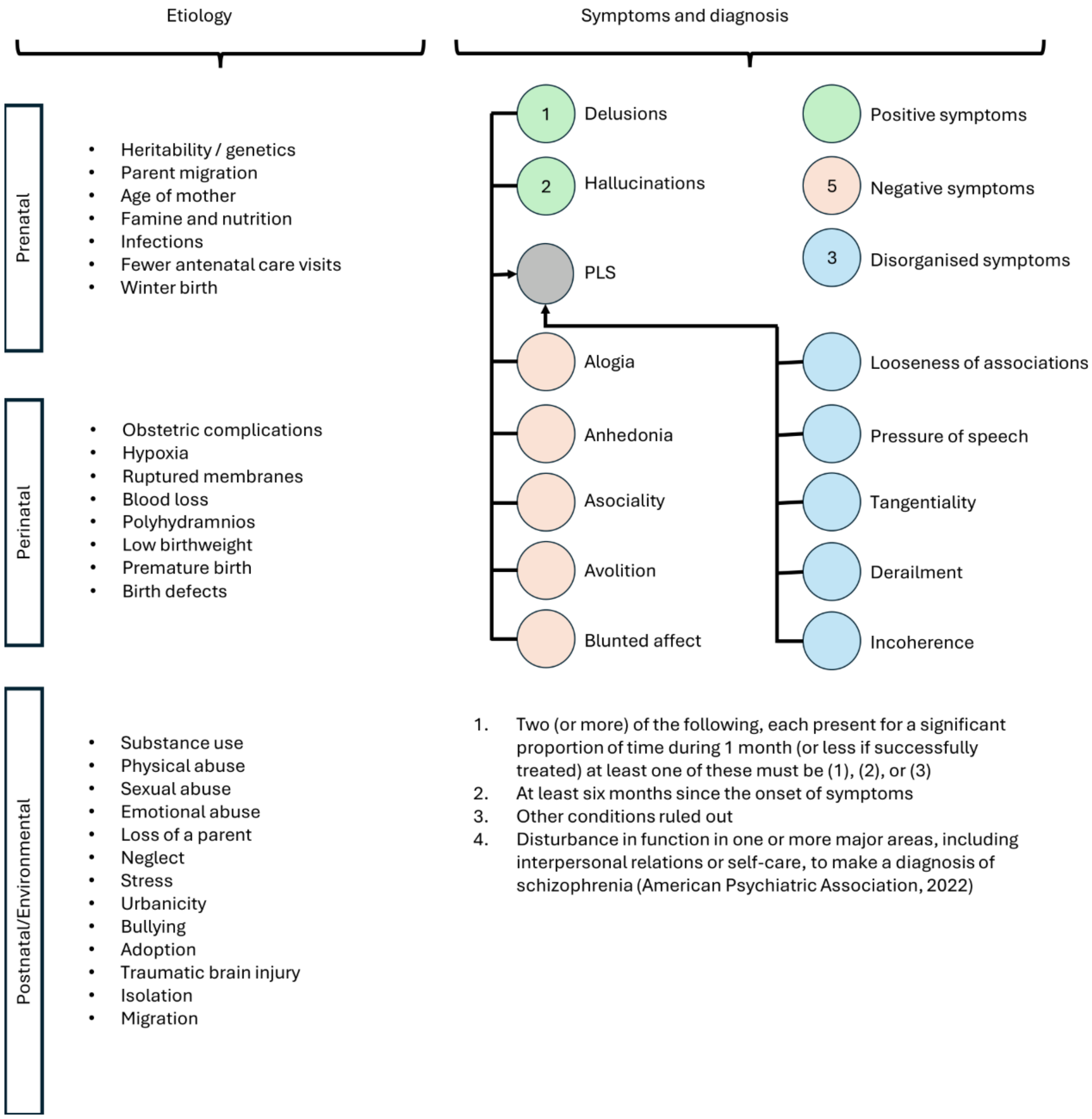

Figure 4. Symptom Groupings, DSM-5 Diagnostic Criteria, and Aetiology of Schizophrenia.

2.6 Course and prognosis

Schizophrenia is best characterised as having a heterogeneous course and outcomes, and outcomes of schizophrenia have improved considerably over the decades (Altamura et al., 2014; Sommer et al., 2020). The course of schizophrenia can be separated into two categories: the natural course, which represents the natural evolution of symptoms without medical intervention, and the course of schizophrenia following treatment with antipsychotics (Wyatt, 1991). Other considerations include the specific symptom dimension and its course. Positive symptoms, for example, have a different course than cognitive impairment for schizophrenia, which is again different from symptoms of depression in schizophrenia (Häfner, 2019). Although the overall course is heterogeneous (Heilbronner et al., 2016), people usually progress through stages of schizophrenia, where the stages are the premorbid, prodrome, and prepsychotic stages, onset, and then outcome, recovery, or long-term course (Wójciak et al., 2016). Premorbid stages here are discussed under the section's aetiology and developmental causes, and prepsychotic stages are discussed below under the prodrome of schizophrenia.

2.6.1 The prodrome of schizophrenia

According to Yung and McGorry (1996a), the prodrome of psychosis refers to a period of disturbance that deviates from previous behaviour or experiences and occurs before the development of florid features of psychosis. The prodrome is identified after a diagnosis of schizophrenia is confirmed, and hence, often, the experiences are described retrospectively, knowing that definitive signs and symptoms of schizophrenia did manifest. People at ultra-high risk of schizophrenia, however, may not transition to schizophrenia and, therefore, may not experience the prodrome of schizophrenia (Modinos & McGuire, 2015; Yung et al., 2008). Furthermore, given the heterogeneity of schizophrenia, not all people experience the prodrome of schizophrenia before becoming diagnosed (Benrimoh et al., 2024). Given the working definition of the prodrome by Benrimoh et al. (2024), approximately 78% of people experience the prodrome before transitioning to first-episode psychosis. In addition to this variability, there is also variability in terms of the experiences of the prodrome in schizophrenia.

People in the prodrome of schizophrenia may have various experiences that mark abnormality. These experiences include impaired functioning, cognitive impairment, such as speed and verbal memory, social reasoning, and emotional processing; mood and behavioural changes, including anxiety, depression, mood swings, sleep disturbances, irritability, anger, and suicidal ideation; social withdrawal; alogia; anhedonia; odd beliefs or magical thinking; and subclinical auditory hallucinations, among others (George et al., 2017; Olsen & Rosenbaum, 2006). Given these experiences, the prodrome of schizophrenia was considered a candidate for inclusion in the DSM-5 as a diagnosable condition named attenuated psychosis syndrome (Tsuang et al., 2013). However, the working group for the DSM-5 considered that it should remain as a condition for further study (Tsuang et al., 2013). In addition to inclusion in the DSM-5, some authors challenge the specificity and sensitivity of markers of the prodrome, identifying that they may be predictive of other mental health conditions (Woodberry et al., 2016). Additionally, it is unclear if these variables are causal or serve as indicators of impending psychosis

(Woodberry et al., 2016). Nevertheless, a considerable amount of work has been conducted on people at ultra-high risk in distinguishing between people who will or will not become diagnosed with schizophrenia. Distinguishing between people who will or will not become diagnosed with schizophrenia may have treatment implications in preventing schizophrenia.

Two key cohort studies have been conducted on people at ultra-high risk of schizophrenia, reported herein. The first study is derived from the personal assessment and crisis evaluation clinic, a specialised clinic for people at ultra-high risk of schizophrenia (Nelson et al., 2013). It was through patients from this service that the Comprehensive Assessment of At-Risk Mental States (CAARMS) was developed. The CAARMS is used to assess the psychopathology of people who are at ultra-high risk of psychosis and identify people who meet ultra-high risk criteria (Yung et al., 2005). Additionally, a major study on ultra-high-risk individuals was conducted by the University of California San Francisco (Addington et al., 2022), known as the North American Prodromal Longitudinal Study 3 (NAPLS3). According to Addington et al. (2022), people included in this study were assessed as clinically high risk of schizophrenia using the Criteria of Psychosis-Risk Syndromes based on the Structured Interview for Psychosis-Risk Syndromes. In both studies, individuals were help-seeking individuals referred by government or non-government services or self-referrals by the young person or their family (Addington et al., 2022; Phillips et al., 2002). These studies were implemented not only to identify predictors of transition to schizophrenia but also to identify possible treatments for people at ultra-high risk, which may reduce the transition rate to psychosis.

Although a considerable amount of research has focused on the prediction of the clinical outcome in people at ultra-high risk, some studies have focused on delaying or preventing psychosis (Worthington & Cannon, 2021). Although the prevention of psychosis is often the primary outcome, other treatment goals include a change in positive or negative symptoms, improved functioning, or reduced anxiety or depression (Worthington & Cannon, 2021). The transition rate of someone ultra-high risk transitioning to schizophrenia, based on psychological assessments, is approximately 16% in a two-year follow-up period (Yung et al., 2008). Evidence-based therapies are now available for people at ultra-high risk of schizophrenia (McGorry et al., 2009; Preti & Cella, 2010). Several meta-analyses have been published on reducing transition rates in people at ultra-high risk of psychosis. One meta-analysis by Mei et al. (2021) found that the pooled effect of all psychosocial interventions reduced the transition to psychosis with a risk ratio of .50 at 12 months, whereas pooled pharmacological interventions had no effect at 12 months. This provides sound evidence that supports psychosocial interventions such as cognitive behavioural therapy as a method to reduce the risk of transitioning to psychosis. The benefits of cognitive behavioural therapy have been supported in other meta-analyses for follow-ups of 12 months or 18 months (Devoe et al., 2020). Another recent meta-analysis identified that cognitive behavioural therapy did not reduce transition rates to schizophrenia compared with controls (Devoe et al., 2019). Although antipsychotics do not appear to reduce the rate of transition to schizophrenia, antipsychotics seem to reduce positive symptoms during the first episode, in those who transition to schizophrenia (Worthington & Cannon, 2021). Evidence suggests that the side effects of antipsychotics may be more harmful to people than reducing positive symptoms in the first episode, where withholding antipsychotics in people at ultra-high risk does little harm at the onset of psychosis (McGorry et al., 2021). The relatively new complex systems approach to psychopathology may be useful for building models with strong predictive validity in classifying people who will become diagnosed with schizophrenia and identifying treatment effects, as these models are predictive models that can introduce time into the model (Scutari & Denis, 2021).

2.6.2 Onset

The onset of schizophrenia has been defined and explored within research, and formal definitions have been proposed. People are usually defined to have schizophrenia when florid or frank psychotic symptoms are present and experience symptoms that meet the threshold for a diagnosis (Yung et al., 2005). However, this transition to psychosis may be fluid and continuous as opposed to discrete (Yung & McGorry, 1996b). What is essential, in terms of onset, is whether the onset of psychotic symptoms is insidious or abrupt. The longer the person experiences subthreshold symptoms, the more insidious the onset. With insidious onset, there is a higher probability of a worse prognosis (Juola et al., 2013). An insidious onset could refer to the collection of symptoms in the prodrome and the length of time people with psychosis had subthreshold symptoms. In addition to this, people with an insidious onset are more likely to have a longer duration of untreated schizophrenia (Qiu et al., 2019). The duration of untreated schizophrenia, or the duration during which clinical treatment is delayed after onset, is a key factor in the prognosis of schizophrenia. Duration of untreated schizophrenia refers to the interval between the onset of florid symptoms of schizophrenia and the initiation of pharmacological intervention (Norman & Malla, 2001). However, other researchers have broadened this notion of treatment to psychosocial intervention, contact with treatment providers, or hospital admission (Penttilä et al., 2014). The international target for treatment is three months following onset, as strong evidence suggests a short time between onset and treatment is predictive of better prognosis, including illness course, cognitive impairment, and functional outcome, among others (Cotter et al., 2017).

2.6.3 Outcome, recovery and long-term course

Overall, the long-term course of schizophrenia is heterogeneous, and there have been many attempts to identify the proportion of people in remission from schizophrenia or who have recovered (Griffiths et al., 2022). Most of the evidence of the long-term course of schizophrenia is in people who are medicated. In terms of the natural course, schizophrenia is considered a lifelong disease, although a deteriorating course is unusual for schizophrenia, as schizophrenia is usually marked by stability or is episodic (Isohanni et al., 2020). In a systematic review of approximately 19,000 individuals with first-episode psychosis, symptoms and functional remission (greater than six months) from schizophrenia were found in 58% of the pooled sample (Lally et al., 2017). In terms of recovery, symptom improvement, and social, occupational, and educational functional improvement for at least two years were observed in 38% of cases, with a mean follow-up of 7.2 years (Lally et al., 2017). However, Lally et al. (2017) identified that they did not take into consideration confounding variables such as medication adherence and substance abuse. In terms of chronicity or treatment-resistant outcomes, approximately 20% to 30% of PLS are treatment-resistant to antipsychotics, or more formally, people are non-responsive to two sequential antipsychotic trials, which have sufficient dose, duration, and adherence (Correll & Howes, 2021). In addition to the relief of positive symptoms of schizophrenia, negative symptoms and cognitive impairment are not considered to be treatable with pharmacological agents (Galderisi et al., 2021; Javitt, 2023; McCutcheon et al., 2023). Negative symptoms, cognitive impairment, and depression may have a course separate from positive symptoms of schizophrenia.

2.6.4 Trajectory of symptom domains

In schizophrenia, the course of various symptom domains varies and may be independent or dependent on other symptom domains. Because positive symptoms are treatable with antipsychotics, PLS usually have an intense first episode of positive symptoms, which remits following treatment (Austin et al., 2015). Despite this, Austin et al. (2015) found that recovery from positive symptoms is heterogeneous and identified various trajectories of positive symptoms. Other studies identified that some PLS have constant positive symptom severity, although most have found improvement over time (Heilbronner et al., 2016). Another study found that positive symptoms increase linearly over a year following discontinuation of antipsychotics (Takeuchi et al., 2017). Most people typically experience improvements in positive symptoms but less so for negative symptoms, likely due to the scarcity of treatments available for negative symptoms (Starzer et al., 2023).

Early conceptualisations of negative symptoms identified that the course may be independent of positive symptoms (Addington & Addington, 1991; Pogue-Geile & Harrow, 1985) and that negative symptoms follow a stable course over the illness (Eaton et al., 1995). Starzer et al. (2023) identified two-course profiles of negative symptoms in schizophrenia. Half of the sample exhibited a continuous symptom profile characterised by a high level of negative symptoms at baseline, with no change in symptom severity thereafter. The other half of the sample had low negative symptoms at baseline, followed by remission in the first few years (Starzer et al., 2023). Other studies have found that negative symptoms have a remitting course (an der Heiden et al., 2016; Savill et al., 2015).

Cognitive impairments in schizophrenia tend to have an onset before starting primary school, and the gap in cognitive functioning between people who will eventually be diagnosed with schizophrenia and HC increases over the schooling period (Keefe, 2014). PLS have severe cognitive impairments after the onset of schizophrenia, and evidence suggests that second-generation antipsychotics have little to no efficacy in improving cognitive impairments in PLS (Keefe, 2014). One meta-analysis showed that although PLS may experience improvement in both positive and negative symptoms after the first episode, cognitive impairment tends to be stable throughout the illness (Heilbronner et al., 2016). Although stability was reported by Heilbronner et al. (2016), the authors noted considerable heterogeneity in the magnitude of the difference between PLS and HCs. Despite this, some evidence exists that cognitive remediation is more clinically meaningful and generalisable if administered early in the course of schizophrenia. Aside from cognitive impairment, an overview of the stages of schizophrenia and positive and negative symptom trajectories is presented in Figure 5, based on the work by Starzer et al. (2023) and Weinberger and Harrison (2011).

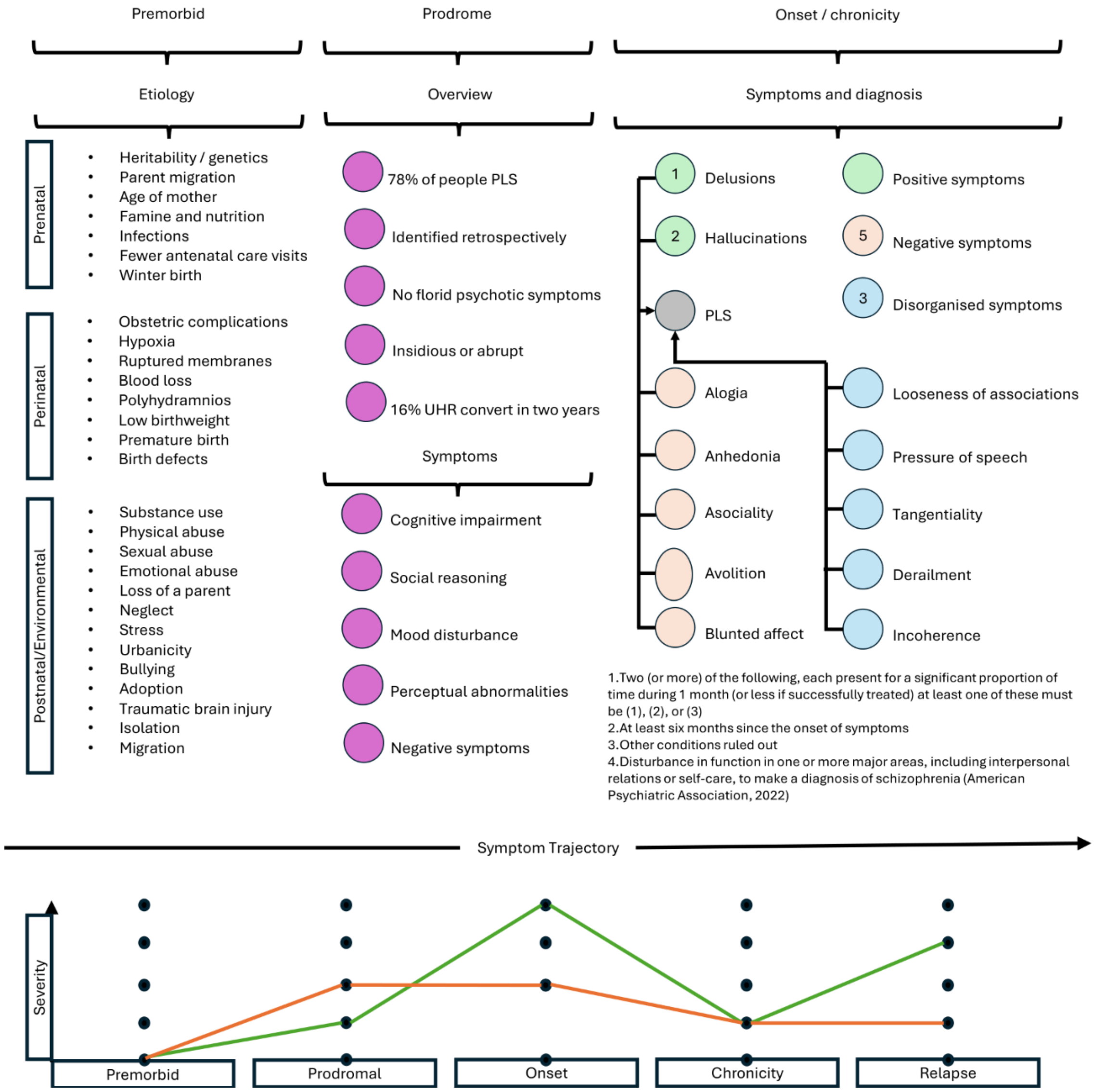

Figure 5. Symptom Groupings, DSM-5 Diagnostic Criteria, Aetiology, Stages, and Symptom Trajectories of Schizophrenia.

2.7 Cognition

Given that cognition is central to schizophrenia in predicting long-term outcomes and functional capacity, some regard schizophrenia as a disorder of cognition (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). According to a meta-analysis by Trotta et al. (2015), PLS have, on average, a significant decrease in intelligence compared to HCs in premorbid intelligence (standardised mean difference = -.60) and have a large reduction in post-onset intelligence (standardised mean difference = -1.37). Although these figures are based on standardised mean difference, this translates into a reduction of the intelligence of approximately nine intelligence quotient (IQ) points before the onset of the first episode and 21 IQ points post-onset. Although PLS have specific deficits in particular functions, overall, schizophrenia is considered heterogeneous and associated with diffuse impairments (McCutcheon et al., 2023), and this has led to cognition being viewed as central in schizophrenia. This may be because people with schizophrenia have diffuse structural impairments across brain regions (Khalil et al., 2022; Wheeler & Voineskos, 2014). Some cognitive impairments may be specific to structural changes in particular brain regions, although cognitive impairment may be more related to diffuse white matter integrity and network connectivity between brain regions (Khalil et al., 2022; Wheeler & Voineskos, 2014), although grey matter loss has also been implicated (Moustafa et al., 2016). White matter integrity may be crucial for specific cognitive impairments, such as processing speed (Alloza et al., 2016). Although schizophrenia is associated with general cognitive impairment, some cognitive abilities are more impaired than others (Mihaljević-Peleš et al., 2019).

PLS often experience difficulties with processing speed, episodic memory, working memory, executive functioning, and attention (Siegert, 2000). Although a paucity of research identifies which cognitive domain is central to schizophrenia, some authors argue that processing speed is most impaired and contributes most to general mental ability (Dickinson et al., 2007; Schaefer et al., 2013). Despite this, a key consideration is whether to identify an impairment in isolation or identify an impairment as interdependent with other cognitive functions. Cognitive domains may naturally be interconnected and dependent on each other, as good performance in one domain may be dependent on performance in other domains. Statistical methods such as network analysis may be able to highlight these dependencies rather than treating them as independent phenomena. Concordantly, many authors emphasise the importance of processing speed in contributing to higher cognitive functions such as working memory and executive functioning (Thuaire et al., 2022),

Memory, in general, is considered to be severely impaired in schizophrenia (Gold & Luck, 2022). Working memory, in particular, is severely impaired in PLS, associated with impairments in both the storage of information and the updating of representations of working memory objects (Gold & Luck, 2022). Encoding, as opposed to retrieval memory, has been identified to be impaired in schizophrenia (Gold et al., 1992). The impairments in episodic memory may partly be due to either top-down or bottom-up processes. In addition to working memory, executive functioning impairments have also received considerable attention in schizophrenia (Orellana & Slachevsky, 2013), where executive functioning impairments have been associated with social, decision-making, planning, solving complex problems, and working memory impairments in PLS (Orellana & Slachevsky, 2013).

The Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) was a consensus-based collection of psychological assessments to standardise and evaluate various treatments for cognition in schizophrenia (Marder & Fenton, 2004). Figure 6 presents an overview of the MATRICS battery and the course of cognitive impairment in schizophrenia. The development of the collection of assessments was to standardise findings and report on research on therapies to improve cognition in schizophrenia (Marder & Fenton, 2004). The MATRICS cognitive battery includes assessments of processing speed, working memory, attention and vigilance, visual learning and memory, verbal learning and memory, and reasoning and problem-solving (Nuechterlein et al., 2004). Social cognition was also recognised as important to schizophrenia (Harrington et al., 2005; Langdon et al., 2005) and was, therefore, later added as a seventh domain (Nuechterlein et al., 2004). In most studies assessing cognition in schizophrenia, there is no development of medications to target a domain in the MATRICS, nor is there any consensus on which domain in the MATRICS is most important to intervene on (Horan et al., 2022). Methods are available to identify which MATRICS domain would be central to target in future pharmacological therapies, in addition to specifying interrelationships between MATRICS domains, yet few studies have been conducted on this to date (Briganti et al., 2023; Horan et al., 2022).

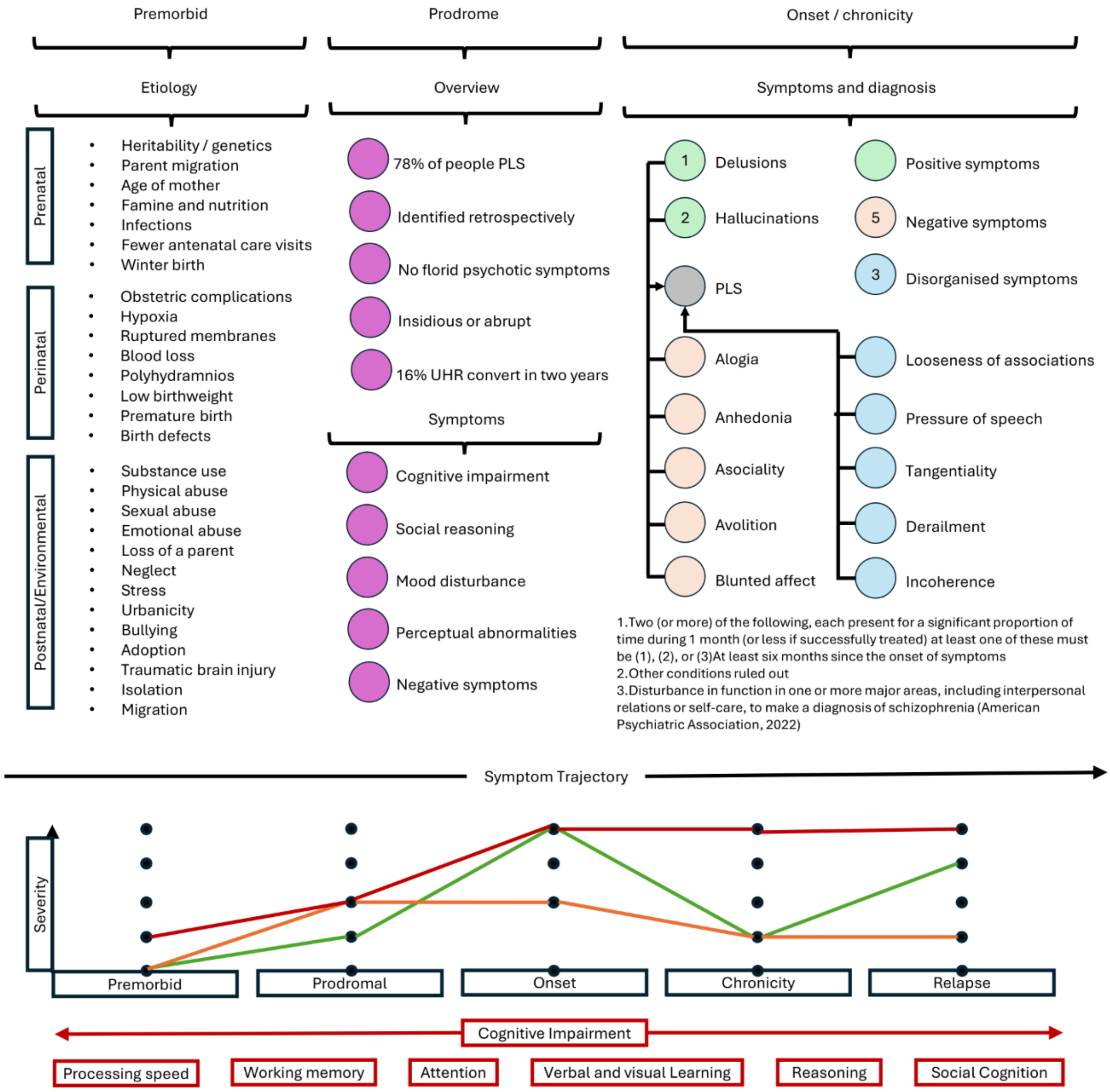

Figure 6. Symptom Groupings, DSM-5 Diagnostic Criteria, Aetiology, Stages, Symptom Trajectories, and Cognitive Considerations of Schizophrenia.

2.8 Treatment

The first line of treatment for schizophrenia, since the 1950s, is antipsychotic medication (neuroleptics) to reduce the severity of hallucinations and delusions. Some regard the discovery of chlorpromazine as marking the beginning of psychopharmacology for PLS, as the clinical effect on PLS was remarkable (Seeman, 2021). There are now many pharmacological agents to treat positive symptoms in PLS, most of which target dopaminergic activity in the subcortical areas by blocking dopamine receptors. In addition to psychopharmacology, there are many evidence-based therapeutic interventions, including social skills training, cognitive behavioural therapy, and cognitive remediation, which are often used to treat symptoms of schizophrenia other than hallucinations and delusions (Lu et al., 2022). Other pharmacological agents for depression and anxiety may also be appropriate for comorbid conditions in PLS. Figure 7 provides information on various treatments for PLS.

2.8.1 Pharmacological treatment mechanisms

Antipsychotic medicine primarily works by blocking dopamine D2 receptors in the mesolimbic pathway. Excess dopamine in the striatum leads to overactivity in the temporal cortex, particularly Broca's area, the superior temporal gyrus, the temporal parietal junction and the hippocampus (Fovet et al., 2022; Jardri et al., 2011). This overactivity leads to auditory hallucinations (Fovet et al., 2022; Jardri et al., 2011). For delusions, feedback loops between cortical areas and the basal ganglia are incorrectly tagged in the basal ganglia during an increase in phasic dopamine release (Morrison & Murray, 2009). Hence, the blockage of dopamine receptors in the striatum leads to the reduction of both hallucinations and delusions. This hypothesis, however, has caveats. Atypical antipsychotics may not necessarily primarily block dopamine receptors (Samanaite et al., 2018). Clozapine is an atypical antipsychotic as it does not carry the same side effects as typical antipsychotics, as it has a high affinity for serotonin receptors (Samanaite et al., 2018). Clozapine is the primary treatment option for people who do not respond well to other antipsychotics (Samanaite et al., 2018). Despite improvements in positive symptoms, antipsychotic medication does not have high efficacy in treating negative symptoms and cognitive impairments (Correll & Schooler, 2020; Strassnig et al., 2015).

Medication development for cognitive impairment and negative symptoms has been studied extensively. Many neurochemical systems have been targeted when assessing the efficacy of novel pharmaceutical agents to treat cognitive impairment, including serotonin, gamma-aminobutyric acid, dopamine, acetylcholine, and glutamate modulators (Martínez et al., 2021). However, no trial medication has been identified to have a moderate effect on improving cognition in schizophrenia (Martínez et al., 2021). Similarly, for negative symptoms, limited evidence has been found for glutaminergic, dopaminergic and cholinergic medications to reduce negative symptoms (Correll & Schooler, 2020). Despite the limited benefits novel medications have on cognitive impairment and negative symptoms, psychotherapeutic interventions have some evidence and have been shown to have some efficacy in conjunction with antipsychotic medication.

2.8.2 Psychosocial treatments

Psychotherapeutic interventions such as cognitive behaviour therapy have been shown to have a beneficial effect on positive (Jauhar et al., 2014) and negative symptoms (Lutgens et al., 2017), although two systematic reviews both found inconclusive small effect sizes of psychotherapy when assessing functioning, distress, and disability at follow-up (Laws et al., 2018; Nowak et al., 2016). Similarly, effect sizes for cognitive remediation for schizophrenia show a small but significant effect for improving cognition (Revell et al., 2015; Vita et al., 2021). The current evidence suggests that cognitive remediation should be introduced early alongside mainstream treatment of PLS with antipsychotics and should be implemented widely in clinical practice (Vita et al., 2021). There has also been some success in treating negative symptoms. In one meta-analysis, other therapies specifically designed for PLS, such as social skills training, have been demonstrated to be more effective at reducing negative symptoms than treatment as usual (Turner et al., 2018). Turner et al. (2018) note that social skills training was superior to treatment as usual and controls for the general subscale of the PANSS but not positive symptoms of schizophrenia. Overall, the consensus is to incorporate psychotherapy into the treatment regimen for PLS alongside antipsychotic medicine to address unmet needs and enhance recovery from the illness (Ventriglio et al., 2020). Furthermore, resources should be allocated to these interventions to ensure the complete delivery of psychosocial rehabilitation to PLS (Ventriglio et al., 2020).

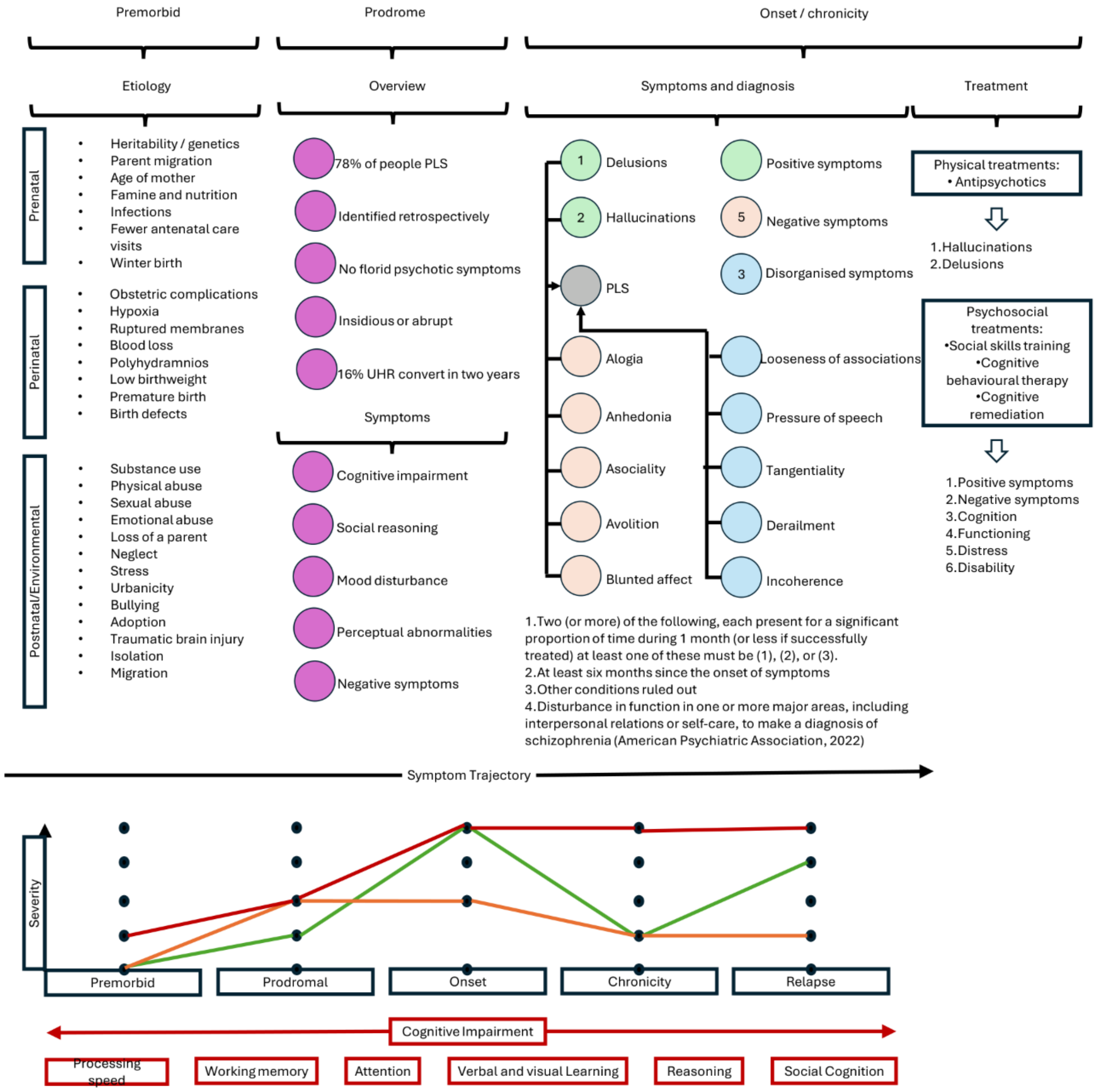

Figure 7. Symptom Groupings, DSM-5 Diagnostic Criteria, Aetiology, Stages, Symptom Trajectories, Cognitive Considerations, and Treatment of Schizophrenia.

2.9 Culture

Schizophrenia has varied outcomes and expression of symptoms across different countries and socio-economic environments (Charlson et al., 2018). For example, people generally have better outcomes in developing countries and poorer outcomes in developed countries (Siegert, 2000). The presentations of schizophrenia also vary across cultures. For example, Turkish patients tend to be more ambivalent, with more inappropriate and inane behaviour, and more euphoric but more disorganised than American patients (Volkan, 2021). A considerable amount of research has been conducted on how culture is associated with the expression of symptoms, particularly hallucinations and delusions. For example, in Western cultures, delusions of paranoia may be centred on technology, whereas in some cultures, such as countries in Africa, delusions may focus on experiences of witchcraft (Ghanem et al., 2023). These emerging phenomena may be due to the underlying belief system of a culture where experiences of psychotic symptoms are appraised as aligning with these underlying belief systems (Ghanem et al., 2023). Attribution of experiences of hallucinations also differs from culture to culture, with some attributions of hallucinations being culturally appropriate and others being signs of illness (Larøi et al., 2014). Additionally, hallucinations also occur in non-clinical populations, with between 10 and 15% of people reporting experiences of auditory hallucinations (de Leede-Smith & Barkus, 2013). Even in Western cultures, experiences of hallucinations are not necessarily considered abnormal. Hence, research on hallucinations should also consider the differing experiences and world views across cultures.

A particular interest has emerged for the relationship between culture, cognition, and schizophrenia (Siegert, 2000). This interest has, in part, been developed from the arguments regarding innate cognitive ability versus learned cognitive ability as they apply to schizophrenia (Siegert, 2000). People with schizophrenia tend to suffer from impairments in theory of mind or inferring other people's thoughts, intentions, and affect from social cues (Frith, 1994; Harrington et al., 2005; Langdon et al., 2005), an innate ability that may be both biological and socio-cultural. Siegert (2000) identifies that some aspects of cognition and symptoms are inherited, but the nature, content, and meaning of those experiences may be culturally determined. These considerations may be time-dependent, as delusions 100 years ago may be focused primarily on religion, compared to contemporary experiences, which again, may focus on technology (Ghanem et al., 2023; Siegert, 2000). Siegert (2000) identifies that cultural contexts may increase the experience of some symptoms. Visual hallucinations, for example, may have a higher prevalence in non-Western countries, as these may have positive cultural connotations (Al-Issa, 1995). As identified by Siegert (2000), these notions arise through the interactions between biology, cognition, and cultural factors. According to Siegert (2000), these interactions should be emphasised above the notion that these experiences are either biological or cultural phenomena.

There may also be differences in how the concept of schizophrenia is viewed in different cultures. Before the seventeenth century, hallucinations used to be valued in a cultural context until they became a medical concern, a symptom of a mental disorder or organic illness (Telles-Correia et al., 2015). Unusual experiences may be given great importance in the history of one's culture (Larøi et al., 2014). For example, Moses and the burning bush, as well as Buddha beneath the Bo tree, are positively valued and can be understood in terms of local beliefs and practices (Larøi et al., 2014). It was not until the eighteenth and nineteenth centuries that hallucinations were fully integrated into psychiatry (Telles-Correia et al., 2015). Although there are currently various conceptualisations of hallucinations and delusions, the Western approach generally pathologises experiences of schizophrenia, whereas, in some Indigenous cultures, PLS play a social role in society, such as a seer (Taitimu et al., 2018). Experiences such as hallucinations in Western cultures are identified as false perceptions, while other cultures may attribute these experiences to supernatural realities or experiences of Jinn's (Larøi et al., 2014). Religious or cultural manifestations of hallucinations or delusions may, however, not be indicative of pathology. Because of the mundaneness of the experiences of schizophrenia in some cultures (Taitimu et al., 2018), medical treatment of schizophrenia may constitute pathologising cultural experiences, both affirming the biomedical approach and refuting culture-specific experiences.

2.10 Theoretical and applied considerations

A multitude of accounts of schizophrenia by authors have been proposed as a view of schizophrenia. These views stem from notions that the underlying theories best explain schizophrenia. These theories provide a paradigm for understanding schizophrenia and serve as an explanatory tool. Many theories on schizophrenia have been proposed, some holistic, biological, social, and developmental, and some implied by methodology. Some theories were developed based on results available through new technologies. For example, some theorists in the early or mid-1990s proposed that schizophrenia is a disconnection syndrome, given observations that people with schizophrenia had lower functional connectivity between brain regions (Friston, 1998, 1999; Friston & Frith, 1995). Evidence for the disconnection syndrome became available when neuroimaging techniques were used as a research tool. Other theories consider schizophrenia a neurodevelopmental disorder (Murray & Lewis, 1987; Rund, 2018; Woods, 1998) based on an increased risk from adverse events during the prenatal and perinatal period and events during later childhood and adolescence (Lewis & Levitt, 2002). More general approaches to the study of psychopathology, such as the LVM and the network model, have received considerable attention and may be used as clinical and research tools in understanding schizophrenia. These models or approaches to schizophrenia offer unique perspectives, with varying degrees of evidence, early or later in the evolution of research on schizophrenia. A visual display of each theoretical orientation discussed, in addition to the previous elements discussed in this chapter, can be found in Figure 8.

2.10.1 Lived experiences

Although considerable research has been done on schizophrenia, often treatment and research do not take into consideration the subjective experiences of a PLS (Kaite et al., 2015). Most research on schizophrenia employs a top-down theory-to-experience approach rather than a bottom-up experience-to-theory approach, which has been the predominant method for the last 200 years (Fusar-Poli et al., 2022). Furthermore, scientific research and evidence may subjugate personal experiences, with clinical experts silencing personal experiences from a Western epistemology (Taitimu et al., 2018). PLS may have a meaningful and subjective experience of symptoms, where the process of acceptance, personal relationships, spiritual practices, and faith may be ignored (Walsh et al., 2016). PLS may feel frightened, confused, and exhausted with hallucinations, or people may feel a loss in their sense of self, a loss of agency or personal identity, or that recovery may better be identified as coping, as there is no end to the journey of schizophrenia (Walsh et al., 2016). These experiences are not often captured in mainstream psychiatric care, where the focus is on positive, negative, cognitive, and disorganised symptoms, treatments, and the side effects of those treatments. Despite intensive education by clinicians, some people with schizophrenia believe that staff do not appreciate what it is like to have schizophrenia and fail to understand the impact of decisions on clients' lives (Walsh et al., 2016). Most scientific research on schizophrenia tends to highlight schizophrenia in a deficit-oriented view, which may affect the person's view of themself (Randhawa et al., 2023).

Although mainstream research looks at deficits associated with schizophrenia, PLS may also have positive experiences of the illness. PLS may express positive experiences in personal, interpersonal, and religious or spiritual domains (Jordan et al., 2018; Ma et al., 2023). PLS may experience greater clarity about themselves and others after their first episode, allowing them to reassess their lives, provide a sense that life should not be wasted, or assign a positive or constructive meaning to their experiences (Jordan et al., 2018). Similarly, PLS report posttraumatic growth as recovery and improvement in physical and mental health and regaining control over one's life (Ma et al., 2023). PLS may also describe increased trust in others, a desire to help others, and greater tolerance towards others following their experience of schizophrenia (Ma et al., 2023). There may also be positive experiences of the symptoms themselves. For example, some people with schizophrenia may report that visual hallucinations may be viewed positively, although these may also cause distress (Silverstein & Lai, 2021). Additionally, delusions may also be experienced by an individual as a process of meaning-making and self-interpretation, although delusions can also be a source of distress (Ritunnano et al., 2022). For the majority of the participants, negative views of their illness predominate, and it is unclear whether this is due to the adoption of Western concepts to the understanding of their mental health and wellbeing, stigma and discrimination, or because of the innate distress caused by the symptoms (Walsh et al., 2016).

Research with PLS who face stigma and discrimination that may worsen their health outcomes (Baba et al., 2017). Most research looks at reports of public attitudes toward mental health clients as opposed to the experiences of people living with mental distress who are stigmatised or are the targets of discrimination (Rose et al., 2011). People who experience stigma and discrimination often feel that it is worse than the condition itself (Thornicroft et al., 2022). Stigma and discrimination can be sourced publicly and interpersonally from the self, mental health staff, family, or embedded structurally, where policies and practices systematically disadvantage the stigmatised group (Thornicroft et al., 2022). PLS may be perceived as dangerous, which may lead to social distancing and the desire for avoidance by the person with schizophrenia (Mannarini et al., 2022). Additionally, PLS may experience reduced marital prospects, social exclusion in education, the workplace, and the community, loss of property, inheritance, or voting rights, and poorer healthcare compared to physical conditions (Thornicroft et al., 2022). According to Thornicroft et al. (2022), self-stigma of schizophrenia is highest among Southeast Asian or Middle Eastern countries compared to European and North American countries. Evidence suggests that lived experiences of shame and embarrassment from stigma may also occur in Indigenous cultures, which may depend on the socio-cultural factors of that Indigenous group (Goetz et al., 2023). The notion that stigma and discrimination can be regarded as a *second illness* has led the Lancet Commission to advocate for the end of stigma and discrimination among people with mental distress, who noted that self-stigma was highest among PLS (Thornicroft et al., 2022).

2.10.2 Indigenous models

No matter how dominant a worldview may be, there are other worldviews, worldviews that refute colonial processes (Little Bear, 2000). These colonial processes suppress diversity and create a singularity, fuelling oppression and discrimination of non-Eurocentric knowledge and belief systems (Little Bear, 2000). Indigenous models of health may, in part, be agnostic to Western models of health, which are frequently based on objectivism, reductionism, and empiricism. The continuous recolonisation of Indigenous peoples, such as Māori, with Western epistemology is incessant, and Indigenous knowledge and belief systems must continue as a collective commitment (Walker et al., 2016). Often, Indigenous views are proposed in contrast with Eurocentric views, colonialism, or to reduce recolonisation, and these form a knowledge system that is subjugated by the dominant Western paradigm (Nelson & Wilson, 2017; Smith, 2021; Taitimu et al., 2018; Ypinazar et al., 2007). Each indigenous view of schizophrenia may be based on broader world views on health and well-being, specific to that culture. Indigenous models of mental health are both diverse and specific to the cultural group and their views of mental health. In many instances, Indigenous worldviews of mental health and schizophrenia are ignored, and the experiences of mental health conditions such as schizophrenia are pathologised and labelled as abnormal (Taitimu et al., 2018; Ypinazar et al., 2007).

Each view on schizophrenia depends heavily on the worldviews of that social group, although some phenomena in each culture specifically relate to what Western society calls experiences of schizophrenia. Māori worldviews of schizophrenia encompass notions of matakite, a spiritual gift that includes the role of a seer (Taitimu et al., 2018). Other features of schizophrenia, according to Taitimu et al. (2018), include mate (mar-tear) Māori or Māori illness, institutions silencing personal views, trauma, and notions of tapu and noa (which suggest there is an imbalance that is unrestored). Māori views of schizophrenia, or mental health in general, tend to focus on the integration of many components of health above and beyond physical health, and experiences are seen as holistic or interrelated parts of a whole (Durie, 1994). Māori models of health may share some features with other models of health, such as complex systems approaches or biopsychosocial models, as integrative models, as these do not explicitly view one component of health and well-being in isolation.

In terms of other Indigenous cultures, for Aboriginal persons, mental health represents a dichotomy of healer and sorcerer, which may be viewed as supernatural and spiritual and may be used for good and evil (Brown, 2001). Another consideration, similar to Māori worldviews, is the connection to the land and nature, which is inseparable from the health of Aboriginal persons (Brown, 2001; Durie, 2004). Similar to other Indigenous groups, the Indigenous peoples of Canada view mental health as a holistic phenomenon, and physical, mental, emotional, and spiritual considerations are important (Lavallee & Poole, 2010). For the Indigenous peoples of Canada, the spirit becomes ill first, which then carries over to physical, mental, and emotional well-being (Lavallee & Poole, 2010). Although this is not an exhaustive list of Indigenous views, these views are not well aligned with Western medical practices and the disease model of health, which may recolonise Indigenous people with Western epistemology.

2.10.3 Medical model

The medical model of mental health dates back to early Western civilisation, probably as early as Hippocrates, who separated mental health into epilepsy, mania, and melancholia (Thumiger & Singer, 2018). The medical model of health identifies that signs and symptoms of schizophrenia point to a likely diagnosis of an individual, which is caused by biological and environmental factors (Wilshire et al., 2021). These signs and symptoms are not treated as theory-dependent and are, for the most part, universal across cultures and can be observed empirically (Wilshire et al., 2021). The diagnostic system is based on the medical model and divides disorders into discrete entities, which are regarded as real and measurable. In terms of schizophrenia, the symptoms in the DSM-5-Text Revision are used to identify possible schizophrenia and to serve as markers that separate schizophrenia from other conditions, such as bipolar disorder. Essentially, the differences between diseases or conditions, or groups of conditions, are viewed as differences in biology.

The biomedical model also identifies that a mental disorder, such as schizophrenia, can be traced to biology or the environment's impact on biology (Rocca & Anjum, 2020). These authors suggest that pathology can be explained by continuously reducing body systems into their constituent parts, which are dysfunctional (Rocca & Anjum, 2020). The continual reductionism of parts, from a brain to neurons to receptors, treats humans as physical entities with observable properties, and pathology can be understood by observing the properties of parts (Rocca & Anjum, 2020). Environmental influences can be causal factors via the changes they make in biology. For example, the use of cannabis or other substances is identified as a risk factor for schizophrenia, because of the associated effect it has on the physical properties of the brain and body, in some individuals. The medical model of schizophrenia is derived from an objectivist ontology and an empiricist epistemology and is a primarily Western view of health. Later models, particularly the neurodevelopmental model and biopsychosocial models, have integrated the medical model of schizophrenia with other paradigms, which may be more holistic or integrative in their assumptions and explanations.

2.10.4 Traumagenic model

Under a biopsychosocial model, several explanations of schizophrenia have focused on the relationship between adversity during childhood and the later onset of schizophrenia. This theory proposes a traumagenic model of schizophrenia. The traumagenic neurodevelopmental model of schizophrenia does not explicitly rule out biological causes of schizophrenia or psychosis but integrates the literature on the impact of stress or adversity on biological subsystems that are typically dysfunctional or impaired in schizophrenia. For example, Read et al. (2014) identify that the hippocampus, frontal lobes, brain-derived neurotrophic factor, mesocorticolimbic system, and other biological factors are typically responsive in people's responses to stress for PLS. Read et al. (2005) further note that there is a dose-response relationship between the severity of trauma and the likelihood of developing schizophrenia. The experience of hallucinations or delusions can also be viewed as a typical response to cope with previous traumatic experiences, regardless of the diagnosis (Read et al., 2005). Post-traumatic stress disorder, dissociative disorders, and other disorders occur primarily due to trauma and may also include psychotic symptoms. Given the propositions made by Read et al. (2005), integrating social factors alongside biological risk factors from a traumagenic lens provides an integrative approach to the understanding of schizophrenia and related disorders.

2.10.5 Diathesis-stress model

The diathesis-stress model integrates environmental and biological causes of a mental disorder and is a well-researched view of mental illness. The diathesis-stress model assumes that genetic causes are specific to schizophrenia and environmental causes are non-specific (Fowles, 1992). More evidence is emerging on epigenetics and the neural diathesis-stress models of schizophrenia (Jones & Fernyhough, 2007; Pruessner et al., 2017; Walker & Diforio, 1997). In the neural diathesis-stress model, a predisposition in neurobiology or genetics of schizophrenia leads to schizophrenia and heightened susceptibility to stressors (Walker & Diforio, 1997). In the presence of a predisposition, the interactions between genetics and environmental stressors lead to the onset of schizophrenia. Stress in the diathesis-stress model can include many environmental factors that are not limited to trauma, as specified in the traumagenic model of schizophrenia. Although the aforementioned theories of psychopathology have gathered considerable evidence, such as the diathesis-stress model, newer and older methodological theories of psychopathology may change the way we conceptualise mental illness and schizophrenia.

2.10.6 Latent variable model

Unlike the earlier conceptual models, an LVM is a computational, mathematical, and statistical model that can be used to model hidden (latent) constructs of schizophrenia. The LVM is essentially a psychometric approach based on the notion that multiple observed variables are caused by hidden or latent variables that are unobserved (Bringmann & Eronen, 2018). People can then differ on the severity or intensity of these latent variables, such as how extreme positive symptoms are for an individual diagnosed with schizophrenia. The LVM has been used in classical test theory, which identifies that hidden variables may cause responses to some items or questions. For example, a person reporting a racing heart or avoiding social situations identified on a self-report questionnaire is responding according to their underlying level of anxiety, which is not directly observable. In schizophrenia, these hidden variables may be the concept of schizophrenia, positive symptoms, negative symptoms, depression, functioning, cognition, well-being, etc, depending on the nature of the items. Items that specifically assess hallucinations may be represented by a latent variable named *severity of hallucinations*, and items on broad symptoms of schizophrenia may be represented by a latent variable named *schizophrenia*. The LVM is a dimensional approach to schizophrenia, as these constructs are measured on a continuous scale from abnormality to normality, from negative to positive, or from weak to strong, etc. Many people have attempted to find the latent variable structure of assessments related to schizophrenia. A meta-analysis has been conducted on the factor structure of the PANSS (Shafer & Dazzi, 2019), Brief Psychotic Rating Scale (BPRS; Shafer, 2005), and a systematic review has been conducted on LVM of the Calgary Depression Scale for Schizophrenia (CDSS; Lako et al., 2012). The LVM can be specified through confirmatory factor analysis, in which the user defines the LVM structure and evaluates its fit against competing models. LVMs have been employed for extended periods of time in psychology, psychiatry, and psychometrics, and the utility of LVMs has been well-established. Because the LVM identifies hidden variables, these methods have an objectivist ontology and a realist epistemology (Haig & Evers, 2015). Other methods, such as network statistics, are new to the field and may be integrated with LVMs. However, LVMs differ in the modelling assumptions and the inferences generated from such models.

2.10.7 Symptom network model

The network approach adopts a complex systems approach to studying psychopathology. Similar to LVM, SNs are computational, mathematical, and statistical models that may be applied to model symptoms of a psychological disorder. Recently, SNs have been proposed to be used as a tool to conceptualise an underlying disorder (Borsboom, 2017; Borsboom & Cramer, 2013). A small portion of research has been conducted on SN models of schizophrenia, yet several gaps need to be addressed (Buchwald et al., 2024). The network model of schizophrenia assumes that symptoms of schizophrenia (or other conditions) interact: Symptoms cause or are associated with the expression of other symptoms (Borsboom, 2017). For example, hallucinations may cause alogia, which then causes asociality. This contrasts with LVMs, as good LVMs generally aim to find an association between latent variables and items, whereby items become independent (Borsboom et al., 2003). In SNs, where the items of variables are dependent, the structure and parameters lead to inferences about the characteristics of schizophrenia and characterise schizophrenia (Borsboom, 2017). Here, the system's complex expression of schizophrenia may not be reducible to basic elements or parts (Guyon et al., 2017). Instead, an attractor, the psychological attribute (schizophrenia), is an emergent property arising from a complex dynamic system of components (Guyon et al., 2017). Further, instead of inferring that there is an underlying latent variable that causes the expression of behaviour, SNs do not necessarily observe manifestations of a hidden variable; the structure and parameters of a network constitute a condition or phenomenon (Guyon et al., 2017). Additionally, the naming of the complex system as a whole could be considered in line with a constructivist epistemology (Guyon et al., 2017). This methodology is different from the medical model, which assumes that symptoms are a product of schizophrenia, where signs and symptoms point to the presence of schizophrenia, or the LVM, where observed behaviour (or responses to items of a test) are independent and caused by a hidden or latent variable (Bringmann & Eronen, 2018; Wilshire et al., 2021). Given this, the network approach to psychopathology has been viewed as an attractor model and is based on a realist epistemology (Guyon et al., 2017).

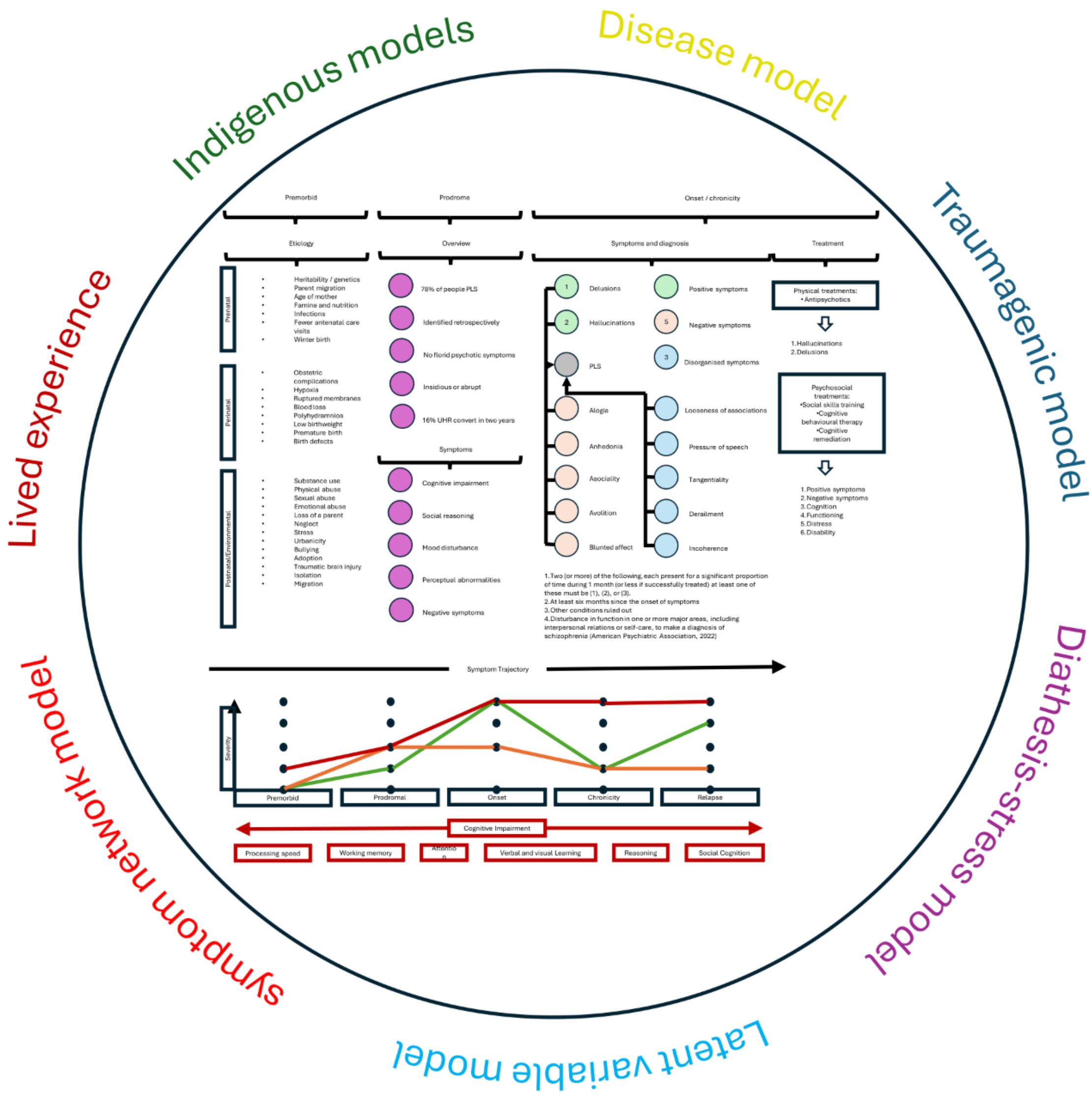

Figure 8. Symptom Groupings, DSM-5 Diagnostic Criteria, Aetiology, Stages, Symptom Trajectories, Cognitive Considerations, Treatment, and Theoretical Orientations of Schizophrenia.

2.11 Conclusion

Although many questions remain about the phenomenon of schizophrenia, it is important to emphasise that a very detailed understanding of schizophrenia currently exists. These are in part due to the diversity of perspectives on schizophrenia and the increase in the literature on schizophrenia over the years. Many tools and methods have been developed to assess and explain schizophrenia experiences, including recent advances such as neuroimaging technologies or SN models of health. This collection of methods, perspectives, and research has allowed researchers to be closer to developing targeted interventions that may ameliorate the distress and dysfunction of schizophrenia or provide an acceptance of the syndrome. It is unclear how much or when new technologies, mathematical models, and statistical models will advance progress for PLS. New methods or theoretical orientations may help with treatments specific to PLS, leading to novel innovations that have been largely untouched since the development of neuroleptics in the 1950s and the deinstitutionalisation movement in the 1970s and 1980s. SNs are one possible method to advance the understanding of schizophrenia by treating schizophrenia as a complex system of interacting components. It is unclear how well SN models apply to PLS. However, current understanding suggests that SN models may have substantial applied value to PLS due to the heterogeneity in the causes, presentations, and outcomes of this condition (Isvoranu et al., 2018). The next chapter focuses on SN methodology and methods, in addition to SN's theoretical orientation as a mental health or illness model, with applications to schizophrenia.

Chapter 3 Literature Review. Symptom Networks: Methodological and Theoretical Considerations

3.1 Overview

The SN paradigm is a relatively novel approach to understanding and explaining psychopathology using a complex systems framework. An SN is a graphical tool used to model the directed or undirected interrelationships between symptoms, which are modelled as random variables. Network models in statistics were developed long before their application to symptoms or psychopathology and any theoretical development of SNs as a theory of psychopathology (Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2010; Crane & Dempsey, 2021; Pearl, 1985). Currently, various network methods have been developed and are now being used in the study of psychopathology (Briganti et al., 2023; Isvoranu et al., 2022). In SNs, one symptom causes, predicts, or is associated with the expression of another symptom (Buchwald et al., 2024). In SNs, it is the sometimes-dynamical complex interrelationship between symptoms that is proposed to represent a mental disorder, such as schizophrenia (Borsboom, 2017). Hence, given the interactions between symptoms, the expression of a condition, disease, or syndrome is an emergent property given the properties of the SN (Guyon et al., 2017). The properties of the network are used as evidence for inferring characteristics about the sample or population under investigation, such as inferences from centrality statistics or by querying the network, as described in Section 3.5.6 (Borsboom, 2017; Fried et al., 2017). A diagnosis can also be included as a node if more than one condition (PDS, depressive disorders, HC, etc) is modelled. That node can be conditioned on to make inferences about that diagnosis. SNs are usually implemented on observed variables, subscales, or item scores that represent psychopathology. Alternatively, the network can also be constructed using a combination of observed and latent variables (Epskamp et al., 2017).

The theory for SNs has been explored, delineating the assumptions and principles of the NTMD (Borsboom, 2017). There are differences between the inferences drawn from theoretical models for SNs and the possible inferences from network methods (Isvoranu et al., 2022). The theory of SNs proposes far-reaching assumptions, such as the causal effect of one symptom on another. Such assumptions are crucial for delineating an SN theory but are difficult to verify with most network methods (Isvoranu et al., 2022). Hence, network theory may not perfectly align with the inferences that could be made using current statistical methods (Isvoranu et al., 2022). Despite this, some assumptions, such as the complexity principle, as described in Section 3.3.2, may be evaluated using empirical methods and SNs by comparing the results of SNs to other models of health. Although some overlap exists between various network methods, key constraints or assumptions make each method unique when studying complex systems. Given the development of various SN techniques, nomenclature regarding the units and analyses of SNs has been developed for transparency across network methods.

Networks are comprised of *nodes*, which represent random variables, and *edges* (or arcs), which represent relationships between variables. Edges usually represent a statistical relationship between variables, like a correlation or regression coefficient, and edges can be directed or undirected. Some networks are fully directed. In directed networks, a *parent* node is a predictor variable of a *child* node, which is the response variable. This does not necessarily imply a causal relationship. A fictitious example of this, a directed symptom network of schizophrenia, is provided in Figure 9 below, where the severity of asociality is dependent on the severity of alogia, which is dependent on the severity of hallucinations. Another way to describe this is that hallucinations predict alogia, which predicts asociality, as in Figure 9. Some networks are also partially directed or undirected. Here, the directional relationship between two variables, such as parent and child node relationships, is not specified, as in Gaussian graphical models (GGM) or mixed graphical models. GGMs and mixed graphical models are described briefly in Section 3.4. Typically, undirected relationships are correlation coefficients or partial correlation coefficients, which can be *regularised* or not (Isvoranu et al., 2022). Some network methods allow cycles (feedback loops), i.e., hallucinations may cause alogia, which causes asociality, which then causes hallucinations. A fictitious example of this can be found in Figure 10, in Section 3.4. These can be inferred from models such as GGMs and mixed graphical models. Other methods do not allow cycles, such as in some BNs. BNs are described and introduced in Section 3.5. Some models can introduce time in the model, such as in dynamic mixed graphical models (Epskamp et al., 2018b) or dynamic BNs (Murphy & Mian, 1999). Lastly, some networks can be used to infer causation, and these are called causal networks (Pearl, 1995).

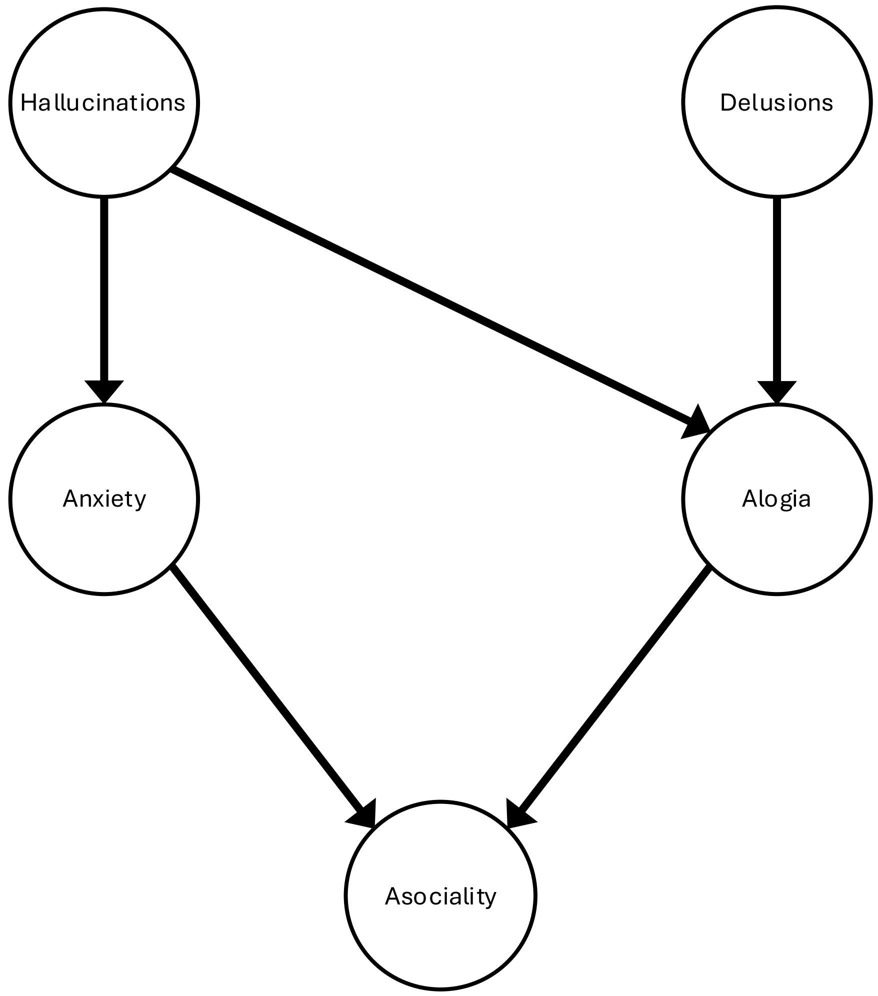

Figure 9. Example Directed Bayesian Symptom Network of Schizophrenia

The network is usually learned using algorithms that find a locally optimal solution, and parameters are estimated for the relationships between variables. In other instances, the network can include an expert's prior knowledge in addition to observed data, called belief updating. The network can be learned using a score criterion such as the Bayesian information criterion (BIC) or extended BIC (EBIC), which penalises overly complex networks in their fit to the data for improving theoretical properties, such as consistency, as the sample size approaches infinity (Zuk et al., 2012). Network parameters are estimated by assuming a distribution for the variables, e.g., multivariate Gaussian. Structure and parameter learning are implemented simultaneously, e.g. with an Expectation-Maximisation (EM)-like strategy and are part of most network learning methods. Additionally, the structure is often specified entirely in terms of the presence or absence of parameters of the network. For example, finding partial correlations between nodes indicates an edge, or a lack of association between nodes indicates this edge is not included in the network, such as partial correlations in a GGM. Usually, the goal of implementing an SN is to estimate the structure and parameters of the population from which the sample was derived. Hence, researchers may try to minimise false positive edges (edges in the sample network, not found in the true network) and false negative edges (edges not in the sample network, found in the true network) in the reconstructed network (Epskamp & Fried, 2018; Scutari, 2009). Next, this thesis will provide an overview of the NTMD, an overview of PMRF and BNs, followed by SCMs.

3.2 Complex systems approach

The complex systems approach is an approach, not limited to psychopathology, that partly aims to provide a unifying framework for science and revolutionise the understanding of systems of behaviour (Ladyman et al., 2013). According to Ladyman et al. (2013), the scientific community has used the term complex systems to define phenomena, structures, aggregates, organisms, or problems that share some common theme, and have applications to ecology (Anand et al., 2010), neuroscience (Turkheimer et al., 2022), genetics (Angelin-Bonnet et al., 2019), and mental health (Fried et al., 2017), among many others. A formal definition for a complex system is somewhat elusive, but it may be generally identified as a system composed of many interacting parts, and the collective behaviour of the parts may be more than the sum of the individual elements of the system (Estrada, 2024). In particular, Ladyman et al. (2013) notes that systems may be predisposed to unexpected outcomes because of emergent behaviour, which is not deducible from their parts. The mind may be an example of an emergent property of the brain given a complex system of self-organising functional activity (Mainzer, 2007).

In general, complex systems are a distributed set of entities with many interconnections and have properties such as non-linearity, feedback mechanisms, and emergent properties (Estrada, 2024). The complex systems may also be hierarchical, have particular ordering, or adaptivity (Estrada, 2024). Complex systems may also lack a central control point, robustness, or a large number of parts and interactions (Ladyman et al., 2013). Other notions of complex systems highlight the role of non-linearity, where a system need not change proportionally to a change in the variable (Bishop, 2011). However, these properties of a complex system are neither necessary nor sufficient conditions for defining a complex system (Estrada, 2024).

Although a formal definition for a complex system is elusive, complex systems have rich implications for metaphysics and epistemology (Bishop, 2011). According to Bishop (2011), some implications include determinism, prediction, confirmation, causation, reductionism, and emergence. A key notion in complex systems that undies these implications is faithfulness (Scutari & Denis, 2021), the idea that the state model accurately represents the real-world target system or probability distributions. This has particular importance for applications of complex systems. For example, treating mental disorders as complex systems must include notions that the reconstructed network accurately represents the probability distribution of symptoms of a mental disorder (Borsboom, 2017). The assumption highlights that if the data underlying the model is continually refined or the uncertainty of the data is reduced, the model will converge to the target system, identifying that the model is faithful (Bishop, 2011). There is also the assumption of asymptotic consistency, where as the sample size increases, the network model will converge to the population network (Bishop, 2011). In hypothesis testing approaches, evidence against the null hypothesis in the population can be obtained, given sample data. However, it is assumed that a model of a complex system approximates the target system, yet no statistics on this can be obtained without access to the population data. Research using simulated datasets has therefore been conducted on identifying prediction error using simulated datasets, which has identified asymptotic consistency from some approaches (Isvoranu & Epskamp, 2023; Kalisch & Bühlman, 2007; Scutari et al., 2019).

These implications are crucial for implementing complex systems on networks of symptoms of mental disorders. Concepts such as faithfulness and emergence are crucial for inferences about network properties in networks related to mental disorders, based on complex associations between symptoms. To identify that a mental disorder is an emergent property of complex associations between parts of a network, not deducible from individual components, requires strong mathematical, statistical, methodological, and epistemological backing from assumptions and concepts in the complex systems approach. Given the applied value of conceptualising mental disorders as complex systems, the development of a theory of mental disorders as complex systems has been proposed (Borsboom, 2017; Fried et al., 2017). Given this, the complex systems approach adopts an alternative epistemological and ontological perspective on understanding and conceptualizing mental disorders, distinct from other paradigms identified in Section 2.10. Next, a theory of mental disorders as complex systems is discussed (Borsboom, 2017), serving as the theoretical cornerstone of this thesis.

3.3 Network theory of mental disorders

The principle in the NTMD is that symptoms of a mental disorder interact, cause, or are associated with the expression of other symptoms (Borsboom, 2017). This notion is not a key component in other paradigms of psychopathology, such as the disease model or LVMs (Borsboom, 2017). SNs explicitly allow for the expression of symptoms in one diagnosable mental health condition to be interrelated with symptoms of another diagnosable mental health condition. Comorbidity of conditions, such as schizophrenia and depression, can, therefore, be modelled as a complex interplay between the shared expression of symptoms from each disorder (Cramer et al., 2010). Given this, symptoms, such as symptoms of the DSM-5-TR, can be modelled in the network, and clusters of symptoms may represent conditions (Goekoop & Goekoop, 2014; Nuijten et al., 2016). The notion that a condition is reflective of network properties is one assumption that is proposed under this theory of psychopathology (Borsboom, 2017).

3.3.1 History and development

The NTMD is a comparatively new theory of psychopathology that was expanded between 2010 and the present day. The earliest notion that symptoms are interrelated was found in a publication by Borsboom (2008), who identified that there has been no known account of how symptoms can be causally related. This notion was then explored by Cramer et al. (2010) and colleagues, who identified that comorbidity between disorders arises not from the bidirectional relationship between multiple latent variables but instead stems from the direct relationships between symptoms of various disorders. This was the first known implementation of an SN. The term "symptom network" was then coined in that publication (Cramer et al., 2010). Since its inception, over 350 studies have been published on SNs between 2008 and 2020, and this growth appears to be exponential (Robinaugh et al., 2020). Given the growth in research, theorists have attempted to delineate the principles and assumptions of SNs of mental disorders. Two notable publications were developed to expand on this theory. The first article was published in 2013 by Borsboom and Cramer (2013), who identified the notion of symptoms and their causal relationships and identified that network methods may be more plausible than the medical model or the LVM. The other fundamental article published by Borsboom (2017) is discussed in the next section: Principles and assumptions.

3.3.2 Principles and assumptions

Borsboom (2017) listed four principles of the NTMD. These principles are, in essence, assumed when making inferences about a mental health condition and its corresponding SN. Borsboom has proposed the principles below as underpinning the NTMD:

1. Complexity: Mental disorders are best characterized in terms of the interaction between different components in a psychopathology network.
2. Symptom-component correspondence: The components in the psychopathology network correspond to the problems that have been codified as symptoms in the past century and appear as such in current diagnostic manuals.
3. Direct causal connections: The network structure is generated by a pattern of direct causal connections between symptoms.
4. Mental disorders follow network structure: The psychopathology network has a non-trivial topology, in which certain symptoms are more tightly connected than others (Borsboom, 2017, p.7).

The first principle identifies that components interact with each other in a network. Components could refer to observed variables, latent variables, or symptoms. Borsboom (2017) identifies that a mental disorder arises due to the complex interplay of these components, or a change in the relationship between components may be identified as a mental disorder. The complexity principle is underpinned by both the shared expression of symptoms and the notion that mental health conditions are multifactorial in aetiology, constitution, and causal background (Borsboom, 2017).

Regarding the second principle, Borsboom (2017) argues that the components should represent symptoms of a condition from a diagnostic manual if the symptoms are well-established or based on a consensus that a symptom is part of a mental disorder. Borsboom (2017) allows components other than symptoms to be present in the network, but these symptoms must be present in the external field of the network. Identifying whether symptoms are best represented by a summed score or an item in a psychological assessment may be challenging. For example, do ratings of a question about the presence of hallucinations have validity to assess actual hallucinations? These measures may serve as proxies for an actual symptom, and evidence of construct validity for these measures may be necessary. Typically, items are not evaluated for validity but are often used as nodes in SNs (Buchwald et al., 2024). This assumption has been challenged by Wilshire et al. (2021), who identify that symptoms in SNs are treated as observed variables and are not theory-laden. This assumption may be problematic for theory-laden symptoms, such as a symptom of excessive introspection in schizophrenia, which is asserted by theories of the disorder of the self in schizophrenia (Sass & Parnas, 2003). Borsboom (2017) identifies that symptoms must have the right level of granularity and that the component is valid, both of which are key to the second principle of this theory.

SNs can be generated using cross-sectional, longitudinal, non-experimental, or experimental data, and inferences about causation may be limited by the design or analysis method of the study. The third principle, posited by Borsboom (2017), asserts that the relationships between components in the network are causal. This assumption may be problematic in non-experimental cross-sectional designs, as found in most network analyses (Isvoranu et al., 2022). This is where the theory and statistical modelling part ways, as causality is not assumed in most network statistics (Briganti et al., 2023; Isvoranu et al., 2022). Although we have many experimental studies on symptom relationships, inferring causation from network statistics presents a challenge. Bringmann and Eronen (2018) note that relationships between symptoms in a network may not necessarily be causal; for example, life stress causes anxiety, while third variables, such as the loss of an intimate partner, might cause both stress and anxiety. If causation is not identified, relationships are characterised by dependency in the form of correlations or regression coefficients. If the correlation or regression coefficient is estimated to be zero, this may be interpreted as partial or conditional independence. There are methods to identify causal relationships in SNs, both in experimental and non-experimental designs, although in non-experimental designs, it may be challenging to establish causal relationships between variables as several assumptions need to be met (Scutari & Denis, 2021; Verma & Pearl, 2022). Causation in SNs may be particularly challenging even with experimental designs (Briganti et al., 2023). The assumptions for inferring causation in BNs can be found in Section 3.5.4.

The last principle of the NTMD, mental disorders follow network structure, asserts that the properties of a network of symptoms underlie the existence of a mental disorder and that the network properties are non-trivial (Borsboom, 2017). This principle is difficult to support empirically or through network methods, although attempts to identify mental disorders based on the clustering of symptoms have been proposed (Goekoop & Goekoop, 2014; Nuijten et al., 2016). Additionally, replication of networks across independent samples may be needed to estimate the network for a specific psychological condition, and some evidence suggests that SNs may be replicable (Borsboom et al., 2017). However, this has not been supported unanimously (Forbes et al., 2017). It is also unclear whether the diagnosis used in recruitment, in the traditional medical sense, is a goal of modelling an SN or whether a named emergent trait is the preferred inference. Hence, although some networks may be replicable and non-trivial, it is unclear how the results of networks represent psychological disorders.

In addition to this, networks may not reflect the population under investigation. Therefore, identifying the specificity and sensitivity of edges in the network of a sample, compared to a known population, is one method to check the network's predictive validity (Scutari et al., 2019). Verifying that the sample SN represents the population SNs continues to be challenging (Scutari et al., 2019). One study by Isvoranu and Epskamp (2023) found that SNs do not perfectly represent population networks, although as the sample size increases, specificity and sensitivity in identified edges tend to improve. The authors note that some optimisation strategies for GGMs can be used to either improve specificity and sensitivity or select the appropriate trade-off between specificity and sensitivity (Isvoranu & Epskamp, 2023). Additionally, network averaging can be used to improve external validity, which may be more effective, particularly for diverse or heterogeneous groups (Scutari & Nagarajan, 2013). Unlike hypothesis testing methods, it is difficult to establish how well the sample network represents the population network without a gold-standard dataset. Given this, this principle strongly assumes that network properties on a sample may represent a condition in the population.

3.4 Pairwise Markov random field models

PMRF models are a popular SN method to identify relationships between symptoms of one or more mental disorders (Isvoranu et al., 2022). Similar to other network models, the network is comprised of nodes and edges. Nodes represent random variables, and edges in this model represent the pairwise dependency after controlling for all or a subset of other variables (Finnemann et al., 2021). The edges are weighted according to an association statistic. We can represent negative associations with red edges and positive associations with blue (or green) edges (Epskamp et al., 2018b). The edges in a PMRF are undirected. The association statistics is classically chosen to be the partial correlation coefficient; hence, many people refer to GGMs, one method of a PMRF, as partial correlation networks. When there is no edge between variables, it is determined that these two variables are independent or conditionally independent, given a set of other variables, including or excluding interactions (Epskamp et al., 2018b). Computational time may get very large when checking conditional independence with large sets of variables with various levels of interactions. Since the network is undirected and does not require acyclic edges, nodes can be part of a feedback loop or cycle(Isvoranu et al., 2022). Most partial correlations in the networks are non-zero; therefore, existing methods have been used to prune networks to simpler models (Isvoranu et al., 2022). Inferences can be made from the network estimated using graph-theoretic measures, as discussed in Section 3.5.6. Although there are many types of PMRF models, there are three primary subclasses of PMRF models, and these are GGMs, mixed graphical models, and Ising models (Isvoranu et al., 2022).

The typology of networks includes the various models that can be applied for a PMRF, which vary by the distribution assumed and the nature of the data in terms of whether it is cross-sectional or time series data. The network typology could also consider spatial locations, which this thesis does not cover. The typology of networks can be separated by the distributional assumptions made when constructing the model. The distributional assumptions arise depending on the type of variable included in the model. GGMs are based on normal distributions, assumed when the variables are continuous and normally distributed (Epskamp et al., 2018b). Hence, when implementing a GGM model, the model is assumed to be multivariate normal. Mixed graphical models include discrete, continuous, count, or other variable types in the network (Haslbeck & Waldorp, 2015). Ising models are used when the model includes binary variables and logistic regressions are required (Brusco et al., 2019). Using mixed graphical models, as opposed to GGMs, increases the complexity of the estimation of the model considerably, especially in high-dimensional data (Cheng et al., 2017; Eunho et al.). Further information on typology and PMRF in general can be found in Appendix B. Furthermore, a fictitious example of an undirected PMRF network can be found in Figure 10 below.

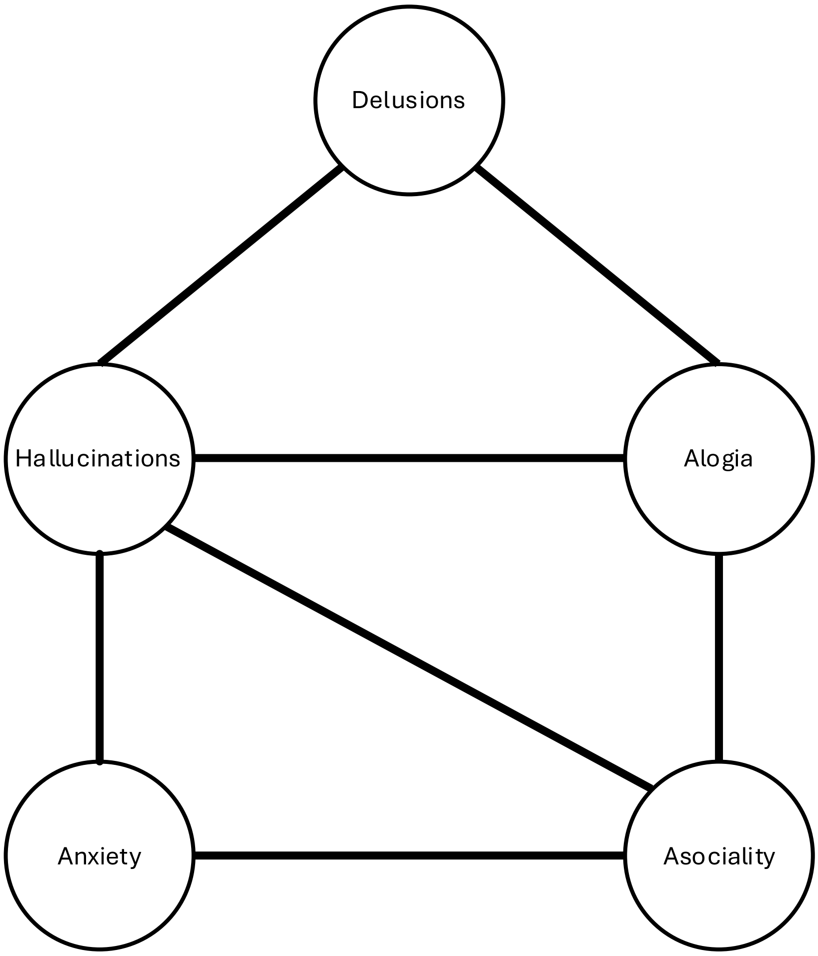

Figure 10. Example Undirected Symptom Network of Schizophrenia

3.5 Bayesian networks

BNs represent a method to model the relationship between random variables as a complex system of interacting components (Mihajlovic & Petkovic, 2001). BNs encode conditional probability relationships in a DAG. This DAG model aims to represent a joint distribution from a set of random variables (Li & Mahadevan, 2018). A fictitious example of a BN can be found in Figure 9. The graph is comprised of nodes and edges. Nodes represent random variables. Edges in BNs represent a directed dependency between two variables. Parent nodes are nodes where the edge is outgoing (directed away from the node), and child nodes are nodes where the edge is incoming. A node could be both a parent and a child node depending on its relationships with other neighbouring variables. The relationships in the network are conditional; the probability of the child node depends, conditionally, on the values of the parent node. A BN is specified from all encoded conditional probability relationships. In a BN, all edges are fully directed. DAGs are graphical network models which are directed and acyclical. More specifically, DAGs do not contain feedback loops or cycles. In completed partially DAGs, some edges may be undirected (Scutari & Denis, 2021). Directed edges in completed partially DAGs are compelled in the network to avoid cycles and in the presence of convergent edge relationships, as discussed below (Scutari & Denis, 2021). In a partially directed graph, there could be many possible distribution-compatible fully directed graphs, and these are said to have the same equivalence class (Scutari & Denis, 2021). The skeleton of the DAG is a graph made of the same set of edges, but no direction is associated with it. A fully directed graph must be specified to construct a BN (Scutari & Denis, 2021). DAGs can be sparse or dense depending on the number of edges in the model (Scutari & Denis, 2021). BNs have been used in a wide variety of applications, and the use of BNs may extend to assessing or improving predictive validity, making casual inferences, assessing variable importance, improving model fit, identifying predictor and response variable orientation, and hypothesis testing for the relationship between variables and the model.

An edge between two nodes indicates a directed dependency, whereas edge structures between three or more nodes may force two of those variables to be conditionally dependent or conditionally independent. This depends on the type of edge structure that exists between the three or more variables. Figure 11 shows the three elementary types of connections in DAGs: serial (pipe), diverging (fork), and converging (collider). *Serial connections*, as in Figure 11, indicate that variable A is independent of variable C, given the values of variable B. Here, variable B d-separates (d refers to dependence) variable A and variable C. Note that in serial connections, a relationship between variable B and variable C occurs after controlling for the variance in the relationship between variable A and variable B (Kline, 2023). Hence, controlling for A allows the relationship between B and C to be independent of A. This is not true for the relationship between variable A and B, i.e. the relationship between A and B has not controlled for the relationship between B and C. Similarly, in *diverging connections*, variable A is independent of variable C, given the values of variable B. Again, the relationship between variable A and variable B exists after partialling out the variance between variable B and variable C (Kline, 2023). The same is true for the relationship between the variables B and C. *Converging connections* are crucial in BNs (Scutari & Denis, 2021). In converging relationships, variable B is the collider variable. Conditioning on variable B does not d-separate variable A and variable C. Instead, conditioning on variable B gives information about the values of variable A and variable C, which could induce a spurious dependence relationship between variable A and variable C (Kline, 2023).

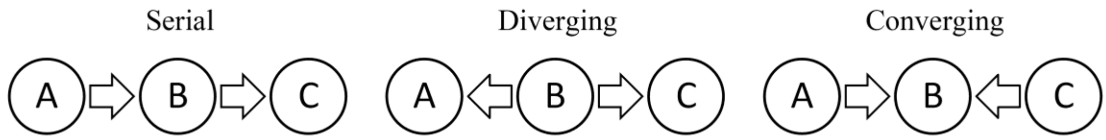

Figure 11. Types of Directed Relationships in a DAG.

3.5.1 History and development

BNs emerged from research which tried to identify a knowledge-derived rule-based system to account for logic and exceptions within logical reasoning (Pearl, 2018). Here, researchers attempted to identify whether an expert system could account for many events that result in an outcome (Pearl, 2018). Although these rule-based systems were pioneering and valuable at the time, the difficulty of dealing with uncertainty became clear (Pearl, 2018). Deterministic rules were used to identify an outcome based on an event, but this was based on knowledge-derived rule-based systems using the knowledge of experts (Pearl, 2018). An example of a knowledge-derived rule-based system is in the design of the DSM-5-TR. For a simple example, if the person experiences hallucinations (and other criteria in the DSM-5-TR), the clinician may rule in the diagnosis of schizophrenia; however, if the person experiences both hallucinations and manic episode (and other criteria in the DSM-5-TR), the clinician may rule in a diagnosis of bipolar disorder or schizoaffective disorder. These rules are based on a consensus of experts. Hence, knowledge-derived rule-based systems have been utilised previously and are currently utilised to organise systems. However, other methods were developed to base decisions on probabilistic models rather than the knowledge of experts.

In place of rules derived from expert panels, Judea Pearl attempted to resolve issues with knowledge-derived rule-based systems by introducing probabilistic graphical models in 1982 (Pearl, 1982). This method was coined *Bayesian networks* in the seminal 1985 paper (Pearl, 1985). The development of this method was to model nature rather than base relationships solely on expert judgement in terms of cause-and-effect relationships and to be compatible with sound probability theory and Bayesian reasoning (Pearl, 2018). Since then, there has been a tremendous development of methods and algorithms for the application of BNs, such as searching the parameter space for candidate models (Scutari et al., 2019; Spirtes et al., 2001; Verma & Pearl, 1990), of statistical packages and software to assist researchers in using BNs (Scutari, 2009), and of theory, particularly for making causal inferences (Pearl, 1995). BNs have now been used in a wide range of contexts, from genetic applications (Murphy & Mian, 1999), to protein signalling (Sachs et al., 2005), to neuroimaging data (Mumford & Ramsey, 2014), to the context of modelling symptoms of psychological disorders (Briganti et al., 2023), including schizophrenia (Buchwald et al., 2024). Various methods can now be used within the context of BNs to handle various data types and applied problems (Pourret et al., 2008).

3.5.2 Typology

BNs can be categorised into subtypes depending on the nature of the data and model implemented. A multinomial BN is a network where all the nodes are discrete variables, and a multinomial distribution is assumed. A Gaussian BN is a network where all the nodes are continuous, and a multivariate normal distribution is assumed. A hybrid BN includes both discrete and continuous variables or other types of variables, such as count variables or time-to-event variables. Often, researchers have longitudinal or time series data and need to model relationships between variables over time, dynamic BNs. Dynamic BNs can model two or more time periods. In dynamic networks, edges cannot be directed into previous time periods. Causal BNs allow the user to make causal inferences from the probabilistic relationship between variables in the network. More information on causal BNs can be found in Section 3.5.4. Further information on specific types of BNs, such as homogeneous or non-homogeneous dynamic BNs, spatial BNs, naïve Bayes, tree augmented naïve Bayes, and hierarchical BNs, is outside the scope of this thesis.

3.5.3 Structure and parameter learning

A BN structure can be specified a priori or estimated using various algorithms available. The network structure refers to the specified DAG structure, and parameters can be estimated assuming some distribution for the data. Both the structure and parameters of the network need to be estimated to reconstruct the network and make inferences and predictions from the network. The structure and parameters can be obtained using various algorithms that are roughly divided into three main categories: score-based algorithms, constraint-based algorithms, and hybrid algorithms.

Score-based algorithms, in particular hill climbing or tabu, usually start with an empty graph, and then an edge is added, an edge is deleted, or the direction of the edge is reversed until no improvement in a score criterion can be made (Scutari & Denis, 2021). A score criterion is a model fit index such as BIC, Akaike information criterion (AIC), EBIC, Bayesian Dirichlet equivalent, and other methods. Other methods for score-based algorithms include genetic algorithms and simulated annealing (Scutari & Denis, 2021).

Constraint-based algorithms are based on Pearl's early research on BNs (Verma & Pearl, 1990). These authors developed the inductive causation algorithm for BNs (Verma & Pearl, 1990). Essentially, a network begins as a fully connected, undirected graph. The algorithm first identifies which variables are connected by an edge, regardless of direction, and that these edges cannot be independent given any other set of variables (Scutari & Denis, 2021). This is done by conducting conditional independence tests and pruning the model (Scutari & Denis, 2021). The algorithm then identifies converging edges, as these do not create directed separation between two variables (Scutari & Denis, 2021). Then, the compelled edges are identified, and the partially directed graph is constructed (Scutari & Denis, 2021). Other algorithms have been developed based on this principle, including the PC algorithm (Spirtes et al., 2001) and forward stepwise selection algorithms such as grow-shrink (Margaritis, 2003), incremental association (Tsamardinos et al., 2003), and variations on incremental association algorithms.

Hybrid algorithms are those which combine constraint and score-based algorithms. They are typically conducted in steps, alternating steps borrowed from constraint and score-based algorithms. This offsets some of the weaknesses of each approach (Scutari & Denis, 2021). Some benefits include computational time and the accuracy of the network (Scutari, 2017). To speed up computational time, local computations are implemented for score-based algorithms, and for constraint-based methods, redundant tests are ignored, and a maximum number of tests is specified (Scutari, 2017). This is particularly important when there is a large number of variables to include in the network (Scutari, 2017). Two widely used hybrid algorithms are the sparse candidate algorithm (Friedman et al., 2013) and the max-min hill-climbing algorithm (Tsamardinos et al., 2006). These methods have two steps: restrict and maximise. Restrict refers to the constraint algorithm procedure, while Maximise refers to the score-based algorithm procedure. A test and score can be selected from the available options to conduct a hybrid algorithm.

In this PhD, there is the assumption of parametric distributions for parameters of the network, but non-parametric BNs can also be explored (Ickstadt et al., 2011), but are beyond the scope of this PhD. For parametric models, distributions are usually based on the variable type, although there is no such restriction on the distribution assumed for the relationships between nodes. There are two ways to estimate the parameters of the network. The first method is to estimate parameters using many local distributions, such as through linear models (Scutari & Denis, 2021). The second method is to jointly estimate the parameters using a global distribution, such as a multivariate normal distribution. This latter option is computationally expensive, even for a small number of nodes (Scutari & Denis, 2021).

3.5.4 Causal networks

Causal networks infer that nodes in a network have a causal relationship with other nodes instead of a dependence relationship. In the network, a directed edge from node A to node B stipulates that node A causes node B. For example, alogia in schizophrenia causes asociality. In terms of inferences, causal relationships between nodes are ideally identified by conducting queries on the nodes, setting them to a value to make inferences on the outcome of another variable (Nagarajan et al., 2013). Several universal criteria must be met to infer causation, and these do not necessarily imply that an interventional study was conducted (Pearl, 1995). The three criteria are (Briganti et al., 2023; Nagarajan et al., 2013):

1. The Markov property: Each variable is conditionally independent of its non-effects, both direct and indirect, given its direct causes.
2. Faithfulness assumption: There must exist a network structure that is faithful to the dependence structure of the set of random variables.
3. There must be no latent variables acting as confounding variables, thus inducing spurious associations between variables.

The Markov assumption states that nodes depend only on their parents and that all confounding variables have been included in the network (Heckerman, 1998; Korb & Nicholson, 2008). The faithfulness assumption stipulates that all connections are as specified by the probability distribution of variables observed in the real world (Heckerman, 1998; Korb & Nicholson, 2008). The latent variable assumption is a corollary of the first two assumptions and states that all latent variables have been accounted for in the model (Nagarajan et al., 2013). Once these assumptions have been satisfied, this network is a causal network (Pearl, 1995). The problem with identifying causal networks from BNs is that the structure of the DAG could be specified in many ways that have an equivalent fit to observed data (Heckerman, 1998). Each possible model competes for the solution as the causal model (Heckerman, 1998).

Some methods are available to identify causal networks when implementing a BN. According to Chickering (2002), some algorithms produce equivalent structure BNs if the distributions representing one DAG are the same as those representing another DAG, as in completed partially DAGs. Once a completed partially DAG has been identified, a set of DAGs can be identified as candidates for a causal structure. The procedure is usually applied through constraint-based algorithms, such as the PC algorithm, to estimate the completed partially DAG (Moraffah et al., 2021). An evaluation among equivalent structures is then made using domain knowledge or interventions (Chickering, 2002; Moraffah et al., 2021).

Unfortunately, it is difficult to identify whether SNs can be causal networks (Briganti et al., 2023). BNs have traditionally been used in SCMs under a structural equation modelling (SEM) framework introduced in Section 3.6. However, causal inferences explicit in SCMs may not be identified in the context of modelling symptoms (Briganti et al., 2023; Kline, 2023). SNs may not meet certain assumptions needed to infer causality. For example, in causal BNs, an underlying latent variable or common cause variable may have been unknowingly omitted from the network (Briganti et al., 2023). SNs usually use summed scores from a range of assessments or items from one or more assessments, and latent variables do not always need to be included in the networks. In SNs, it is also unclear whether one symptom causes another, whether both symptoms mutually cause each other, or whether a latent variable causes both symptoms (Briganti et al., 2023). Lastly, selection bias is also a concern in SNs, as it would violate the faithfulness assumption needed for causality (Briganti et al., 2023). These limitations make it difficult to infer causality in SNs. However, other aspects of SNs, like improving predictive validity, have been widely used to make more robust inferences from an SN.

3.5.5 Averaged networks

Averaging networks is a technique aimed at improving the predictive validity of a reconstructed network (Claeskens & Hjort, 2012). Averaged networks amalgamate many usually sub-optimal networks usually derived from bootstrapped data samples, aka random samples of the data with replacement of the same size as the original data (Scutari & Denis, 2021). By reconstructing many suboptimal networks and averaging them, the averaged network more robustly represents the population network or networks from samples drawn from the same population in other studies (Scutari & Denis, 2021). Overall, the fit to the data might be poorer than reconstructed networks on the complete dataset (Dash & Cooper, 2004). However, according to Dash and Cooper (2004), a reconstructed network on the complete dataset may overfit the network to the data. This can be problematic, in particular if there is sampling bias (Fan & Davidson, 2007). A network that has been overfitted to the data may not represent the same network as the true population. Given a network from the population, the network on the complete data may have lower specificity and sensitivity in classifying the edges in the population network compared to an averaged network (Claeskens & Hjort, 2012). Hence, averaged networks are used when the goal is to improve predictive validity.

To reconstruct an averaged network, a common choice is to use bootstrapped samples. For example, the resampling procedure could create 100 bootstrapped versions of the complete data. For each version, a BN (structure and parameters) is learned. This is repeated for all bootstrapped samples. Following this, the edges from all networks - 100 networks in my example - are collated. This is named the edge list. The number of times an edge between two particular nodes is present out of the 100 networks is called the edge strength. An averaged network usually specifies a minimum edge strength for that edge to be included in the averaged network. The minimum edge strength used to construct an averaged network is called a significance threshold (Scutari & Denis, 2021). For example, a significance threshold of 60 means an edge between node *alogia* and node *asociality*, for example, must have been found in 60 or more of the 100 bootstrapped networks to be included in the averaged network. After obtaining the edges where the edge strength is equal to or above the significance threshold, these edges form a weighted averaged network. This network could contain cycles. The graph must be acyclical to be a BN, and edges can only be present in one direction instead of being bidirectional. Typically, edges occur more in one direction than the other; in this case, the edge with higher edge strength is included (Scutari & Denis, 2021). One edge could be selected arbitrarily when edges in both directions occur equally and are above the significance threshold. Edges in one direction would be selected if the significance threshold is greater than 50. The edge in one direction may be selected to ensure the graph is acyclical, if desired. There are methods to obtain a fully directed DAG from an edge list, as reported in the R package bnlearn (Scutari, 2009). However, sometimes, it is only feasible to obtain a fully directed DAG from an edge list by removing or adding edges from or to the edge list, respectively. Lastly, although the significance threshold can be selected arbitrarily, mathematical methods can optimise the significance threshold, such as the method presented by Scutari and Nagarajan (2013). A statistically motivated threshold, as presented by Scutari and Nagarajan (2013), may be preferred. The statistically motivated threshold approximates the ideal asymptotic empirical cumulative distribution function with a finite sample estimate (Scutari & Nagarajan, 2013).

3.5.6 Inferences

3.5.6.1 Centrality statistics

Several network metrics can be used to make inferences about a particular condition or trait. Many of these metrics originated in social network analysis and have since been applied to understanding psychopathology (Bringmann et al., 2019). Most inferences are based on node, edge, and network topology statistics. Node statistics may identify which nodes are centrally located or are important in the network based on their associations with other nodes. Edge statistics assess the strength of the associations with different variables or parent-child relationships. Network topology statistics assess the network's integration, segregation, or information transferability as a whole (Hevey, 2018). These statistics can then provide information on a particular condition or trait, the attractor. Some authors argue that centrality statistics should not be used to develop psychotherapeutic interventions (Bringmann et al., 2019). These interventions often target more than one variable, and common factors contribute to their efficacy (Bringmann et al., 2019). The authors note that centrality and other network statistics may be used to understand a condition, trait, or cluster of symptoms (Bringmann et al., 2019). It is unclear whether an intervention could target a single node in a network, such as administering medicine to treat hallucinations or delusions. Isolated interventions on nodes may defy the premise of a complex systems approach to psychopathology, which emphasises dependency and interconnectedness. Centrality statistics have been used in systematic reviews (Buchwald et al., 2024; Malgaroli et al., 2021) and a meta-analysis (Isvoranu et al., 2021) to assess the importance of variables in SN.

In terms of node metrics, the *degree* is the number of edges a node has. It can also be expressed as the number of incoming or outgoing edges. The s*trength* is the sum of the weight of edges that are incoming and outgoing from a node (Hevey, 2018). *Closeness* identifies the relationships between one node and all other nodes in the network by considering the indirect connections from that node (Hevey, 2018). *Betweenness* is a metric that measures the importance of a node by considering all pathways between all other pairs of nodes in the network (Hevey, 2018). Both closeness and betweenness depend on the edge weight that connects two nodes. Another metric that has received attention is *expected influence*. One-step expected influence is the same metric as node strength but retains the positive and negative values of the edge coefficient (Robinaugh et al., 2016). Two-step expected influence considers the relationships between nodes two edges away from the target node (Robinaugh et al., 2016). Lastly, it is possible to obtain these statistics for nodes that act as bridge nodes, often linking symptoms between two or more conditions (Jones et al., 2021a). These symptoms are important because they may mediate the risk of acquiring or exacerbating a second comorbid condition (Jones et al., 2021a). Centrality statistics may identify node importance, although some research questions this notion when used in SNs (Bringmann et al., 2019). Metrics on aspects of a network other than variables can also be obtained to make inferences.

Several edge statistics are commonly used within the literature. Edge statistics are often based on the measure of association between two variables. The statistic could be a partial correlation, regression coefficient, or edge strength if the network is averaged. Some edges may not be included in the list if they have been omitted from the network because the correlation or another coefficient is too small. The underlying notion of edge statistics is the relationship between variables and how one node would change if the other node changed in value. Edge statistics can be calculated from their weight in model averaging, addressed in Section 3.5.5, and used in network probability queries, discussed in Section 3.5.6.

The last group of statistics is focused on the network's global features. These metrics are often used in neuroscience studies and social network analysis. For example, the six degrees of separation statistic, based on a study by Milgram (1967), was adopted into social network analysis to identify the notion of "small-worldness", although other criteria are now used to determine if a network exhibits a small-world property. Small-world networks have high levels of transitivity and small average path lengths. Path lengths, or average path lengths, sum the weights of the edges in the pathway between two nodes, taking the shortest path only (Hevey, 2018). Scale-free networks are networks with several hub nodes connected to many other nodes (Hevey, 2018). Here, nodes have a seemingly unlimited number of edges, and no node is typical of the others (Bonacich & Lu, 2012). Clustering is also an important feature of the network. Clustering can be identified for a node (clustering coefficient), which is defined as the fraction of edges allowed that exist over the theoretical limit of edges, or for the entire network (Chung, 2019). For the entire network, the overall cluster coefficient is based on the average of the clustering coefficient across all nodes (Chung, 2019). Aside from metrics, PMRF models can be used to identify clusters or communities of nodes, based on various algorithms developed outside of SNs. Methods to identify clusters or communities of nodes are outside the scope of this thesis.

3.5.6.2 Querying Bayesian networks

BNs are probabilistic graphical models that encode (conditional) independence relationships. These relationships make it possible to treat the network as an expert system that can be queried (Pearl, 1988). Here, probability queries state the probability of the values of one or more variables given the values of one or more other variables. An example could be, what is the probability that someone with schizophrenia scores above the mean on asociality, given they score above the mean on alogia? This could also be, but does not necessarily need to be, causal in nature. For example, what is the probability that a person develops schizophrenia if medication A is administered? Here, the intervention is how the administration of a medication (compared to a placebo, for instance) affects the onset or diagnosis of schizophrenia. This method aims to estimate the posterior distribution based on some evidence using Bayes theorem (Li & Mahadevan, 2018). The notion that BNs can answer probability questions makes them especially useful in SNs and other applications (Briganti et al., 2023). Consequently, two general methods have been developed to make probability queries on the data.

There are two types of general inference strategies: approximate and exact. The exact method calculates the probability of a variable given the value (evidence) of another variable using the joint probability distributions (Scutari & Denis, 2021). According to Scutari and Denis (2021), this may be difficult when the number of edges increases, and it may not be possible for all distributions assumed for the data (Scutari & Denis, 2021). The treewidth is also an important property of a network, where treewidth is an important consideration in the choice of exact or approximate inference (Peyrard et al., 2019). Typically, exact inference can be performed for Gaussian, discrete, hybrid, and conjugate exponential family models (Salmerón et al., 2018). According to Salmerón et al. (2018), various algorithms exist to perform exact inference for various probability distributions assumed for static and dynamic models. When exact inference cannot be implemented, approximate inference can be used. Approximation methods may use Monte Carlo or Markov Chain Monte Carlo to estimate probabilities by sampling local distributions or from the parameter space, respectively, although other methods exist (Salmerón et al., 2018). The Gibbs sampler is one type of Markov Chain Monte Carlo algorithm, which uses the Markov blanket. The Markov blanket is defined as a subset of nodes that makes the rest redundant when performing inference for a particular node (Scutari & Denis, 2021). Other Markov Chain Monte Carlo methods, such as the Metropolis-Hastings algorithm or Hamiltonian Monte Carlo, are available (Salmerón et al., 2018). Approximate inference usually provides a probability for the conditional relationship between variables, and this probability may change depending on random variability. Because of the complexity of the distributions assumed for the variables, performing exact inference may be challenging. Hence, approximate inference is often used instead.

3.6 Structural causal models

3.6.1 Overview

This thesis includes an SCM to model a BN to obtain regression coefficients, p-values, and fit statistics of a reconstructed BN; hence, an overview of SCMs, a branch of SEMs, is provided below. SEM is a family of methods developed using multivariate techniques to examine simultaneous complex relationships among variables (Crawford & Lamarre Jean, 2021). SEMs can handle complex directed relationships between a set of variables that overcome the simplicity of models of univariate tests, such as multiple regression, logistic regression, or analysis of variance (Hair et al., 2021). SEMs are usually confirmatory as opposed to exploratory (Heck, 1998). According to Sarstedt et al. (2020), SEMs have the added ability to simultaneously model complex relationships between observed and/or latent variables. This makes SEMs of potential value for examining data-driven models such as those reconstructed using BNs (Kline, 2023). SCMs are one type of SEM. SCM, as a branch of SEM, can be viewed as a hypothesis-testing alternative to a DAG estimated using a BN. However, there are some fundamental differences between an SCM and a BN (Kline, 2023).

An SCM makes inferring causality explicit, compared to a BN, where causality is implicit. An SCM was developed to model the causal relationships between variables. In contrast to BNs, SCM relationships between variables are identified as dependence, independence, conditional dependence or conditional independence relationships and assuming causality requires various assumptions to be met in BNs (Pearl, 2022; Scutari & Denis, 2021). Although SCMs are a method to explore complex causal relationships, using cross-sectional observational data in an SCM is not sufficient to infer causation, and the relationships in the model can only be described as associations rather than direct causal relations (Morgan & Winship, 2014). An SCM cannot allow causal inferences to be made with observational, cross-sectional, and non-experimental data, regardless of how the model is built, unless various assumptions are met (Morgan & Winship, 2014). Like a DAG estimated using a BN, the Markov assumption and faithfulness assumption are needed to infer causation (Kline, 2023). An additional assumption, the negligible randomness assumption, is needed for an SCM (Kline, 2023). Despite this, SCMs are designed to model directed causal associations (Pearl, 2022).

SEMs are uniquely positioned to test hypotheses about latent variables. In SEMs, the LVM model structure is usually specified a priori, although techniques can be useful to generate a possible structure to evaluate (Orcan, 2018). Similarly, BNs can be used to generate the structure to test. SCMs also allow latent variables to be expressed in a BN, something not usually enabled in some software packages for learning BNs (Scutari & Denis, 2021). In one SEM, confirmatory factor analysis, the assumption of causality is also inferred in the relationship between latent variables and observed variables (Zheng & Pavlou, 2010), where changes in the latent variable cause changes in the associated observed variables (Kline, 2023). In an SCM, this is not necessarily true as there are dependencies between observed variables (Borsboom, 2008a). Hence, in models where observed variables are assumed to interact, like network models, changes in the latent variables may not necessarily cause changes in observed variables. In confirmatory factor analysis, a good model will render the relationships between observed variables independent (Borsboom et al., 2003). If the LVM does not fit the data well and the error of the model has not been fully captured, relationships between observed variables can be included in the model (Bringmann & Eronen, 2018). This allows for both BN and LVM to be combined into a single model (Bringmann & Eronen, 2018). SCMs can be used, in addition to BNs, to make causality explicit, to model latent variables, and to confirm or reject hypotheses. This makes SCMs useful for studying BNs and DAGs, and SCMs have other advantages for mainstream network analysis.

3.6.2 Inferences

SEMs and SCMs are powerful methods that have been widely used across the literature to support or reject theoretical propositions (Marsh et al., 2014). Compared to BNs, the relationships between variables are identified as predictor and response relationships, and hence, an SCM is a complex representation of variables through their relationships in regressions. SCMs also identify independence between variables depending on the nature of their relationships in a DAG, as described in Section 3. (Kline, 2023). There is a multitude of inferences that can be drawn from an SCM, based on the structure and parameters of the model.

The model inferred in an SCM can be tested along with its individual components. The covariance matrix of the implied model can be compared with the covariance matrix of the observed model to identify if the model is an accurate representation of the data, or whether the covariance structure of the implied model is the same as the population model (De Carvalho & Chima, 2014; Yuan & Chan, 2016). However, according to Yuan and Chan (2016), a significant result indicates that the model is incorrect for the sample and is not the same as in the population, and a non-significant result is meaningless: There is not enough evidence that the implied covariance structure is different from the population covariance structure. This leads to a problem in the utility of using the chi-squared test for these inferences (Yuan & Chan, 2016).

Other fit statistics can be used to evaluate model fit, often available in SEM software (Rosseel, 2012). These model fit statistics can be categorised into three categories: absolute fit indices, which measure how well the model explains the data without other references; parsimony-adjusted fit indexes, which compare the degrees of freedom of the model to the maximum possible number of degrees of freedom, and some may give a complexity penalty; and incremental fit indices which compare the fit of the implied model to a baseline model (Kline, 2023; Tanaka, 1993). These measures include but are not limited to: AIC, BIC, comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and standardised root mean square residual. According to Hu and Bentler (1999), CFI and TLI should be greater than .95, RMSEA should be approximately .06, and standardised root mean square residual should be close to .08. Kline (2023) identifies that the cut-off values from Hu and Bentler (1999) are intended to be rules of thumb rather than fixed thresholds.

It is also possible to compare competing models using model fit indices and likelihood ratio tests. Likelihood ratio tests can be beneficial for comparing the significance of nested models, identifying whether a simpler model is rejected in favour of a more complex model. However, likelihood ratio tests cannot be used to compare non-nested models. Despite this, likelihood ratio tests do not penalise complexity. Instead, BIC and AIC can be used as a model fit index that penalises complexity by including a complexity penalty in the formula. AIC adds a penalty for each additional parameter, in addition to identifying the likelihood of the data, and BIC also penalises the sample size in addition to the number of parameters in its calculation.

Lastly, SCMs encode predictor and response relationships in the model and, therefore, have the added advantage of the inferences made when performing regression. Coefficients and effect sizes can be obtained, and therefore, the significance of the relationship can be established. The significance of a relationship in a regression can be helpful for identifying if the relationship between two or more variables is unlikely to be due to chance. The effect sizes can be standardised or unstandardised. Standardised relations in a network allow for the easy comparison between relationships with different scales, which, if an SCM of subscales from various assessments is included, direct comparisons can be made. Unstandardised coefficients are helpful for establishing the effect on the original scale of the measures. These added inferences in SEM and its statistical packages add to the utility of implementing a BN as an SCM.

3.7 Conclusion

SNs is a methodology to explain psychopathology from a complex systems approach and has been made possible through the development of statistical methods such as PMRFs, BNs, and the variations of these methods. BNs benefit from the ability to query conditional probabilities from the network and treat it as an expert system (Briganti et al., 2023). Limited literature has been dedicated to BN for SNs in the mental health literature compared with PMRFs, but the value of DAGs and BNs has been recognised in recent years (Briganti et al., 2023; Isvoranu et al., 2022). The applications of directed networks can be combined with other methods, such as SCMs (Kline, 2023), and advances in these areas may be the future focus of SNs. More theoretical development and empirical testing of the assumptions, if possible, could also be a future direction for SNs, and this is needed to evaluate the value and validity of these methods as models of health and well-being for people with mental illness and PLS. On the schizophrenia research front, there has been an array of publications on SNs of PLS, but it is unclear which methods have been used in these studies, and an overall synthesis of the findings has been lacking to date. Research on SN studies of PLS is the focus of the following four chapters of this thesis.

Chapter 4 Centrality Statistics of Symptom Networks of Schizophrenia: A Systematic Review

Prelude to Chapter 4

Since the development of SNs in 2010, increasing research has looked at SNs of schizophrenia (Cramer et al., 2010; Isvoranu et al., 2018). It is unclear how many of the 350 studies published between 2008 and 2020 on SN of mental illness are studies on PDS, and it is not certain how many more studies on PDS since the year 2020 have been published (Robinaugh et al., 2020). It is also not clear what future research can be conducted on SNs of schizophrenia that extends on previous research. Hence, the need for a systematic review. For studies included in the systematic review, the details of each method implemented across the networks can be recorded. Following a summary of the methods applied across studies, this information assisted in developing studies implemented for the research presented later in this thesis and for other researchers interested in presenting novel research on SNs of schizophrenia. Additionally, as discussed in Chapter 3, SN is a complex systems approach and therefore can provide inferences not usually made using empirical methods. SNs have the added ability of incorporating confounding effects of variables, so all necessary variables can be included in future networks (Briganti et al., 2023; McNally et al., 2017; McNally, 2016). Based on the novelty of SNs, it is unclear what current research has found on the SNs of schizophrenia to date. A systematic review can be used to survey the most central variables across studies. Because of the variability in the assessments used in SNs, it is possible for variables to be allocated a domain, and the domains can be ranked from most central to least central. This will inform readers which symptoms or domains are most central to schizophrenia from SN studies of schizophrenia. Hence, the following research will focus on the gaps, methodological features, and key outcomes of the SN studies of PDS.

4.1 Abstract

The network theory of mental disorders posits that systems of symptoms cause, or are associated with, the expression of other symptoms. Substantial literature on symptom networks has been published to date, although no systematic review has been conducted exclusively on symptom networks of schizophrenia, schizoaffective disorder, and schizophreniform (people diagnosed with schizophrenia; PDS). This study aims to compare statistics of the symptom network publications on PDS in the last 21 years and identify congruences and discrepancies in the literature. More specifically, I will focus on centrality statistics. Thirty-two studies met the inclusion criteria. The results suggest that cognition, and social and occupational functioning are central to the network of symptoms. Positive symptoms, particularly delusions were central among participants in many studies that did not include cognitive assessment. Nodes representing cognition were most central in those studies that did. Nodes representing negative symptoms were not as central as items measuring positive symptoms. Some studies that included measures of mood and affect found items or subscales measuring depression were central nodes in the networks. Cognition, and social and occupational functioning appear to be core symptoms of schizophrenia as they are more central in the networks, compared to variables assessing positive symptoms. This seems consistent despite heterogeneity in the design of the studies.

4.2 Introduction

Schizophrenia is a complex clinical syndrome that has diverse presentations, comorbidities, and outcomes. Whilst efforts to understand the causes and ameliorate the effects of schizophrenia have made considerable scientific progress since Meynert, Wernicke, Kraepelin, and Bleuler, the exact etiology is not yet well understood. Despite the lifetime prevalence of schizophrenia being relatively low (0.7%) (Moreno-Kustner et al., 2018), there is considerable impact on people diagnosed with schizophrenia, schizophreniform, schizoaffective disorder (people diagnosed with schizophrenia; PDS), their family, and their community. For example, PDS live for 15 fewer years when compared to healthy controls (HC), primarily due to concomitant physical illnesses such as cardiovascular disease, and suicide (Hennekens et al., 2005; Laursen et al., 2012; Saha et al., 2007). The heterogenous etiology, presentation, and prognosis of schizophrenia, schizophreniform, and schizoaffective disorders have led some authors to suggest these disorders may be better characterised as syndromes as opposed to distinct disease entites (Andreasen & Olsen, 1982; Carpenter, 2007; Kendell, 1987).

The network theory of mental disorders conceptualises psychopathology as a system-level network of interconnected symptoms and posits that symptoms may interact to cause or exacerbate, or are associated with, the expression of other symptoms (Borsboom, 2017; Borsboom & Cramer, 2013). Traits or conditions are emergent properties of a network, depending on the characteristics or properties of a network for a given population (Fried et al., 2017). Using statistical techniques to underpin the construction of symptom networks may reveal a cascading effect of connected symptoms. For example, auditory hallucinations can cause anxiety, which can cause asociality, which, in turn, results in alogia. The strength of the connections in time and with each other and the density of the connections may indicate a person who has a higher risk of, or has greater intensities of, psychopathology (Borsboom, 2017). Furthermore, highly comorbid conditions such as schizophrenia and depression are accounted for as co-occurring due to mutual interactions between symptoms, as opposed to being distinct diseases or psychological disorders operating in parallel (Fried et al., 2017). The network approach may be especially relevant for the study of the symptomatology within PDS as: (1) schizophrenia is a syndrome with heterogenous presentations and outcomes; (2) no unique symptom in schizophrenia is pathognomonic to the disorder; (3) schizophrenia has an increased prevalence of co-morbid conditions; and (4) there is diversity in the pathogenesis of schizophrenia (Isvoranu et al., 2018; Weinberger & Harrison, 2011).

Symptom networks graphically and statistically model the relationships between nodes (e.g. items of an assessment, observed or latent variables) via edges (relationships between nodes). There are numerous methods to implement a symptom network, for example, the edges can be directed (with arrows from parent nodes to daughter nodes), partially directed, or undirected.

The direction in networks is not necessarily causal in nature but does identify associations, or conditional dependence relationships. For a reconstructed network to be fully specified, parameters need to be estimated for the obtained structure of the graph to be used for quantitative interpretations or predictions. Once a network has been specified, information on the properties of the network can be obtained.

Examining the nodes and edges of symptom networks in PDS and HCs enables identification of the strength of relationships between nodes, and the influence of these nodes within the networks (Chung, 2019; Hevey, 2018). A node (i.e., a symptom) that is most central, is more likely to impact on other nodes in the network. Centrality statistics in symptom networks are drawn from social network analysis and identify the relative importance of nodes within a network (Bringmann et al., 2019). The three commonly used centrality statistics are betweenness, closeness, degree, and strength. Betweenness is defined as how well a node acts as a connecting point by using the number of paths through that node to any other pair of nodes. Closeness is defined as how close a node is to all other nodes using the average partial correlation of the paths from that node. Strength is the sum of all partial correlations from or to that node. Degree is the number of edges from or to a node (Hevey, 2018). See the supplementary materials section (Appendix C1) for the mathematical formulae for these node metrics in the effect measures section. Hence, network metrics can be used as an effect measure to synthesize and integrate the literature to identify which nodes or edges may be most interconnected for a particular condition.

Adding nodes into the network itself is analogous to controlling for confounding variables when using empirical statistics (McNally, 2016). Some arguments against the network approach to psychopathology posit that the networks themselves do not have predictive validity or the results are difficult to replicate (Forbes et al., 2017). However, other authors later rejected this notion and found support for the replicability of networks (Borsboom, 2017; Fried et al., 2021; Funkhouser et al., 2020; Jones et al., 2021b). Given no systematic review has been published solely on network studies of schizophrenia, a systematic review may therefore be useful to identify whether the networks produce consistent results when including or excluding key confounding variables or whether the network literature on schizophrenia is in alignment with the general understanding on schizophrenia. A synthesis can clarify whether cognitive and negative symptoms are more central than positive symptoms like hallucinations and delusions.

With the novelty of symptom networks, research on symptom networks in schizophrenia is growing rapidly, yet no systematic review specifically on symptom networks in schizophrenia has been undertaken to date. A systematic review is needed to: (1) synthesise networks identified to date; (2) identify the key methodological limitations of extant research and (3) identify the priorities for ongoing research and (4) identify any clinical implications from the results. Henceforth, the objective of this systematic review is to synthesise the literature and identify any congruences and discrepancies in the literature. This may identify if the outcomes of psychopathology networks of schizophrenia align with the current understanding of schizophrenia, if the networks are replicable, we may be able to identify key symptoms or nodes that are hypothetical core features of the illness.

4.3 Methods

4.3.1 Literature search

The present study aims to identify the current state of knowledge on networks in PDS. Because of the novelty of the network theory of psychological disorders we aimed to capture all symptom network studies that met the inclusion criteria over the 21 years prior to the search. We followed the systematic review guidelines documented by Perestelo-Pérez (2013). Two differences between the guidelines and our implementation of the systematic review were: (1) We did not used the population, intervention, comparison, outcomes, and study (PICOS) question framing tool as we did not compare treatment and control groups, nor did we specify treatment effects; and (2) one author collected the data (KB). Additionally, to avoid bias or errors in the data collection process, each result reported was quality checked against the original publications by KB. This strategy was preferred due to the large amount of unused data collected. We also aligned with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guidelines (Page et al., 2021), found in the Supplementary Materials (Appendix C1).

We systematically searched and selected studies based on pre-determined inclusion and exclusion criteria. A research librarian specialising in systematic reviews supported developing and testing search terms and variations, and to identify suitable databases. The search covered the following databases: (1) Medline and (2) CINAHL through EBSCO Host, (3) Scopus, (4) PsycINFO through Ovid, and (5) Google Scholar (https://scholar.google.com/). The last search was undertaken on the 27th of June 2022 for Medline, CINAHL, Scopus, and PsycINFO, and the 08th of July 2022 for Google Scholar. Hand searching the reference lists of the articles in the full text review occurred on the 5th of August 2022. We updated the list from Medline, CINAHL, Scopus, and PsycINFO on the 08/05/2023 to ensure this systematic review is up to date with current research. The search strategy can be found in the Supplementary Materials (Appendix C1).

Because of the novelty of the network theory of psychological disorders we aimed to capture all symptom network studies that met the inclusion criteria to date. Furthermore, we included only people that had a confirmed primary diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder, and no other disorders (unless these conditions were comorbid or were presented in separate networks). Therefore, participants whom the network was reconstructed on needed at least one of these three diagnoses. Publications that only used the term psychosis, without reference to a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform, are not included in our study. The full systematic review methods with inclusion and exclusion criteria, search methods, information sources, data collection process including data extraction, management and data items, a list of variables collected, risk of bias assessment, effect measures used in the study, and the synthesis method are published in the supplementary materials (Appendix C1).

4.3.2 Inclusion criteria

The inclusion criteria for study selection were as follows: (1) the network pertained to a treatment group with participants who had a DSM IV, DSM-5, International Classification of Diseases (ICD) 10, or ICD-11 primary diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder, (2) the nodes in the networks contained at least one symptom from criterion A in the DSM-5 for a diagnosis of schizophrenia (differences between criterion A in the DSM-IV and DSM-5 pertain only to the examples of negative symptoms), (3) the publication was a peer reviewed journal article, (4) the study was original research and not a review or discussion piece, (5) the study was written in English, (6) a graphical network model was applied, (7) the study had quantitatively derived networks, (8) the network was based on human participants, (9) the human participants were living at the time of the research or of the assessment, (10) the data was observed as opposed to simulated, and (11) the record was available in the search engine (12) given the dataset, variables included, and methodology of the study, this study was not a replication of previous research. Hence, we allowed studies that used the same dataset (several studies used a common dataset such as from the CATIE trial; Keefe et al., 2003) so long as the variable set or treatment and control groups differed.

4.3.3 Exclusion criteria

The exclusion criteria for study selection were as follows: (1) research on a mental disorder other than schizophrenia, schizophreniform, or schizoaffective disorder, where this disorder was not used as a comparison group to schizophrenia, schizoaffective, or schizophreniform, (2) participants did not meet the DSM-IV, DSM-5, ICD-10, or ICD-11 diagnostic criteria for schizophrenia, schizophreniform, or schizoaffective disorder, (3) the nodes in the networks did not contain at least one symptom from criterion A in the DSM-5 for a diagnosis of schizophrenia, (4) the publication was not a peer reviewed journal article, (5) the study was not original research or was a discussion piece, (6) the study was not written in English, (7) a graphical network model was not applied, (8) the study did not have quantitatively derived networks, (9) the network was not based on human participants, (10) the human participants were not living at the time of the research or of the assessment, (11) the data was simulated as opposed to observed, (12) the record was not available in the search engine and (13) the dataset, variables included, and statistical methodology of the study was a replication of previous research.

4.3.4 Search methods for identification of studies

4.3.4.1 Information sources

4.3.4.1.1 Selection process

The search engines returned 2,211 studies, 975 of which were duplicates. Conflicts were 5.3% (κ = .58) between KB and KA in the initial screen and were 10.0% (κ =.58) between MS and KB for screening the updated literature search. Consensus was reached on each publication through discussion. The full-text reviewers of the initial search KB and KA disagreed on 17 studies (25.8%, κ = 0.48) and the updated search MS and KB disagreed on three studies in the full text review (13%, κ = .74). A consensus was reached for each disagreement between KB and MS.

4.4 Results

4.4.1 Description of studies

4.4.1.1 Study selection

Database searches yielded 2,211 studies to be screened, of these 975 were duplicates and removed. The remaining 1,236 studies proceeded through abstract screening, from which 89 manuscripts were full text reviewed. The full text of two studies could not be retrieved. Search results for electronic searches and hand searching are found in a PRISMA flowchart (Page et al., 2021) see Figure 12. Thirty-two studies were included in this research. Most exclusions were because the study was on other mental disorders (*N* = 36) or studies where nodes in the network were not a DSM-5 symptom of schizophrenia (*N* = 8).

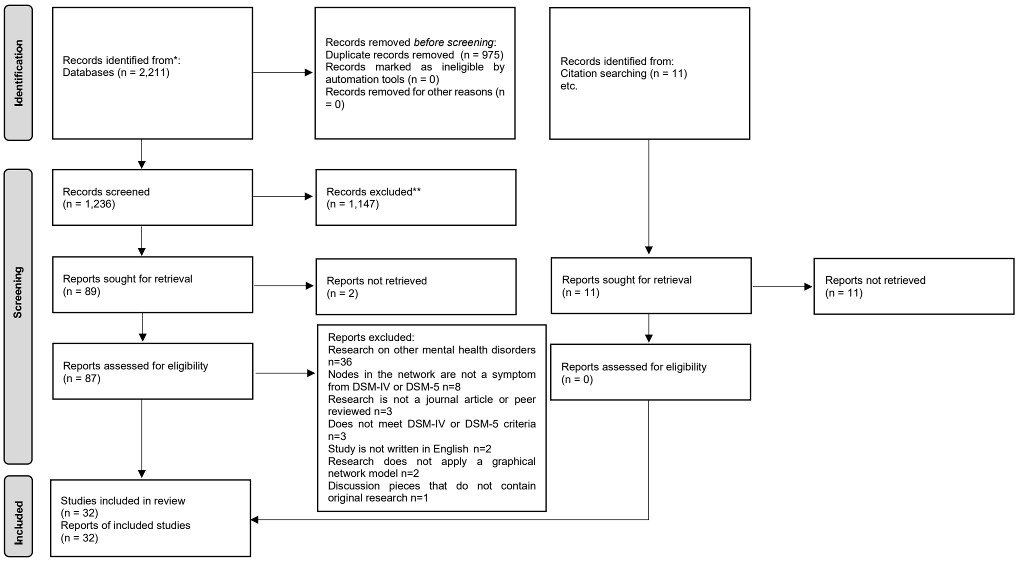

Figure 12. PRISMA Flow Chart.

4.4.1.2 Study characteristics

Table 1 shows an overview of the studies included in this systematic literature review. Overall, there was considerable heterogeneity across the assessments included in the studies, including assessments that examined positive and negative symptoms, language, functioning, cognition, biomarkers, social constructs such as resilience or perceived discrimination, and side effects from medication. A list of assessments administered can be found in the Supplementary Materials (Appendix C1) in the List of Assessments section. Most (*N* = 28) of the studies included networks of PDS participants only, whereas three studies compared PDS to HC, one study compared schizoaffective disorder to other disorders and HC, and one study compared schizoaffective disorder to other psychological disorders only. Of the 32 studies, 13 studies used the same dataset as in another study included in this systematic review.

Table 1. Characteristics of Included Studies.

Author	No. of patients	Mean age (SD); N males	Country	Comparisons	Assessments	Dataset
Abplanalp et al. (2023)	173	42.8 (12.6); 124	USA	None	MATRICS, SANS	FCFS
Amore et al. (2020)	921	40.21 (10.7); 641	Italy	None	PANSS, CDSS, BNSS, ISMI, PDD, MATRICS, FEIT, TASIT, SHRS	INRP
Badal et al. (2021)	105	51.9 (9.2); 75	Not Stated	PDS and HC	EMA	Unnamed
Bak et al. (2016)	1	46 (0); 0	Netherlands	None	EMA	Unnamed
Brasso et al. (2023)	167	Duration of illness < 5 years 27.3 (8.7); 59; Duration of illness > 5 years: 43.5 (10.2); 59	Italy	Duration of illness <5 years and >5 years	BNSS, CDSS, MAS, MSCEIT, MATRICS, PANSS, SLOF	Unnamed
Charernboon (2021)	64	37.0 (12.6); 27	Thailand	None	SAPS, SANS, ACE III, REMT, FT, PSP	Unnamed
Choi et al. (2022)	1438	39.9 (12.5); 830	Multinational	None	BPRS	REAP-AP
Dal Santo et al. (2022)	446	26.0 (6.0); 312	Multinational	None	PANSS, CDSS, PSP	OPTiMiSE
Demyttenaere et al. (2022a)	460	40.5 (10.9); 262	Multinational	None	PANSS, CDSS	CRS
Demyttenaere et al. (2022b)	Acute = 2193; PNS = 460	37.8 (10.6); 1552 (Acute). 40.5 (10.9); 264 (PNS)	Multinational	Acute and PNS	PANSS	CCT; CRS
Esfahlani et al. (2017)	TResis = 316; TRespon = 733		USA	TResis baseline, TResis follow up, TRespon baseline, and TRespon follow up	PANSS	CATIE
Esfahlani et al. (2018)	TResis = 316, TRespon = 733		USA	TResis and TRespon	PANSS	CATIE
Galderisi et al. (2018)	740	40.0 (10.9); 519	Italy	None	PANSS, BNSS, CDSS, MATRICS, FEIT, TASIT, MSCEIT, SLOF, UPSA-B, SES, ISMI, RSA	INRP
Galderisi et al. (2020)	618	45.1 (10.5); 427	Italy	Baseline, follow up; recovered, not recovered	PANSS, BNSS, CDSS, RSA, MATRICS, TASIT, FEIT, MSCEIT, UPSA-B, SLOF, SES, ISMI	INRP
Hajdúk et al. (2019)	226	42.3 (12.0); 144 (PDS).	USA	PDS and HC	PS, SFS, SLOF	SCOPE
Hasson-Ohayon et al. (2018)	81	49.7 (10.8); 77 (PDS, SZA)	USA	None	PANSS, MAS-A, HT, BLERT, MATRICS, SAT, PST	Unnamed
Hopkins et al. (2022)	4,863	Not stated	International	Enriched Marder PANSS negative symptom construct and de-enriched Marder PANSS negative symptom construct	PANSS	RCT
Hu et al. (2022)	269	38.8 (11.4); 135.	China	None	PANSS, CAINS, SAS, BARS, SOFAS	Unnamed
Levine and Leucht (2016)	437	34.0 (9.4); 319	Multinational	Baseline and follow-up	SANS	RCT
Li et al. (2022)	3,681	39.9 (12.9); 2,164	Multinational	None	Clinical interview, medical records	REAP-AP
Moffa et al. (2021)	1208	40.8 (11.0); 743	Multinational	None	PANSS, CDSS	EuroSC
Monteleone et al. (2021)	875	NA (NA); 607	Italy	None	PANSS, BNSS, MSCEIT, FIET, TASIT, MATRICS, SHRS.	INRP
Monteleone et al. (2022)	571	Not stated ;391	Italy	Baseline and follow up	BNSS, CDSS, PANSS, SRHS	INRP
Park et al. (2020)	167	46.5 (11.2); 86	Korea	None	CLANG	Unnamed
Peralta et al. (2020)	124	39.9 (14.9); 62	Spain	Schizoaffective, bipolar, and psychotic depression	CASH	Unnamed
Strauss et al. (2019a)	USA = 201, Italy = 912	41.6 (12.1); 146 (USA). 40.1 (10.7); 637 (Italy)	Multinational	USA and Italy	BNSS	MPRC; SUNYB; INRP
Strauss et al. (2019b)	201	41.6 (12.1); 146.	USA	PDS and schizoaffective, bipolar, and HC	BNSS	MPRC; SUNYB
Strauss et al. (2020)	Roluperidone = 161, Placebo = 83	40.2 (10.4); 89 (Roluperidone). 40.0 (10.2); 48 (Placebo)	Multinational	Roluperidone and placebo	BNSS	RCT: EudraCT number: 2014-004878-42
Sun et al. (2023)	2,334	31.3 (7.9); 1,207	China	Baseline and three follow ups; response and resistant networks	PANSS	CAPC
van Rooijen et al. (2018)	Remitted = 150, non-remitted = 316	26.0 (6.6); 150 (Remitted). 27.2 (6.6); 316 (non-remitted)	Netherlands	Remitted and non-remitted	PANSS, CDSS	GROUP
Wang et al. (2023)	204	49.4 (10.2); 99	China	None	BNSS, SANS, SNS	Unnamed
Yan et al. (2022)	79	34.4 (11.9); 25	China	None	PANSS, BPRS	Unnamed

Note. PDS = People diagnosed with schizophrenia; HC = Healthy controls; PNS = Predominately negative symptoms; TResis = treatment resistant; TRespon = Treatment responsive; ACE III = Addenbrookes cognitive examination version III; BARS = Barnes Akathisia Rating Scale; BLERT = Bell–Lysaker Emotional Recognition Task; BNSS = Brief negative symptom scale; BPRS = Brief psychiatric rating scale; CAINS = Clinical assessment interview for negative symptoms; CASH = Comprehensive assessment of symptoms and history; CDSS = Calgary depression rating scale for schizophrenia; CLANG = Clinical language disorder rating scale; EMA = Ecological momentary assessment; FEIT = Facial emotion identification test; FT = Faces test; HT = Hinting task; ISMI = Internalised stigma of mental illness; MAS = Metacognition assessment scale; MATRICS = Measurement and treatment research to improve cognition in schizophrenia; MSCEIT = Mayer-Salovey-caruso emotional intelligence Test; PANSS = Positive and negative syndrome scale; PDD = Perceived devaluation and discrimination scale; PS = Paranoia scale; PSP = Personal social performance scale; PST = Picture Sequencing Task; REMT = Reading the mind in the eyes test; RSA = Resilience scale for adults; SAT = Social Attributions Test; SANS = Scale for the assessment of negative symptoms; SAPS = Scale for the assessment of positive symptoms; SAS = Simpson-Angus Extrapyramidal Side Effects Scale; SES = Service engagement scale; SFS = Social functioning scale; SHRS = St Hans rating sale; SLOF = Specific level of functioning scale; SNS = Self-Evaluation of Negative Symptoms Scale; SOFAS = Social and occupational functioning assessment scale; TASIT = The awareness of social inference test; UPSA-B = UCSD Performance-Based Skills Assessment—Brief; CAPC = Chinese Antipsychotics Pharmacogenomics Consortium; CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CCT Cariprazine Clinical Trials; CRS = Cariprazine-Risperidone Study; EuroSC = European Schizophrenia Cohort; GROUP = Genetic Risk and Outcome of Psychosis; INRP = Italian Network for Research on Psychoses; MRPC = Maryland Psychiatric Research Center; OPTiMiSE = Optimisation of Treatment and Management of Schizophrenia in Europe; REAP-AP = Research on Asian Psychotropic Prescription Patterns for Antipsychotics; RCT = Randomised Control Trials; SCOPE = Social Cognition Psychometric Evaluation; SUNYB = State University of New York at Binghamton; Unnamed = Dataset or study was private and was not given a public name.

4.4.1.3 Risk of bias in studies

Table 2 Shows the results of applying an adapted McMasters critical review form to each retrieved source. Five studies did not review the literature on symptom networks of schizophrenia or other conditions in their study (Bak et al., 2016; Galderisi et al., 2018; Monteleone et al., 2022; Yan et al., 2022). Most of the research designs were descriptive studies or one sample pre-test only designs ($N = 19$). Two studies did not document the network sample sizes or the sample sizes in the networks could not be derived from previous studies (Demyttenaere et al., 2022a; Hajdúk et al., 2019). Two studies presented a network based on ecological momentary assessment and therefore the outcome measures were not assessed as reliable or valid (Badal et al., 2021; Bak et al., 2016). Most studies did not address the reliability ($N = 19$) or validity ($N = 18$) of the assessments they included. Results of Individual Studies.

Table 2. Quality Appraisal of Included Studies.

Author	Was the purpose stated clearly?	Was relevant background literature reviewed?	Research Design	Sample size	Was the sample described in detail?	Was sample size justified?	Were the outcome measures reliable?	Were the outcome measures valid?	Intervention was described in detail?	Contamination was avoided?	Cointervention was avoided?	Results were reported in terms of statistical significance?	Were the analysis method (s) appropriate?	Clinical importance was reported?	Drop-outs were reported?	Conclusions were appropriate given study methods and results
Abplanalp et al. (2023)	Yes	Yes	Descriptive study	151-	Yes	Yes	NA	NA	NA	N/A	N/A	No	Yes	Yes	No	Yes
Amore et al. (2020)	Yes	Yes	Descriptive study	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
Badal et al. (2021)	Yes	Yes	Cohort	151-	Yes	Yes	No	No	NA	N/A	N/A	No	Yes	Yes	Yes	No
Bak et al. (2016)	Yes	No	Single case design	1-50	Yes	Yes	No	No	NA	N/A	N/A	No	No	Yes	N/A	Yes
Brasso et al. (2023)	Yes	Yes	Descriptive study	151-	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Charernboon (2021)	Yes	Yes	Descriptive study	51-100	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Choi et al. (2022)	Yes	Yes	Descriptive study	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Dal Santo et al. (2022)	Yes	Yes	Descriptive study	200+	Yes	Yes	NA	NA	NA	N/A	N/A	No	Yes	Yes	No	Yes
Demyttenaere et al. (2022a)	Yes	Yes	Descriptive study	200+	Yes	No	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
Demyttenaere et al. (2022b)	Yes	Yes	Descriptive study	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Esfahlani et al. (2017)	Yes	Yes	Before and after	200+	No	No	NA	NA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Esfahlani et al. (2018)	Yes	Yes	Descriptive study	200+	No	NA	NA	NA	NA	N/A	N/A	No	No	Yes	NA	Yes
Galderisi et al. (2018)	Yes	No	Descriptive study	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	No	Yes	Yes	Yes
Galderisi et al. (2020)	Yes	Yes	Before and after	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
Hajdúk et al. (2019)	Yes	Yes	Descriptive study	200+	Yes	No	Yes	Yes	NA	N/A	N/A	Yes	Yes	Yes	Yes	No
Hasson-Ohayon et al. (2018)	Yes	Yes	Descriptive study	51-100	Yes	Yes	Yes	Yes	NA	N/A	N/A	No	Yes	Yes	No	Yes
Hopkins et al. (2022)	Yes	No	Descriptive study	200+	No	Yes	NA	Yes	NA	N/A	N/A	No	Yes	Yes	No	Yes
Hu et al. (2022)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Levine and Leucht (2016)	Yes	Yes	Before and after	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	No	Yes	Yes
Li et al. (2022)	Yes	Yes	Cohort	200+	Yes	Yes	No	No	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Moffa et al. (2021)	Yes	Yes	Cohort	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
Monteleone et al. (2021)	Yes	Yes	Case Control	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	No	Yes	Yes
Monteleone et al. (2022)	Yes	No	Cohort	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	No	No	Yes
Park et al. (2020)	Yes	Yes	Case Control	151-	Yes	Yes	NA	NA	NA	N/A	N/A	No	Yes	No	No	Yes
Peralta et al. (2020)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	NA	NA	N/A	N/A	Yes	Yes	Yes	No	Yes
Strauss et al. (2019a)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	No	Yes	No	Yes
Strauss et al. (2019b)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	No	Yes	No	Yes
Strauss et al. (2020)	Yes	Yes	RCT	200+	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Sun et al. (2023)	Yes	Yes	Cohort	200+	Yes	Yes	NA	NA	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
van Rooijen et al. (2018)	Yes	Yes	Cohort	200+	Yes	Yes	NA	Yes	NA	N/A	N/A	Yes	Yes	Yes	Yes	Yes
Wang et al. (2023)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	No	No	Yes
Yan et al. (2022)	Yes	No	Descriptive study	101-	Yes	Yes	NA	NA	NA	N/A	N/A	No	No	Yes	No	Yes

Note. NA = Not addressed; N/A = Not applicable

Figure 13 provides the results of the centrality statistics of variables added as nodes in each network. For each network and centrality statistic, variable domains included were either the most central (dark blue), second most central (medium blue), or third most central (light blue). Cells in Figure 13 were coloured in grey if this domain was not assessed or included in the centrality statistics. Cells in white are domains in which the variables were included but were not most central. The method to allocate items and subscales to the domain's depression, cognition, functioning, positive symptoms, and negative symptoms can be found in the Supplementary Materials (Appendix C1) . Additionally, the text version of this figure can be found in Table 3. In Figure 13, variables that were excluded because they do not belong to these domains were occasionally more central in the network, however, these were removed because (a) they were less frequently included the networks across all the studies or (b) they assessed general psychopathology. Overall, there were 43 networks that reported on the centrality statistics in Figure 13. Many of the datasets were the same across studies hence caution needs to be taken when interpreting similar findings across these studies. Furthermore, some publications included more than one network in their results.

In terms of the domain cognition, variables allocated to the cognition domain featured in the top three for seven of nine networks for betweenness, four of nine networks for closeness, three of four networks for strength, and seven of seven networks for degree. Functioning appeared in the top three most central variables in eight out of 11 in betweenness and closeness, five out of seven for strength, and in three out of six networks for degree. Considering only networks that compared cognition to functioning, cognition was more central in 13 of 24 networks, across all centrality statistics. However, these results might be skewed by Galderisi et al. (2020) who conducted four networks on subsamples of their dataset. Furthermore, Galderisi et al. (2018) and Galderisi et al. (2020) used the same dataset for both their studies. When comparing cognition to positive symptoms, in every network that included both cognition and positive symptoms, cognition was more central in every network. Similarly for functioning, in six of nine networks functioning had higher betweenness. For closeness, functioning was more central than positive symptoms in seven of nine networks. For strength, in five of seven studies, functioning was more central than positive symptoms.

In studies that compared negative symptoms to positive symptoms, where negative symptoms or positive symptoms featured in the top three most central, variables in the domain negative symptoms were most central in one of eight studies for betweenness. Similarly for closeness, in one study of nine, variables in the negative symptoms domain were more central than positive symptoms. In five of 17 studies negative symptoms had higher strength than positive symptoms, and for degree, three of four networks had variables allocated to the negative symptom domain with higher degree. However, Demyttenaere et al. (2022a) and Demyttenaere et al. (2022b) used the same dataset, and Choi et al. (2022) and Li et al. (2022) also used the same dataset.

Furthermore, Demyttenaere et al. (2022b), Esfahlani et al. (2018), Hu et al. (2022) included multiple networks on the same dataset.

Of all studies that included variables in the depression and positive symptom domains, where either depression or positive symptoms was the top 3 most central, depression variables had higher betweenness than positive symptoms in two of eight studies. For closeness, depression was more central in three of eight studies. For strength, depression was more central in four of nine studies and for degree, depression was more central than positive symptoms in one out of one study. In these studies, Bak et al. (2016), Hu et al. (2022), had included multiple networks on the same sample. Additionally, none of the studies that included items or subscales measuring positive and depression used the same dataset. Some assessments were not exclusively developed to measure depression but include items that aim to measure depression. As in the Table 3 table, Dal Santo et al. (2022) and Demyttenaere et al. (2022a) found that in their network the item from the Positive and Negative Syndrome Scale (PANSS) on depression was more central than items representing positive symptoms. However, positive symptoms were more central that the item measuring depression in the studies on the PANSS by Demyttenaere et al. (2022b) and Esfahlani et al. (2018). This is true despite seven items in the PANSS measuring positive symptoms and one item measuring depression. Likewise, in terms of the BPRS, depressive mood was more central than positive symptoms in betweenness, closeness and strength in the study by Choi et al. (2022), despite 3 items measuring positive symptoms and two items measuring depression.

Network	Betweenness					Closeness					Strength					Degree				
	Cognition	Functioning	Positive symptoms	Negative symptoms	Depression	Cognition	Functioning	Positive symptoms	Negative symptoms	Depression	Cognition	Functioning	Positive symptoms	Negative symptoms	Depression	Cognition	Functioning	Positive symptoms	Negative symptoms	Depression
Brasso et al. (2023); Duration of illness < 5 years	1			3		1	2									1			1	
Brasso et al. (2023); Duration of illness > 5 years	1					1										1				
Hasson-Ohayon et al. (2018)	1					1					1									
Galderisi et al. (2020); Recovered	1															1				
Charernboon (2021)	2	1		3			1		2			1		2						
Galderisi et al. (2018)	3	1					1				1	2								
Galderisi et al. (2020); Baseline	3	1				3	1									1	2			
Hu et al. (2022); Item level		1	2	3			1	3	2			1		2						
Galderisi et al. (2020); Follow-up		1					1									1	2			
Galderisi et al. (2020); Not recovered		1					1									1	2			
Hajdúk et al. (2019)		2	1					1					1							
Hu et al. (2022); Symptom dimension		3	1	2			3	1	2			1	3	2						
van Rooijen et al. (2018)			1	2				1	2				1	3	1					
Bak et al. (2016); Impending relapse			1		2			1		2			1		2					
Bak et al. (2016); Full relapse state			1		3			1					1		3					
Demyttenaere, Leenaerts, et al. (2022); Acute population			1					1	3				1	3						
Demyttenaere, Leenaerts, et al. (2022); Predominant negative symptoms			1					1	3				1							
Demyttenaere, Anthonis, et al. (2022)			1					2		1			2		1					
Wang et al. (2023)				1					1					1					1	
Levine and Leucht (2016); Baseline				1					1					1						
Levine and Leucht (2016); Endpoint				1					1					1						
Levine and Leucht (2016); Change				1					1					1						
Gregory Paul Strauss, Esfahlani, Kirkpatrick, et al. (2019); Both genders				1															1	
Gregory Paul Strauss, Esfahlani, Kirkpatrick, et al. (2019); Male				1															1	
Gregory Paul Strauss, Esfahlani, Kirkpatrick, et al. (2019); Female				1															1	
Bak et al. (2016); Stable state			2		1			2		1			2		1					
Choi et al. (2022)			3	2	1			3	2	1			3	1	2					
Esfahlani et al. (2018); Treatment resistant								1	2									1	3	
Esfahlani et al. (2018); Treatment responsive								1	3									3	1	
Gregory P. Strauss et al. (2020); Treatment									1										1	
Gregory P. Strauss et al. (2020); Placebo									1										1	
Li et al. (2022)												1	2	3						
Dal Santo et al. (2022)													1	2	3					
Sun et al. (2023); t2													1	2						
Sun et al. (2023); t4													1	2						
Sun et al. (2023); response													1	2						
Sun et al. (2023); t3													1	3						
Sun et al. (2023); resistant													1	3						
Sun et al. (2023); t1														1					1	
Amore et al. (2020); Extended network											2		3		1					
Amore et al. (2020); Depressive symptoms and insight															1					
Yan et al. (2022); PANSS																2			1	3
Yan et al. (2022); BPRS																			1	2

Figure 13. Ranks of Domains Across Centrality Indices.

Note. Dark blue cells identify that a variable is the most central; Medium blue cells identify that a variable is the second most central; light blue cells identify that a variable is the third most central; Cells in Figure 13 were coloured in grey if this domain was not assessed or the centrality statistics were not included in the results of the study; Cells in white are domains in which the variables were not most central; Ties are included in this figure; If a domain in the occurs more than once in the first, second, and third most central variable, only the most highest rank is reported; an empty row represents the variables had equal centrality for a centrality statistic.

Table 3 presents the results for the subscales which has the highest ranked betweenness, closeness, strength, and degree in each of the studies included in the systematic review. Colours within the table identify which domain each of the subscales was associated with. Depending on the study, the node may represent an item, a subscale, or a total score from the assessment. In terms of cognition, working memory and visual learning from the MATRICS were generally most central across other studies that included them. Processing speed was most central in a few studies. In terms of functioning, various assessment tools were used, and the total score was often reported. Despite this heterogeneity, the total score for the Specific Level of Functioning scale was central across multiple studies. Across studies that included the PANSS and where positive symptoms were central, delusions generally featured as the most central item in the network. Hallucinations did not appear to be among the most central across studies. In terms of negative symptoms, alogia and expression of emotion were frequently central, although there was considerable variation in the centrality of negative symptoms across assessments and studies.

Table 3. Node Metrics for all Variables Included in the Domains, Text Version.

Author	Betweenness	Closeness	Strength	Degree
Amore et al. (2020) ; Depressive symptoms and insight			1. Depression (CDSS; F) 2. Hopelessness (CDSS; F) 3. Observed depression (CDSS; F)	
Amore et al. (2020) ; Extended network			1. Depression (CDSS; F) 2. Social cognition (Factor analysis; F) 3. Positive (PANSS; F)	
Bak et al. (2016); Stable state	1. Down (EMA; I) 2. Paranoia (EMA; I) 3. Loss of control (EMA; I) = Hearing voices (EMA; I)	1. Down (EMA; I) 2. Paranoia (EMA; I) 3. Loss of control (EMA; I) = Hearing voices (EMA; I)	1. Down (EMA; I) 2. Paranoia (EMA; I) 3. Hearing voices (EMA; I)	
Bak et al. (2016); Impending relapse	1. Paranoia (EMA; I) 2. Down (EMA; I) 3. Loss of control (EMA; I) = Hearing voices (EMA; I)	1. Paranoia (EMA; I) 2. Down (EMA; I) 3. Loss of control (EMA; I)	1. Paranoia (EMA; I) 2. Down (EMA; I) 3. Hearing voices (EMA; I)	
Bak et al. (2016); Full relapse state	1. Paranoia (EMA; I) 2. Loss of control (EMA; I) 3. Down (EMA; I)	1. Paranoia (EMA; I) 2. Hearing voices (EMA; I) 3. Loss of control (EMA; I)	1. Paranoia (EMA; I) 2. Hearing voices (EMA; I) 3. Down (EMA; I)	
Brasso et al. (2023); Duration of illness < 5 years	1. Visual learning (MATRICS; F) 2. Speed of processing (MATRICS; F) 3. Avolition (BNSS; F)	1. Visual learning (MATRICS; F) 2. SLOF (SLOF; F) 3. Working memory (MATRICS; F); Meta cognition (MAS; F)		1. Speed of Processing (MATRICS; F) = Avolition (BNSS; F) 3. Expressive deficit (BNSS; F)
Brasso et al. (2023); Duration of illness > 5 years	1. Working memory (MATRICS; F) 2. Verbal learning (MATRICS; F) 3. Visual learning (MATRICS; F)	1. Working memory (MATRICS; F) 2. Verbal learning (MATRICS; F) 3. Visual learning (MATRICS; F)		1. Working memory (MATRICS; F) 2. Verbal learning (MATRICS; F) 3. Meta cognition (MAS; F)
Charernboon (2021)	1. Total (PSP; F) 2. Total (ACE-III; F) 3. Asocial (SANS; F)	1. Total (PSP; F) 2. Asocial (SANS; F) 3. Avolition (SANS; F)	1. Total (PSP; F) 2. Alogia (SANS; F) 3. Avolition (SANS; F)	
Choi et al. (2022)	1. Depressed mood (BPRS; I) 2. Motor retardation (BPRS; I) 3. Unusual thought content (BPRS; I)	1. Depressed mood (BPRS; I) 2. Motor retardation (BPRS; I) 3. Unusual thought content (BPRS; I)	1. Motor retardation (BPRS; I) 2. Depressed mood (BPRS; I) 3. Unusual thought content (BPRS; I)	
Dal Santo et al. (2022)			1. Delusions (PANSS; I) 2. Emotional withdrawal (PANSS; I) 3. Depression (CDSS; I)	
Demyttenaere et al. (2022a)	1. Delusions (PANSS; I) 2. Suspiciousness (PANSS; I) 3. Excitement (PANSS; I)	1. Depression (CDSS; I) 2. Suspiciousness (PANSS; I) 3. Conceptual disorganization (PANSS; I)	1. Depression (CDSS; I) 2. Delusions (PANSS; I) 3. Conceptual disorganization (PANSS; I)	
Demyttenaere et al. (2022b); Acute population	1. Delusions (PANSS; I) 2. Suspiciousness (PANSS; I) 3. Excitement (PANSS; I)	1. Delusions (PANSS; I) 2. Suspiciousness (PANSS; I) 3. Poor rapport (PANSS; I)	1. Delusions (PANSS; I) 2. Suspiciousness (PANSS; I) 3. Poor rapport (PANSS; I)	
Demyttenaere et al. (2022b); Predominant negative symptoms	1. Hostility (PANSS; I) 2. Delusions (PANSS; I) 3. Grandiosity (PANSS; I)	1. Hostility (PANSS; I) 2. Grandiosity (PANSS; I) 3. Stereotyped thinking (PANSS; I)	1. Hostility (PANSS; I) 2. Delusions (PANSS; I) 3. Grandiosity (PANSS; I)	
Esfahlani et al. (2018); Treatment resistant		1. Suspiciousness (PANSS; I) 2. Poor rapport (PANSS; I) 3. Hostility (PANSS; I)		1. Hostility (PANSS; I) 2. Delusions (PANSS; I) 3. Poor rapport (PANSS; I)
Esfahlani et al. (2018); Treatment responsive		1. Excitement (PANSS; I) 2. Delusions (PANSS; I)		1. Blunted affect (PANSS; I) 2. Lack of spontaneity and flow of conversation (PANSS; I)

		3. Blunted affect (PANSS; I)		3. Delusions (PANSS; I)
Galderisi et al. (2018)	1. Everyday life skills (SLOF; F)	1. Everyday life skills (SLOF; F)	1. Working memory (MATRICS; F)	
	2. Total (UPSA-B; F)	2. Total (UPSA-B; F)	2. Everyday life skills (SLOF; F)	
	3. Total (TASIT-1; F)	3. Work skills (SLOF; F)	3. Total (TASIT-2; F)	
Galderisi et al. (2020); Baseline	1. Total (UPSA-B; F)	1. Total (UPSA-B; F)		1. Working memory (MATRICS; F)
	2. Everyday life skills (SLOF; F)	2. Everyday life skills (SLOF; F)		2. Everyday life skills (SLOF; F)
	3. Working memory (MATRICS; F)	3. Working memory (MATRICS; F)		3. Total (TASIT-2; F)
Galderisi et al. (2020); Follow-up	1. Work skills (SLOF; F)	1. Work skills (SLOF; F)		1. Working memory (MATRICS; F)
	2. Everyday life skills (SLOF; F)	2. Everyday life skills (SLOF; F)		2. Everyday life skills (SLOF; F)
	3. Total (UPSA-B; F)	3. Total (UPSA-B; F)		3. Total (TASIT-2; F)
Galderisi et al. (2020); Not recovered	1. Work skills (SLOF; F)	1. Work skills (SLOF; F)		1. Working memory (MATRICS; F)
	2. Interpersonal relationships (SLOF; F)	2. Everyday life skills (SLOF; F)		2. Everyday life skills (SLOF; F)
	3. Everyday life skills (SLOF; F)	3. Total (UPSA-B; F)		3. Total (TASIT-2; F)
Galderisi et al. (2020); Recovered	1. Working memory (MATRICS; F)			1. Total (TASIT-2; F)
	2. Attention (MATRICS; F)			2. Working memory (MATRICS; F)
	3. Verbal learning (MATRICS; F)			3. Total (TASIT-1; F)
Hajdúk et al. (2019)	1. P17 (PS; I)	1. P17 (PS; I)	1.P14 (PS; I)	
	2. IR07 (SLOF; I)	2. P14 (PS; I)	2. P18 (PS; I)	
	3. P03 (PS; I) = P14 (PS; I)	3. P18 (PS; I)	3. P19 (PS; I)	
Hasson-Ohayon et al. (2018)	1. Cognitive (PANSS; F)	1. Cognitive (PANSS; F)	1. Cognitive (PANSS; F)	
	2. Working memory (MATRICS; F)	2. Working memory (MATRICS; F)	2. Visual learning (MATRICS; F)	
	3. Mastery (MAS; F)	3. Social cognition (BLERT; F)	3. Working memory (MATRICS; F)	
Hu et al. (2022); Symptom dimension	1. Positive (PANSS; F)	1. Positive (PANSS; F)	1. Total (SOFAS; F)	
	2. Expressivity (CAINS; F)	2. Expressivity (CAINS; F)	2. Motivation and pleasure (CAINS; F)	
	3. Total (SOFAS; F)	3. Total (SOFAS; F)	3. Positive (PANSS; F)	
Hu et al. (2022); Item level	1. Total (SOFAS; F)	1. Total (SOFAS; F)	1. Total (SOFAS; F)	
	2. Delusions (PANSS; I)	2. Vocational, motivation (CAINS; I)	2. Expression, speech (CAINS; I)	
	3. Recreation, motivation (CAINS; I)	3. Delusions (PANSS; I)	3. Expression, vocal prosody (CAINS; I)	
Levine and Leucht (2016); Baseline	1. Poverty of speech (SANS; I)	1. Decreased spontaneous movements (SANS; I)	1. Decreased spontaneous movements (SANS; I)	
	2. Paucity expressive gestures (SANS; I)	Paucity expressive gestures (SANS; I) =	2. Paucity expressive gestures (SANS; I)	
	3. Decreased spontaneous movements (SANS; I)	Poverty of speech (SANS; I) =	3. Relationships with friends & peers (SANS; I)	
		Poverty of content of speech (SANS; I)		
Levine and Leucht (2016); Endpoint	1. Increased response latency (SANS; I)	1. Increased response latency (SANS; I) =	1. Decreased spontaneous movements (SANS; I)	
	2. Test inattentiveness (SANS; I)	Social inattentiveness (SANS; I) =	2. Ability feel intimacy & closeness (SANS; I)	
	3. Social inattentiveness (SANS; I)	Test inattentiveness (SANS; I)	3. Poverty of speech (SANS; I)	
Levine and Leucht (2016); Change	1. Inappropriate affect (SANS; I)	1. Inappropriate affect (SANS; I)	1. Poverty of speech (SANS; I) =	
	2. Physical anergia (SANS; I)	2. Lack vocal inflections (SANS; I) =	Poverty of content of speech (SANS; I)	
	3. Increased response latency (SANS; I)	Blocking (SANS; I) =	3. Decreased spontaneous movements (SANS; I) =	
		Affective nonresponsivity (SANS; I)	Paucity expressive gestures (SANS; I)	
Li et al. (2022)			1. Social and occupational dysfunction (Clinical interview; I)	
			2. Hallucinations (Clinical interview; I)	
			3. Negative symptoms (Clinical interview; I)	
Strauss et al. (2019b); Male and female	1. Quantity of speech (BNSS, I)			1. Quantity of speech (BNSS; I)
	2. Avolition inner experience (BNSS; I)			2. Asociality inner experience (BNSS; I) =
	3. Spontaneous elaboration (BNSS; I)			Avolition inner experience (BNSS; I)
Strauss et al. (2019b); Male	1. Quantity of speech (BNSS, I)			1. Quantity of speech (BNSS, I)
	2. Spontaneous elaboration (BNSS, I)			2. Spontaneous elaboration (BNSS, I)
	3. Facial expression (BNSS, I)			3. Asociality inner experience (BNSS, I)
Strauss et al. (2019b); Female	1. Vocal expression (BNSS, I)			1. Vocal expression (BNSS, I)
	2. Asociality inner experience (BNSS, I)			2. Asociality inner experience (BNSS, I)

	3. Avolition behavior (BNSS, I)			3. Facial expression (BNSS, I)
Strauss et al. (2020); Treatment		1. Frequency of pleasurable activities (BNSS; I)		1. Frequency of pleasurable activities (BNSS; I)
		2. Intensity of pleasure during activities (BNSS; I)		2. Intensity of pleasure during activities (BNSS; I)
		3. Avolition behavior (BNSS; I)		3. Avolition behavior (BNSS; I)
Strauss et al. (2020); Placebo		1. Intensity of pleasure during activities (BNSS; I)		1. Intensity of pleasure during activities (BNSS; I)
		2. Avolition behavior (BNSS; I)		2. Asociality behavior (BNSS; I) = Avolition behavior (BNSS; I)
		3. Asociality behavior (BNSS; I)		
Sun et al. (2023); t1			1. Emotional withdrawal (PANSS; I)	
			2. Lack of spontaneity and flow of Conversation (PANSS; I)	
			3. Difficulty in abstract thinking (PANSS; I)	
Sun et al. (2023); t2			1. Delusions (PANSS; I)	
			2. Emotional withdrawal (PANSS; I)	
			3. Excitement (PANSS; I)	
Sun et al. (2023); t3			1. Delusions (PANSS; I)	
			2. Excitement (PANSS; I)	
			3. Lack of spontaneity and flow of conversation (PANSS; I)	
Sun et al. (2023); t4			1. Excitement (PANSS; I)	
			2. Emotional withdrawal (PANSS; I)	
			3. Delusions (PANSS; I)	
Sun et al. (2023); resistant			1. Excitement (PANSS; I)	
			2. Delusions (PANSS; I)	
			3. Emotional withdrawal (PANSS; I)	
Sun et al. (2023); response			1. Delusions (PANSS; I)	
			2. Emotional withdrawal (PANSS; I)	
			3. Difficulty in abstract thinking (PANSS; I)	
van Rooijen et al. (2018)	1. Delusions (PANSS; I)	1. Delusions (PANSS; I)	1. Delusions (PANSS; I) = Depressed mood (CDSS; I)	
	2. Poor rapport (PANSS; I)	2. Poor rapport (PANSS; I)		
	3. Stereotyped thinking (PANSS; I)	3. stereotyped thinking (PANSS; I)	3. Emotional withdrawal (PANSS; I)	
Wang et al. (2023)	1. Avolition-apathy (SANS; F)	1. Avolition-apathy (SANS; F)	1. Anhedonia-asociality (SANS; F)	1. Anhedonia-asociality (SANS; F)
	2. Avolition (BNSS; F)	2. Anhedonia-asociality (SANS; F)	2. Affective flattening (SANS; F)	2. Affective flattening (SANS; F)
	3. Anhedonia-asociality (SANS; F)	3. Alogia (SANS; F)	3. Alogia (SANS; F)	3. Alogia (SANS; F)
Yan et al. (2022); BPRS				1. Anergia (BPRS; F)
				2. Anxious depression (BPRS; F)
Yan et al. (2022); PANSS				1. Negative (PANSS, F)
				2. Cognitive (PANSS, F)
				3. Depressive (PANSS, F)

Note. Purple cells = items or subscales that measure cognition; Green cells = items or subscales that measure functioning; Red cells = items or subscales that measure positive symptoms; Yellow = represent items or subscales that measure negative symptoms; Blue cells = items or subscales that measure depression; I = item; F = Factor; ACE III = Addenbrookes cognitive examination version III; BLERT = Bell–Lysaker Emotional Recognition Task; BNSS = Brief negative symptom scale; BPRS = Brief psychiatric rating scale; CAINS = Clinical assessment interview for negative symptoms; CDSS = Calgary depression rating scale for schizophrenia; EMA = Ecological momentary assessment; MATRICS = Measurement and treatment research to improve cognition in schizophrenia; PANSS = Positive and negative syndrome scale; PS = Paranoia scale; PSP = Personal social performance scale; SANS = Scale for the assessment of negative symptoms; SLOF = Specific level of functioning scale; SOFAS = Social and occupational functioning assessment scale; TASIT = The awareness of social inference test; UPSA-B = UCSD Performance-Based Skills Assessment—Brief.

4.5 Discussion

4.5.1 Congruences and discrepancies

This study aimed to identify congruences and discrepancies across studies on symptom networks of schizophrenia. We observed several notable congruences in the evidence across studies, despite considerable heterogeneity in the included studies' designs and methodologies. The heterogeneity in methods is in part due to symptom networks being an emerging area of enquiry and no protocol or direction exists yet to unify the methods used in this area.

We found support for the theory that schizophrenia is a disorder of cognition, as across studies cognitive symptoms of schizophrenia were central in symptom networks of schizophrenia. We also found that functional capacity was a core feature of schizophrenia. Positive symptoms were central in only a few networks in the studies included in our systematic review. When adding variables assessing cognition as nodes in the network as well as the PANSS items, cognitive symptoms were more central than positive symptoms in every network. In many studies, positive symptoms were central but not when assessments of cognition were added to the network. This is analogous to adding a confounding variable in a regression (McNally et al., 2017). However, positive symptoms may not have been central in each study, as most samples include people who were medicated. Hence, the presence of medication may be a confound in these studies as this tends to reduce positive symptoms.

Our study also found that items or subscales that aim to measure depression featured in the three centrality statistics across centrality statistics in several of the studies included. Approximately 40% of PDS have comorbid depression (Upthegrove et al., 2017), depending on the stage of the illness. Upthegrove et al. (2017) identifies that depression is also associated with worse outcomes and is the most significant risk factor for completed suicide in PDS. Furthermore, anhedonia is a shared diagnostic symptom in both PDS and people diagnosed with depression in the DSM-5 (Lambert et al., 2018). Network analysis is useful in this situation to model complex systems such as networks of conditions with high comorbidities, as it takes into consideration relationships between symptoms and diagnostic boundaries that are not accounted for in other models (Cramer et al., 2010). Despite the role symptoms of depression have in the outcomes of schizophrenia, its symptom overlap, and its frequent comorbidity, only eight of the 32 studies selected used an instrument specific to depression. Given that some of the selected studies found items or subscales measuring depression were most central, more research is needed on depression in schizophrenia, in particular research is needed to compare PDS against PDS with a comorbid depressive disorder. Although it is unclear why the centrality of depression is heterogeneous across studies, in a systematic review by Hartley et al. (2013), the authors found the severity of hallucinations and delusions, together with its associated distress and content, is associated with depressive symptoms. Potentially symptom severity is key in moderating the role of depression in people with comorbid schizophrenia and depression.

Previous research suggests that negative symptoms and cognitive functioning have more prognostic value and greater associations with global levels of functioning, and these symptoms are likely to persist longer than positive symptoms during the syndrome (Addington et al., 1991; Heinrichs, 2005; Kahn & Keefe, 2013; Stahl & Buckley, 2007). It is arguable that in line with the results from these studies, cognitive impairments need to be targeted alongside pharmaceutical intervention of positive symptoms, which may be beneficial to global levels of functioning. This also aligns with other researchers, who posit that schizophrenia is primarily a disorder of cognition (Heinrichs, 2005; Kahn & Keefe, 2013). Recent meta analyses identify that cognitive remediation needs to be introduced widely in clinical practice for PDS (Cella et al., 2017; Vita et al., 2021). Although, currently it is unclear whether network variables identified as central should be targeted for intervention (Bringmann et al., 2019), given uncertainty concerning their interpretation and stability, however, we are able to identify in this systematic review that cognition and functioning could be regarded as two of several core features of schizophrenia.

(Bringmann et al., 2019) note the limitations of designing interventions on variables that are most central in a network as interventions rarely target a single variable for remediation and instead have a wider effect on an array of variables. Furthermore, the centrality statistics closeness and betweenness are considered to be unstable in cross sectional and temporal networks (Epskamp et al., 2018a). Intervening on the most commonly reported symptoms may work better, although it would be preferable to select symptoms on the basis of centrality and frequency of endorsement (Rodebaugh et al., 2018).

The diversity of the studies also makes conclusive inferences difficult, particularly the heterogeneity in the assessments administered across the studies. Furthermore, some studies compared PDS to HC, or treatment resistant PDS with PDS who were treatment responsive, PDS with predominantly negative symptoms to acute patients, compared different pharmacological treatments for PDS, or compared PDS to other conditions, or had no comparison group at all. Some studies used directed networks while most were undirected. There was also considerable heterogeneity in the method used to generate the network, although partial correlation with a graphical least absolute shrinkage and selection operator (GLASSO) penalisation was used the most. Lastly, the reporting of centrality statistics was heterogenous across studies, where some authors looked at closeness, betweenness and degree, and others did not include any centrality statistics. This heterogeneity is possibly due to symptom networks in PDS first being researched in 2016, given our exclusion criteria, and most studies to date could be considered exploratory in nature.

Overall, the studies were of reasonable quality but exhibited varying quality indicators in McMasters critical review form. As symptom networks are relatively new, many publications in the systematic review did not adequately address the introduction of this novel method when applied to schizophrenia. More information on network methods is needed for audiences that are unfamiliar with such analysis. Additionally, documenting potential clinical implications of the study is crucial, given network analysis can directly inform practice. Identifying and reporting the reliability and validity of the measures used is also necessary as symptom networks assume that items or latent variables are observable phenomena (Wilshire et al., 2021), and nodes in the network are also assumed to be flat constructs (Wilshire et al., 2021). Furthermore, most studies were secondary research, potentially limiting the quality due to their dependence on the original study.

It is essential that researchers begin to use consistent assessments to enable comparisons to be made between studies. We recommend the PANSS over other clinical assessments as it is reliable and valid and is the most widely used assessment of symptoms in network studies of schizophrenia. Cognition is a key prognostic indicator for schizophrenia so should be assessed in every network study. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) is recommended for assessing cognition as it was developed with PDS. Because depression and schizophrenia are highly comorbid, the utility of symptom networks to account for comorbidities, and because depression in schizophrenia is the largest predictor of completed suicide, it would be useful for future network studies to include a validated assessment specific to depression for PDS (Cramer et al., 2010; Upthegrove et al., 2017). Furthermore, functioning is also a key assessment to administer as it was central in many of the studies that included functional assessments. Researchers may wish to include centrality statistics where appropriate for clinical interest as well as benchmarks for subsequent research.

4.5.2 Limitations

No quality appraisal instruments for network studies exist yet and therefore adaptation of the McMasters critical review form was implemented but not validated (Birkeland et al., 2020). Additionally, homogeneity of the findings may be increased from studies that used the same datasets for their networks. Some of the studies that motivated this systematic review (Isvoranu, van Borkulo, et al., 2017; Boyette et al., 2020) were excluded some participants in their studies did not have a diagnosis of schizophreniform, schizoaffective disorder or schizophrenia, or a network was not reconstructed only on people who have at least one of these diagnoses. Many studies were excluded because other conditions such as brief psychotic disorder, delusional disorder, or substance induced psychotic disorder were included in the sample used to reconstruct the network. This study may have also excluded research that used the term psychosis to describe schizophrenia, with no mention of schizophrenia, schizophreniform, and schizoaffective disorder, and therefore a diagnosis of one of these conditions was never mentioned. This study excluded items that either did not fit into the domains in Figure 13, or were focused on social, medical, or biological variables for Table 14 in the Supplementary Materials section (Appendix C1). In some instances these symptoms may have been the most central nodes in the network or otherwise changed the structure of the observed network and the derived centrality measures.

4.5.3 Conclusions

Given the intertwined nature of symptoms, comorbidities, and mediating factors of symptoms, the network approach offers a new perspective on characterising schizophrenia. However, some aspects of the network theory of mental disorders have not yet been included in the networks due to the novel approach. Future research on symptom networks should use consistent assessments for better integration of findings. Including cognition, functioning, and depression, along with positive and negative symptoms in the network, is crucial to control for their impact.

Due to the central role of cognitive symptoms across studies, we recommend that cognitive remediation should be provided throughout the course of the illness, including when PDS are in remission from positive symptoms. This approach may significantly improve global levels of functioning, also a core feature of schizophrenia. Our research supports the theory that schizophrenia is a disorder of cognition (Buchwald et al., 2024; Heinrichs, 2005; Kahn & Keefe, 2013) as nodes representing cognition when included, were more central than positive or negative symptoms. However, we cannot infer that the centrality of nodes is sufficient to infer treatment implications (Bringmann et al., 2019). However, other meta analyses recommend cognitive remediation to improve functional outcomes for the person with schizophrenia, rather than restricting treatment to target positive symptoms only (Cella et al., 2017; Vita et al., 2021).

Chapter 5 A Symptom Network Approach to Schizophrenia in the CATIE study: Processing Speed as the Central Cognitive Impairment

Prelude to Chapter 5

In Chapter 4, a total of 32 SN studies that met the selection criteria of the systematic review have been published on schizophrenia, for publications before the 30th of April 2024 (Buchwald et al., 2024). Prior studies have highlighted the primacy of cognition in schizophrenia and have argued for reframing schizophrenia as a disorder of cognition (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). The systematic review supported these findings as the results suggest that cognition and functioning are the most central variables for PLS, where positive, negative, and depressive symptoms featured as central variables less frequently or only when cognition and functioning were not included in the network (Buchwald et al., 2024). It is also clear that SNs of cognition in schizophrenia have been published; however, additional variables such as sociodemographics, cognition, QOL, and clinical variables, such as positive and negative symptoms and medication attitudes, have not been included in SN studies of schizophrenia to date (Buchwald et al., 2024). Although other studies have been published, few studies comment on the directed relationships between cognition and other domains of health. Hence, the following study presents a directed network of clinical, cognitive, sociodemographic, and QOL variables, with a focus on cognition and its dependencies.

5.1 Abstract

Background: People diagnosed with schizophrenia (PDS) can have functional impairments in multiple domains. Cognitive impairment is central to schizophrenia as it has a substantial prognostic value compared with other symptoms of schizophrenia. No research has investigated directed relationships in a complex system of cognitive, sociodemographic, clinical, and Quality of life (QOL) variables in PDS.

Aims: We aimed to identify how components of cognition have directed relationships with other cognitive components, as well as with clinical and QOL variables.

Method: This study included data from 1,450 participants in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. This study reconstructed a Bayesian network (BN) on this data on cognition, clinical, sociodemographic, and QOL variables.

Results: Processing speed was a predictor variable of all other cognitive domains. Cognitive domains were independent of positive symptoms but were moderately associated with negative symptoms ($\beta = -.25$; $p < .001$). The positive symptoms subscale was independent of QOL conditioning on third variables. Negative symptoms were moderately associated with QOL ($\beta = -.33$; $p < .001$), and processing speed had a weak association with QOL ($\beta = -.12$; $p < .001$). Processing speed was a central variable in the network.

Conclusion: Intervening on processing speed may be most beneficial to improve other cognitive functions. More research is needed on directed networks that include social cognition and global levels of functioning.

5.2 Introduction

Schizophrenia is a major mental health disorder that often leads to persistent cognitive, social, and functional impairments. Acute schizophrenia carries the highest disability weight of all conditions in the global burden of disease study (Charlson et al., 2018; Salomon et al., 2015). Recently, several theorists have proposed that schizophrenia is, by nature, a disorder of cognition (Buchwald et al., 2024; Heinrichs, 2005; Kahn & Keefe, 2013). Despite the development of the Measurement and Treatment to Improve Cognition in Schizophrenia (MATRICS), no consensus exists on which cognitive abilities to target or prioritise with therapies aimed at enhancing cognition (Best & Bowie, 2017). Applying symptom network analysis is a promising new approach to address this question. Symptom networks are graphical models, applied according to the network theory of mental disorders, which construes a psychological disorder as a complex, dynamic system of interacting symptoms (Borsboom, 2017). Symptom networks may help elucidate the dependencies among different cognitive domains and other clinical or psychosocial variables and assist in clarifying treatment targets for cognitive remediation and psychopharmacology. Our recent systematic review of network studies on schizophrenia, schizophreniform, or schizoaffective disorder identified that no published network studies have examined the directed association that symptoms have on cognitive functioning (or vice versa), other clinical correlates, and QOL outcomes in schizophrenia, despite the importance of cognition for PDS (Buchwald et al., 2024). We use Bayesian networks for the added utility of being able to identify predictor and response relationships. This may help clarify which cognitive impairments have flow-on effects, direct dependencies or conditional independencies, with other cognitive functions, symptoms, and QOL. Consequently, this study hypothesises that cognitive indices are central to the network and that cognitive variables are associated with QOL, general symptoms, and negative symptoms, but not positive symptoms.

5.3 Methods

5.3.1 Participant characteristics

This study analysed data provided by 1,450 PDS from the National Institute of Mental Health Data Archive CATIE study. Participants recruited into this study were aged between 18 and 65, had a research diagnosis of schizophrenia, and were able to take oral antipsychotic medication. Participants were excluded if they: (a) had a diagnosis of schizoaffective disorder, intellectual disability, or other cognitive disorders; (b) previously had severe adverse reactions to the proposed treatments; (c) had only had one schizophrenic episode; (d) previously were treatment resistant; (e) were pregnant or breast-feeding; or (f) were considered to have a severe and unstable medical condition (Swartz et al., 2008). We added no further exclusion criteria to this sample except for removing participants with more than half of their data missing. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the Auckland University of Technology Ethics Committee (22/387 Static Symptom Networks of Schizophrenia) for the subsequent analyses of the CATIE study conducted in this current study. Written informed consent and ethical approval were provided for the original CATIE study (Swartz et al., 2008). Table 4 provides the descriptive statistics for participants selected for the CATIE trial. A total of 1057 (74.4%) of the sample were Males, with the average age of the sample being 40.5 years (SD = 11.1). Participants identified themselves as White or European American (871; 60.2%), Black or African American (504; 34.9%), or Asian American (33; 2.3%). Some participants identified with more than one race (26; 1.8%). Additionally, 863 participants were never married (59.6%), 1,216 did not work (84.9%), and had an average of 11.5 years of education.

Table 4. Demographic Characteristics

Demographic	N (M)	% (SD)	Missing
Sex			29
Male	1057	74.4	
Female	364	25.6	
Age	(40.5)	(11.1)	2
Race			4
White (European American)	871	60.2	
Black (African American)	504	34.9	
Asian	33	2.3	
Native American/Alaska Natives	8	0.6	
Hawaiian/Pacific Islander	4	0.3	
More than one race	26	1.8	
Marital Status			2
Never married	863	59.6	
Divorced	298	20.6	
Married	166	11.5	
Separated	87	6.0	
Widowed	34	2.3	
Education in years	(11.5)	(3.6)	10
Employment			17
Did not work	1216	84.9	
Part-time	120	8.4	
Full time	97	6.8	

Note. N = Frequency; M = Mean; % = Percent; SD = Standard deviation.

5.3.2 Sampling procedures

The CATIE study was a multisite randomised control trial conducted between January 2001 and December 2004 at 57 US sites, including university clinics, veterans' affairs medication centres, mental health agencies, non-profit agencies, private practice centres, and mixed sites. While the

CATIE study compared the effectiveness of medications over time, we selected only the baseline data for analysis in the present study.

5.3.3 Measures and covariates

A range of assessment data was available for this study. We included demographic, clinical, QOL, and cognitive variables for our study. Demographic variables included age, sex, race, education, employment, and marital status. Regarding the clinical assessments, the Positive and Negative Syndrome Scale (PANSS) was developed by Kay et al. (1987) and can be considered the gold standard outcome measure in measuring symptoms in treatment efficacy studies of schizophrenia (Kumari et al., 2017). The PANSS has fair internal consistency and excellent interrater reliability (Bell et al., 1992; Peralta & Cuesta, 1994) and has strong correlations to other symptom assessments of schizophrenia (Bell et al., 1992). We also included the total score from the Calgary Depression Scale for Schizophrenia (CDSS). The CDSS has moderate to excellent reliability, has high divergent validity, strong predictive validity, and correlates well with other measures of depression (Lako et al., 2012). The Drug Attitude Inventory (DAI) (Awad, 1993) and Insight and Treatment Attitudes Questionnaire (ITAQ) (McEvoy et al., 1989) were included to identify illness insight and attitudes toward medication compliance. Another scale used in this study is the Clinical Global Impressions (CGI) scale, which was modified to consider an index of severity for drug and alcohol use rated by a clinician (Guy, 1976). We also included the clinician global impression severity index in the subsequent analyses. The Quality of Life (QOL) assessment tool in the CATIE study was derived from Heinrichs et al. (1984) to assess QOL in schizophrenia. The assessment used to evaluate cognition was MATRICS. In the MATRICS version used during the CATIE trial, five cognitive domains were assessed: verbal, vigilance, processing speed, reasoning, and working memory. These five domains are constructed based on the assessments identified in Table 5. We initially included a measure of defined daily dose of antipsychotic medication. However, this was not a predictor variable and was therefore removed.

5.3.4 Data diagnosis

We removed participants from this study with more than 50 per cent missing information in all variables reported in our study ($N = 10$). The remaining missing data (2.4% of all observations) were imputed using the random forests imputation by Stekhoven and Bühlmann (2012), which allows both categorical and continuous variables to be imputed. All assessment subscales were assumed to be continuous, except the CGI subscales. All demographic variables were considered discrete, except age, for the random forest imputation. The BN algorithm does not allow categorical variables to be daughter nodes of continuous variables in the comprehensive bnlearn R software version 4.9.4 package we used (Scutari & Denis, 2021). Hence, we treated age as a categorical variable (ages <30, 31-45, >45) following imputation to ensure all demographics were discrete variables. We also assumed that the CGI subscales were continuous in the BN despite being based on a Likert scale. No other transformations were implemented.

5.3.5 Analytic strategies

Networks are comprised of nodes (variables) and edges (associations between variables). One graphical network approach, BNs use directed acyclic graphs to decompose the joint probability distribution of the variables (Scutari & Denis, 2021). Directed relationships encode the dependency structure among a set of variables. On a Windows PC, we used R version 4.3.2 (R Core Team, 2024) to analyse and implement the BNs in this study. To reconstruct relationship networks, we implemented a hybrid BN using the hill climbing method from the R package bnlearn (Scutari & Denis, 2021). We used a hybrid BN. Hybrid BNs allow both discrete and continuous variables to be included in the model, using a mixture of multinomial distributions for the parameter estimation of the discrete variables and normal distributions for the parameter estimation of the continuous variables. The hill climbing algorithm was initialised with an empty network; edges are then iteratively deleted, added, or the edge direction is reversed to locally optimise a network score, which reflects a fit to the data and is penalised for complexity. We used the Bayesian Information Criterion (BIC) as a network score criterion. We implemented another score-based algorithm in bnlearn, Tabu, which led to the same solution in the network structure as the hill-climbing algorithm (Scutari & Denis, 2021).

We also calculated a so-called averaged network based on reconstructed bootstrapped networks. More specifically, we created 1,000 bootstrapped versions of the data and implemented a hybrid BN on each of those versions of the data. We then estimated a significance threshold to select edges to be included in the averaged network. A significance threshold is a threshold that identifies the number of networks (from 1000) in which an edge must be present to be included in the averaged network. The optimal significance threshold is estimated by minimising the L1 norm between the cumulative distribution function of the observed confidence levels and their asymptotic counterparts (Scutari & Nagarajan, 2013). Scutari and Nagarajan (2013) identifies that optimising the significance threshold is vital, as ad hoc thresholds have been used despite their impact on model assessment and their pronounced effect on the resulting network. Using this statistically motivated approach has improved sensitivity, specificity, and accuracy compared to ad hoc thresholds (Scutari & Nagarajan, 2013). We optimised the calculation of the significance threshold using the averaged network function in bnlearn (Scutari & Denis, 2021), and the optimal threshold was 491 of 1000 networks. Hence, if an edge was found in 491 bootstrapped networks or more, it was included in our averaged network model. The skeleton of the averaged network model structure is fitted to the complete data to build regressions, and the network parameters are then estimated. After reconstructing the BN on all data and averaged

BN, we used the model structure to subject it to a structural equation model (SEM) and obtained the SEM linear model coefficients. We used the lavaan package (version 0.6-17) by Rosseel (2012) to implement the SEM in R. The results for the averaged network can be found in the supplementary material section (Appendix C2), except for the fit statistics. The network reconstructed on the complete data is now referred to as a BN, and the BN based on bootstrapped samples is named the averaged BN, two networks with different structures and parameters.

We computed several model fit statistics: comparative fit index (CFI), where values above .95 are acceptable on a scale between 0 and 1; Tucker-Lewis index (TLI), where values above .95 are acceptable on a scale between 0 and 1; root mean square error of approximation (RMSEA), where values below approximately .06 are acceptable; BIC, with lower values indicating a better fit; and Akaike information criterion (AIC), with lower values indicating a better fit (Hu & Bentler, 1999). BIC and AIC were extracted from the results of the BN, whereas CFI, TLI, and RMSEA were obtained from the results of the SEM. This is because the likelihood is not available as an output with mixed data types in the SEM of the lavaan package. We also conducted a hypothesis test of the model implied variance-covariance structure versus the observed variance-covariance structure to identify if the reconstructed model could plausibly have generated the data. Lastly, we extracted the model's standardised regression coefficients from the SEM, which scaled the variables to a mean of 0 and a standard deviation of 1, and the significance of each relationship in the regressions.

Following the reconstruction of the BN and averaged BN, we calculated centrality statistics for each of these. Centrality statistics arise from the complex interrelations between entities and are emergent network properties (Guyon et al., 2017). The centrality statistics we calculated are closeness -the relationship between one node and all other nodes by taking into consideration the indirect connections from that node; betweenness -the importance of the node in relationship to all other pairs of nodes in the network; and degree -the number of neighbours a node has in the network (Hevey, 2018). Closeness and betweenness are standardised, and values for degree are unstandardised in this study. It is not possible to estimate closeness for nodes without outgoing edges. Next, we queried the conditional probability between the nodes representing cognition and predictors of QOL, as explained in Briganti et al. (2023). These were used to infer how an event, such as scoring above the median on processing speed, is associated with the probability of other nodes, such as scoring below the median on working memory (Briganti et al., 2023). The R code used to conduct the analysis can be found in the Data Availability Statement section.

5.4 Results

Table 5 presents an overview of the baseline assessment scores for the assessments included before imputation. Participants in this study generally presented with average scores on the positive (50^{th}-55^{th} percentile), negative (40^{th} – 45^{th} percentile), and general (45^{th} – 50^{th} percentile) subscales of the PANSS (Kay et al., 1987). On average, participants scored 4.6 on the CDSS (Addington et al., 1993), corresponding to reporting between absent and mild symptoms on average across the sample and items (M = .51 for each item). On average, the sample had a positive attitude toward medication, as indicated by the DAI (Hogan et al., 1983). Similarly, regarding the ITAQ (McEvoy et al., 1989), participants, on average, responded with scores indicating partial to good insight (M = 1.7 for each item). Both CGI drug use and CGI alcohol use were regarded as scoring on average between abstinent and substance use without impairment. The QOL scale mean scores reflect intermediate but significant levels of impairment (Heinrichs et al., 1984).

Table 5. Clinical Characteristics.

Variable	M	Medi	SD	Min	Ma	Missin
PANSS						
Positive	18.5	18	5.6	7	38	3
Negative	20.2	20	6.4	7	41	3
General	37.0	37	9.3	16	70	3
CDSS Total	4.6	4	4.4	0	22	2
DAI Total	5.0	6	3.9	-10	10	15
ITAQ Total	18.2	21	5.0	0	22	8
CGI drug use	1.4	1	0.7	1	5	2
CGI alcohol use	1.5	1	0.7	1	5	2
CGI severity	4.0	4	0.9	1	7	5
QOL	2.7	2.7	1.1	0.25	5.9	10
MATRICS components						
Verbal						
HVLT: number of items recalled trial 1	4.7	5	1.7	0	11	60
HVLT: number of items recalled trial 2	6.5	6	2.1	0	12	61
HVLT: number of items recalled trial 3	7.5	8	2.5	0	12	60
Vigilance						
CPT: d-prime score: two-digit	2.3	2.4	1.1	-2.3	4.3	330
CPT: d-prime score: three-digit	1.7	1.8	1.0	-3	5.0	324
CPT: d-prime score: four-digit	1.0	0.9	0.8	-4.4	4.0	338
Processing speed						
COWAT: category F	9.8	10	4.1	0	24	58
COWAT: category A	7.9	8	3.7	0	21	59
COWAT: category S	10.0	10	4.3	0	25	59
COWAT: category animals	13.8	14	4.9	0	31	57
COWAT: category fruits	10.1	10	3.4	2	21	58
COWAT: category vegetables	8.6	8	3.4	0	25	57
WAIS-R: digit symbol test	37.2	36	13.5	0	90	71
GP: trial 1	11.7	12	3.9	0	22	79
GP: trial 2	13.2	13	4.0	0	25	79
Reasoning						
WCST: number of perseverative errors	13.6	10	10.1	0	62	189
WCST: number of completed categories	2.1	2	1.6	0	6	192
WCST: additional consecutive cards in	2.1	0	2.9	0	9	225
WISC-R: mazes	17.5	18	6.1	0	28	81
Working memory						
Letter-number Sequencing	10.2	10	4.5	0	23	77
CTVWM: no delay	2.8	1	6.0	0	105	222
CTVWM: five-second delay	28.4	22	19.3	0	128	222
CTVWM: fifteen-second delay	30.6	25	19.3	0	125	222

Note. M = Mean; SD = Standard Deviation; Min =- Minimum; Max = Maximum; PANSS = Positive and Negative Syndrome Scale; CDSS = Calgary Depression Scale for Schizophrenia; DAI = Drug Attitude Inventory; ITAQ = Insight and Treatment Attitudes Questionnaire; DDD = Defined Daily Dose of Medication; MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia; HVLT = Hopkins Verbal Learning Test; CPT = Continuous Performance Test; COWAT = Controlled Oral Word Association Test; GP = Grooved Pegboard; WCST = Wisconsin Card Sorting Task; WISC-R = Weschler Intelligence Scale for Children – Revised; CTVWM = Computerised Test for Visuospatial Working Memory.

Regarding the MATRICS cognitive battery, most participants scored between -1.6 standard deviations and -2.5 standard deviations from the mean on the Hopkins Verbal Learning Test

(Brandt, 1991) based on the results from the CATIE trial in Keefe et al. (2006). Participants also performed 1.5 standard deviations below the mean for males across all ages for the three indices of the Identical Pairs Continuous Performance Test (Cornblatt et al., 1988) based on the norms by Rapisarda et al. (2014). Participants performed between the 9^{th} and 10^{th} percentile for processing speed and the Controlled Oral Word Association Test, based on the norms by Ruff et al. (1996). In terms of the Wisconsin Card Sorting Test, PDS in this study scored near one (.8) SD above the mean for perseveration errors and approximately minus one for the categories completed category based on the information from the CATIE trial in Keefe et al. (2006). Lastly, the participants in this study scored 2.1 *SD* below the mean for Letter Number sequencing based on the norms by Gold et al. (1997).

The results in Table 6 present the fit statistics of each model and the significance of the implied variance-covariance matrix and the observed variance-covariance matrix. The results suggested that the averaged BN has a considerably worse CFI and TLI than the BN. RMSEA was lower on the BN, and BIC and AIC favoured the BN compared to the averaged BN. Both models were significant ($p < .001$), indicating that the model-implied variance-covariance matrix significantly differs from the observed variance-covariance matrix in both models. Given that the BN had a better fit than the averaged BN, the remaining results are now based on the BN. Furthermore, many of the relationships in the averaged BN were also found in the BN. Twenty-nine edges in the averaged network and BN were shared, 18 edges were unique to the BN, and 16 edges were unique to the averaged BN. The remaining results for the averaged network can be found in the supplementary materials (Appendix C2).

Table 6. Fit Statistics of the Bayesian Network and Averaged Bayesian Network.

Model	CFI	TLI	RMSEA	Chi	df	p	BIC	AIC
BN	.934	.935	.048	680.031	157	<.001	65979.34	65261.36
BN Averaged	.919	.920	.055	843.975	156	<.001	66040.07	65411.83

Note. BN = Bayesian network; CFI = Comparative fit index; TLI = Tucker-Lewis index; RMSEA = Root mean square error of approximation; df = Degrees of freedom; p = P-value; BIC = Bayesian information criterion; AIC = Akaike information criterion.

Figure 14 shows the structure of the reconstructed BN. Edges are coloured in green if the estimated regression coefficient was positive in the SEM and red if the coefficient is negative. These coefficients take into consideration the effect of other confounding predictor variables. Age, employment, and race were not daughter nodes of other variables. The MATRICS vigilance subscale, MATRICS verbal subscale, and ITAQ total score were outcome variables and were not predictors of other variables. The MATRICS processing speed was a predictor variable of all other MATRICS scales (positive relationship). Furthermore, MATRICS reasoning is conditionally independent of MATRICS vigilance, given the values of MATRICS working memory. The PANSS general subscale depends on MATRICS working memory (negative relationship, as inferred by the SEM fit), and the PANSS negative subscale depends on MATRICS processing speed (negative relationship). The PANSS positive subscale is independent of cognition assessed by the MATRICS and conditionally independent of the MATRICS given either the PANSS negative subscale or the PANSS general subscale. QOL was dependent on: the DAI total (positive relationship), the CDSS total (negative relationship), the CGI severity index (negative relationship), the PANSS negative subscale (negative relationship), MATRICS processing speed (positive correlation), and employment (negative relationship). QOL was independent of age, education, sex, MATRICS working memory, PANSS Positive, PANSS general, CGI drug use, and CGI alcohol use, given the predictors DAI total, CDSS total, CGI severity index, the PANSS negative subscale, MATRICS processing speed, and employment. CGI Drug use index depends on the CDSS total (positive relationship), and the PANSS positive subscale (positive relationship) depends on CGI drug use. The CGI alcohol use index was a predictor of the PANSS negative subscale (negative relationship), and the PANSS positive subscale was conditionally independent of CGI alcohol use given the PANSS negative subscale.

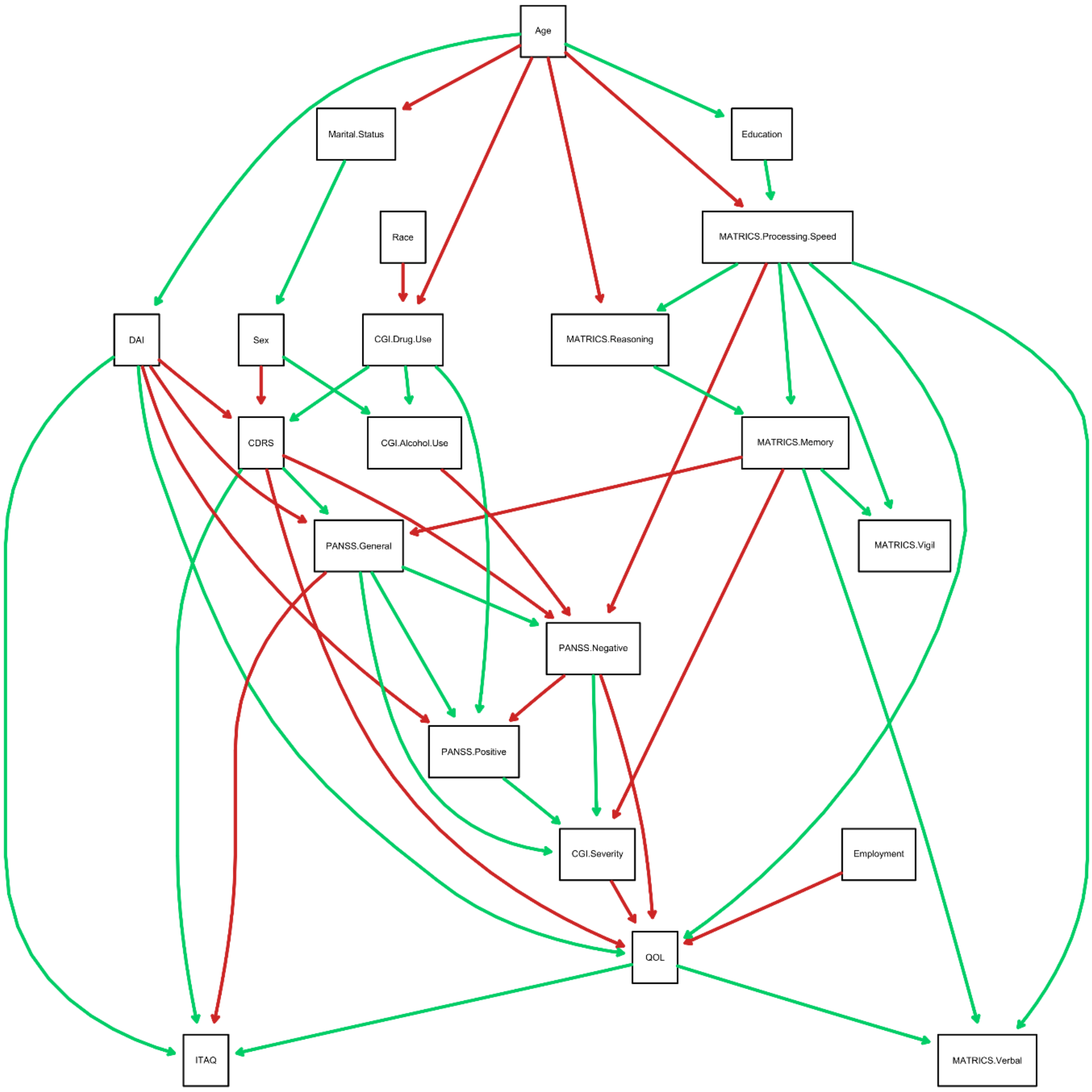

Figure 14. Bayesian Network of Sociodemographic, Cognitive, Clinical, and Quality of Life Measures.

Figure 15 presents the same network structure as Figure 15 but adds standardised regression coefficients and significance values for the relationships between response and predictor variables. All p-values were subject to the multiple comparison correction method by Holm (1979), and all Holms adjusted p-values can be found in the supplementary materials section (Appendix C2). All the relationships between the MATRICS subscales are positive and significant. Scores on the MATRICS processing speed scale had the highest relationship with scores on the MATRICS vigilance and MATRICS working memory subscales, compared to the other relationships between the subscales of MATRICS. The MATRICS processing speed subscale had a significant and moderate negative association with the PANSS negative subscale ($b = -.25$; $p < .001$), and the MATRICS memory subscale was a negative and significant moderate predictor of the PANSS general subscale ($b = -.14$; $p < .001$). The PANSS general subscale has a strong significant positive relationship with the PANSS negative subscale ($b = .61$; $p < .001$) and PANSS positive subscale ($b = .64$; $p < .001$). There was also a strong positive relationship between the CDSS and PANSS general (b = 0.35; p <.001), but the CDSS had a moderate, negative, and significant association with PANSS negative (b = -0.14; p <.001). The PANSS positive subscale has a strong positive and significant association with the CGI severity index (b = 0.45; p <.001). The strongest predictor of QOL was from the PANSS negative subscale, which was significant and negatively associated (b = -.33; p <.001). Lastly, the MATRICS processing speed subscale was a moderate but significant predictor of QOL (b = .12; p < .001), and employment was also associated with QOL, which had a strong negative relationship (b = -.32; p < .001).

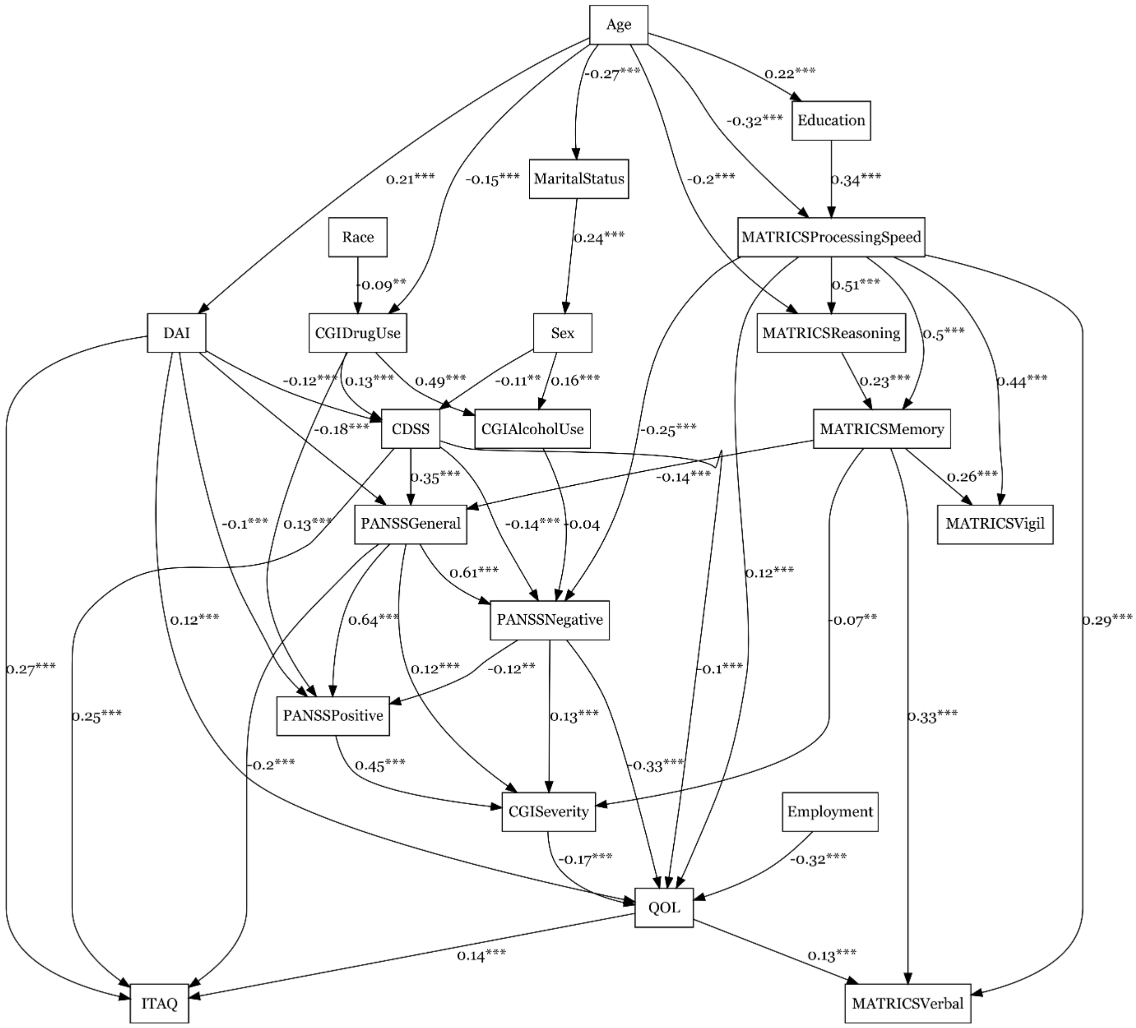

Figure 15. Structural Equation Model of Bayesian Network.

The three charts in Figure 16 shows the centrality statistics for the BN. In the results below, QOL had the highest closeness, followed by employment and the CGI severity index. The CDSS had the highest betweenness, followed by QOL and the MATRICS processing speed subscale. For degree, QOL and the MATRICS processing speed subscale had the highest number of edges, eight edges, followed by the CDSS and PANSS negative and PANSS general subscale with seven edges. The MATRICS processing speed subscale had more outgoing edges than QOL.

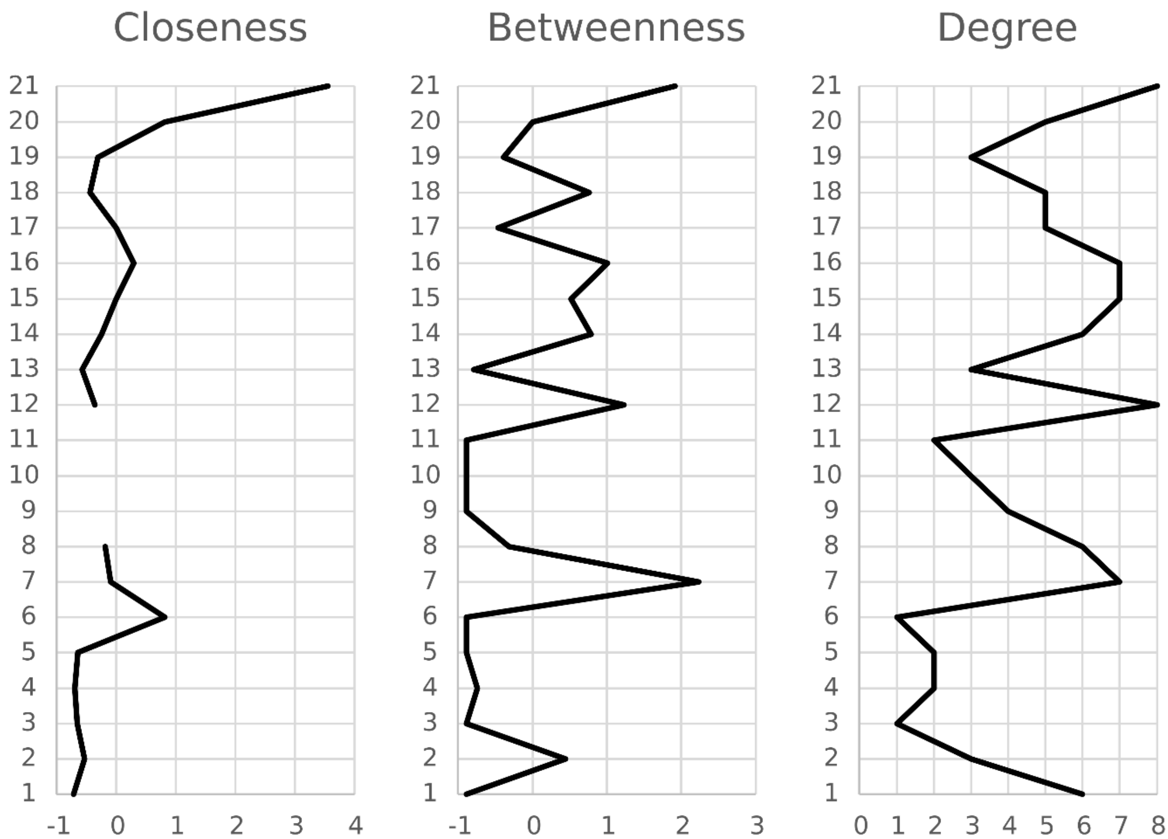

Figure 16. Centrality Statistics of the Bayesian Network.

Note. Standardised values given for closeness and betweenness; 1 = Age; 2 = Sex; 3 = Race; 4 = Marital Status; 5 = Education ;6 = Employment; 7 = CDSS total; 8 = DAI total; 9 = ITAQ total; 10 = MATRICS verbal; 11 = MATRICS Vigilance; 12 = MATRICS processing speed; 13 = MATRICS reasoning; 14 = MATRICS working memory; 15 = PANSS general; 16 = PANSS negative; 17 = PANSS positive; 18 =CGI Drug Use; 19 =CGI Alcohol use; 20 = CGI Severity; 21 = QOL.

Table 7 presents the probability queries on the network's MATRICS subscales and variables dependent on the MATRICS subscales. All values in the table below are based on the median response for that variable. Overall, the results suggest that the probabilities between MATRICS subscales are stronger than dependencies between the MATRICS nodes and nodes representing the PANSS negative subscale, PANSS positive subscale, CGI severity, and QOL, at the median value. For the largest conditional associations, the probability that someone scores less than the median on MATRICS memory, given that someone scores less than the median for MATRICS processing speed, is .767. Additionally, the probability that someone scores less than the median on MATRICS memory, given that someone scores less than the median for MATRICS reasoning, is .724. Regarding QOL as an outcome variable, if the participant was full-time employed, there is a low probability of having less than the median quality of life (.232). Scoring above the median on the PANSS negative was also associated with a .632 probability of scoring less than the median on the QOL index. Regarding processing speed, scoring below the median of processing speed is associated with a .548 probability of scoring below the median on the QOL index.

Table 7. Network Conditional Probability Queries of MATRICS Subscales and Predictors of QOL.

Variable 1	Sign	Value	Variable 2	Sign	Value	Probability
MATRICS processing	<	-0.03	MATRICS	<	0.03	.685
MATRICS processing	<	-0.03	MATRICS memory	<	0.13	.767
MATRICS processing	<	-0.03	MATRICS	<	-0.07	.668
MATRICS processing	<	-0.03	MATRICS verbal	<	-0.04	.659
MATRICS processing	<	-0.03	PANSS negative	>	-0.03	.589
MATRICS processing	<	-0.03	QOL	<	-0.09	.548
MATRICS reasoning	<	0.03	MATRICS memory	<	0.13	.724
MATRICS memory	<	0.13	MATRICS	<	-0.07	.624
MATRICS memory	<	0.13	MATRICS verbal	<	-0.04	.641
MATRICS memory	<	0.13	PANSS general	>	0	.558
MATRICS memory	<	0.13	CGI severity	>	0.04	.526
DAI	<	0	QOL	<	-0.09	.510
CGI severity	>	0.04	QOL	<	-0.09	.564
PANSS negative	>	-0.03	QOL	<	-0.09	.615
CDSS	>	-0.13	QOL	<	-0.09	.522
Employment	=	Full-	QOL	<	-0.09	.232
Employment	=	Part-	QOL	<	-0.09	.304
Employment	=	Did not	QOL	<	-0.09	.498

Note. Sign represents scores less than “<” or greater than “V” the value; Value represents the median value; Probability represents the probability of the variable two being less than or greater than the median value, given that variable one is less than or greater than the median; MATRICS = Measurement and Treatment research to improve cognition in schizophrenia; PANSS = Positive and negative syndrome scale; QOL = Quality of Life; CGI = Clinical global impression.

5.5 Discussion

This study aimed to explore the directed relationships between cognitive, sociodemographic, and clinical characteristics of PDS with a chronic condition, using BNs to reconstruct the network. BN allowed the identification of the dependence structure: predictor and response relationships and dependencies and independencies between variables. The results of the directed network suggested that processing speed predicted all other cognitive processes at least as assessed by the MATRICS subscales. Cognitive variables were independent of positive symptoms, processing speed was a negative predictor of negative symptoms, and the MATRICS working memory subscale was a negative predictor of the PANSS general symptoms subscale. Processing speed and being in employment were also associated with QOL.

This study's central finding was that information processing speed is a strong predictor of all other cognitive assessment subscale scores, suggesting that the primary cognitive impairment in

PDS may be processing speed, not only because it is the largest deficit but also because it is predictive of all other cognitive impairments assessed by the MATRICS. Furthermore, processing speed had high centrality in the network, closeness and degree, which aligned with previous research (Buchwald et al., 2024). Our findings agree with that of Abplanalp et al. (2023), who also conducted a Bayesian network analysis on the MATRICS subscales, social and non-social cognition, and negative symptoms in 173 PDS recruited in the Social Cognition and Functioning in Schizophrenia study in the USA. Abplanalp et al. (2023) note that processing speed was a predictor of all other MATRICS subscales and highlight that processing speed is a key cognitive process to target for the treatment of cognition. We extend on this research to identify other clinical correlates and quality of life, fit an SEM with standardised coefficients for effect sizes, and conduct probability queries on the network. In other research, one meta-analysis concluded that processing speed was the most impaired of all cognitive processes in schizophrenia (Dickinson et al., 2007; Schaefer et al., 2013), and the rank order of MATRICS subscale arrangements in our study approximately aligns with the order of impairment levels reported there for schizophrenia (Dickinson et al., 2007). However, vigilance may have less impairment than working memory (Dickinson et al., 2007). A possible therapeutic application is that targeting processing speed in PDS could be more beneficial than focusing on other cognitive functions, since this cognitive process may underpin other cognitive processes (Salthouse, 1996). However, treating this cognitive process in isolation may also be difficult and not ideal for schizophrenia.

Although processing speed was the most impaired cognitive function and predicted all other cognitive functions in our study, there is no wider scientific or clinical consensus yet on which cognitive functions should be prioritised for treatments of cognition for schizophrenia (Horan et al., 2022). Most research on treatments of cognition use the MATRICS composite score (Horan et al., 2022). In addition to this, treatments may provide improvements across a range of cognitive functions (Lett et al., 2014; Santos et al., 2018). Some authors argue that treating a specific cognitive function can have a general effect rather than an isolated effect, particularly for cognitive remediation, as cognitive remediation may enhance cognition in general (Wykes et al., 2011). For example, improving sustained attention may result in improvements on demanding memory or reasoning tasks. Our study supports this finding, as most cognitive functions are, to some degree, dependent on processing speed. In other words, cognitive functions are frequently interdependent. Additionally, processing speed should be most influential on those tasks that are timed and emphasise speed. In future studies, it might be interesting to include scales measuring vocabulary, semantic memory and verbal abstract reasoning – i.e. cognitive abilities that rely less on speed – to see if processing speed has less effect. In addition, outcomes such as QOL, global functioning or well-being may also be considered when targeting cognitive processes (Vita et al., 2022). In our study, processing speed or working memory was a predictor of clinical or QOL variables.

This study, although focusing on cognition, also included a QOL assessment in the network, and processing speed, the CDSS, negative symptoms, CGI severity, the DAI total score, and employment were all predictors of QOL. Positive symptoms were independent of QOL, when correcting for the association of negative symptoms, which was congruent with previous studies that reported negative symptoms were more associated with decreases in QOL compared to positive symptoms (Carbon & Correll, 2014; Novick et al., 2015). Having full-time employment was associated with a large reduction in the probability of having a lower-than-average quality of life, indicating it is a strong protective factor compared to part-time employment or unemployment. Processing speed in our study had a significant positive relationship when predicting QOL, albeit with a small effect size ($\beta = 0.12$).

Processing speed from the MATRICS subscales was a moderate predictor of negative symptoms, and all other cognitive processes considered in this study were conditionally independent of negative symptoms. Other research did not find an association between cognition and negative symptoms (Bagney et al., 2015; Harvey et al., 2006). One systematic review found a significant but modest negative association between negative symptoms and cognition (Dominguez Mde et al., 2009). Interestingly, Veerman et al. (2017) identified that processing speed may mediate the association between working memory and negative symptoms. Our study found a similar result as verbal working memory, which was independent of negative symptoms given processing speed. However, we also found that the PANSS general subscale also mediated the relationship between working memory and negative symptoms.

Both the negative and the general subscales of the PANSS acted as mediating variables, making cognitive assessment scores and the PANSS positive subscale independent. This aligns closely with previous evidence and suggests that cognition weakly correlates to positive symptoms (Rek-Owodziń et al., 2022) and other evidence suggests these two processes are independent (Weinberger & Harrison, 2011). Independence between these symptom groups was concluded in a meta-analysis (Ventura et al., 2010). One study found that momentary increases in positive symptoms were associated with worse cognitive performance (Dupuy et al., 2022). Other variables were not ruled out in the study by Dupuy et al. (2022) as mediating the relationship between positive symptoms and cognition, particularly negative or general symptom domains.

The present study was the first to use BN and SEM methods on cognitive, clinical, sociodemographic, and QOL variables in PDS (Buchwald et al., 2024). Other undirected network studies have explored the relationship between symptom severity scores and cognition combined or independently. One study by Amore et al. (2020) used partial correlation networks of the positive and negative syndrome scale (PANSS), the CDSS, the MATRICS, and other assessments. Although not commenting on cognition specifically, they found an index representing the scores on the MATRICS was a central variable within the network. Galderisi et al. (2018) found in their network study of schizophrenia that social cognition is closely interconnected with neurocognition and that both are highly associated with functional capacity, which agrees with previous literature described herein. Similar to our study, positive symptoms were not linked highly with other nodes in the network (Galderisi et al., 2018). A later study by Galderisi et al. (2020) found that psychopathology variables were only weakly associated with other symptoms, whereas cognition was strongly associated with functional capacity. Lastly, in a previous review, variables representing cognition and functioning most often had the highest centrality in the networks (Buchwald et al., 2024). Future research should include global functioning as a node in the network. Overall processing speed is the most impaired cognitive function in PDS (Dickinson et al., 2007), consequently, remediating processing speed may have an additional benefit on other cognitive processes, QOL, and negative symptoms (Horan et al., 2022), but not positive symptoms.

5.5.1 Limitations

This study provided the opportunity to examine complex relationships between variables, control for important potential confounders, and identify the orientation of predictor and response relationships, but causation cannot be inferred. It is unclear whether latent variables are potential confounders of the relationship between nodes in the network or whether there are better solutions for the data that we did not take into account (Briganti et al., 2023). Additionally, in the population network we aim to represent, some directions in the network may be in the opposite direction than those reported here. Lastly, edge directions that are not compelled can be included in the network, regardless of orientation, without losing model fit. Notwithstanding these limitations, using Bayesian networks can generate robust statistical models specifying hypotheses about causal relationships among variables that can then be further tested. Another key consideration is that this study was based on the CATIE pharmaceutical trial baseline assessment, and therefore, some of the measures may not be as supported as currently available measures, given this study was conducted between 2001 and 2004. Kumari et al. (2017) identified that the PANSS is now over 30 years old, and the conceptualisation of negative symptoms has changed since then. The Clinical Assessment Interview for Negative Symptoms and the Brief Negative Symptom Scale may be preferred over the PANSS negative subscale because of their reliability and validity to assess current conceptualisations of negative symptoms (Kumari et al., 2017).

Chapter 6 Evidence for the Network Theory of Mental Disorders in People at Ultra High Risk of and Diagnosed With Schizophrenia

Prelude to Chapter 6

As discussed in Chapter 3, SNs have developed from a comorbidity network that looks at the shared expression of variables between various disorders to a theoretical orientation that explains psychological or psychiatric disorders (Borsboom, 2017; Borsboom & Cramer, 2013; Cramer et al., 2010). None of the studies found in the systematic review (Chapter 4) look at comparisons between LVMs and SNs in their model fit (Buchwald et al., 2024). Because SNs are a new way to conceptualise schizophrenia, research that supports or refutes the assumptions of the network theory of mental disorders is needed (Borsboom, 2017). Additionally, research indicates that often theoretical models are posed in opposition to each other, such as the LVMs and the SN models (Abplanalp & Green, 2022; Bringmann & Eronen, 2018; Epskamp et al., 2017). Previously, the idea of an LVM was to try to find local independence between items (Borsboom et al., 2003). However, the LVM may have unexplained variance and a lack of independence between items. Given this unexplained variance, it is unclear whether LVMs benefit from additional edges between items or variables or whether SNs benefit from including latent variables in terms of the model fit. Although the integration has been discussed as possible in theory (Abplanalp & Green, 2022; Bringmann & Eronen, 2018; Epskamp et al., 2017) to date, no known research has compared an LVM with an integrated LVM and SN model on symptoms of PDS (Buchwald et al., 2024). Evidence suggesting that items should interact, rather than be independent, would provide partial support for the complexity principle of the NTMD, proposed by Borsboom (2017). This is partial support due to sampling limitations and the type of models included in this research. Hence, this research aims to present an integrative LVM and SN to identify if the integrative model has a better fit than the standalone LVM or SN model. This may help researchers find models with a better fit or allow researchers to combine inferences from an LVM and SN model, each with a unique applied value.

6.1 Abstract

The network theory of mental disorders proposes that symptoms cause or are associated with the expression of other symptoms. Research on the network theory is increasing, but empirical support is lacking. We aim to assess the viability of an integrated latent variable model (LVM) and network model of psychopathology. We sourced 795 ultra-high-risk participants from the North American Prodromal Longitudinal Three Study and 1,446 participants with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness study. We reconstructed a Bayesian network on the Scale of Psychosis Risk Symptoms and Positive and Negative Syndrome Scale on five training samples and then estimated the parameters on five test samples from each study, respectively. We compared the three models (Network model, LVM, and integrated model) on the five test samples from each assessment (30 models). The integrated model had a significantly superior fit than the LVM and had a better fit than the network model in all test samples. This novel finding provides partial support that items may interact and that networks with latent variables may be used to model the structure of an assessment if there is a poor fit to the LVM structure.

6.2 Introduction

The network theory of mental disorders is a recent paradigm that attempts to model an underlying psychological disorder or trait based on the complex system of interactions among its symptoms (Borsboom, 2017). This theory posits that each symptom can jointly influence, cause, or exacerbate the expression of other symptoms. The network theory proposed by (Borsboom, 2008b) and expanded by Borsboom (2017), Bringmann et al. (2022), and Cramer et al. (2010) has been the subject of considerable research and debate (Abplanalp & Green, 2022; Guyon et al., 2017; Jones et al., 2017; Oude Maatman, 2020) and has been adopted in progressively more publications since its inception. One principle proposed under this theory is the complexity principle, which identifies that mental disorders are best characterized in terms of the interaction between different components in a psychopathology network (Borsboom, 2017, p,7). The interaction between components identifies that: symptoms or observed behavioural variables are associated with the expression of other symptoms or observed behavioral variables in a network. Borsboom (2017) considered that systems of interacting components may be the most plausible explanation for the phenomena of mental disorders. Symptom networks as a theory provide a fresh perspective on modeling mental disorders, and the method may have strong explanatory value, like other modeling techniques, such as the latent variable model (LVM).

Over many decades, scientists have developed network statistical methods to represent complex systems of interacting variables. Network methods have been recently applied to explain the characteristics of psychological disorders, including schizophrenia (Borsboom, 2008b; Contreras et al., 2019; Isvoranu et al., 2018), depression (Borsboom, 2008b; Fried et al., 2016; van Borkulo et al., 2015), and post-traumatic stress disorder (Benfer et al., 2018; Fried et al., 2018), among others. The rapidly growing body of research on networks and mental disorders in recent years has marked the beginning of a paradigm in the field of mental health: symptom networks.

The network approach to psychological disorders takes a complex systems approach to study symptoms, latent traits, observed behavior, and historical factors of an individual. These variables are the nodes in the network, and relationships between variables are encoded in the network's edges. The network model can be directed, with arrows pointing from the parent node (predictor) to the child node (response), partially directed or undirected. Bayesian networks were developed in the 1970s to graphically represent and probabilistically model the components of a complex system for top-down and bottom-up perceptual processes (Pearl & Russell, 2000). Bayesian networks are one statistical method that graphically represents the relationships between variables in a network and encodes conditional probability relationships into a directed acyclic graph. We refer to 'network model' to describe a Bayesian network for the remainder of this work. Networks may have different uses than those of other models of psychopathology. Child nodes are dependent on parent nodes in directed symptom networks. Therefore, relationships between variables may be used to identify nodes to target for clinical interventions (Briganti et al., 2023). They can also identify associations between symptoms and node centrality statistics, as a measure of symptom importance (Fried et al., 2017). Some researchers posit that developing an intervention based on the properties of a single node or edge is not feasible, as most psychosocial therapeutic interventions often target an array of variables (Bringmann et al., 2019). However, theoretical implications may be obtained from a reconstructed network of symptoms of one or more conditions. For example, symptoms, such as those in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, 2013), can be represented in terms of a network, and clusters of symptoms could represent conditions (Nuijten et al., 2016).

Another paradigm of psychopathology, the LVM, proposes that observed behaviors, symptoms, or test scores are caused by underlying latent variables (hidden factors) that exist on a continuum of intensity or severity. Latent variables are inferred to cause the observed responses to items of a psychometric test with a degree of measurement error. LVMs assume that items of a test have local independence, given the relationship with the latent variable (Borsboom et al., 2003). Here, all observed variables should be independent, as in principal components analysis (Borsboom et al., 2003). This assumption has been at the forefront of psychometric theory and can be tested using networks and SEMs.

A structural equation model (SEM) is often used as the statistical method to test LVMs using confirmatory factor analysis. Bayesian networks may be a valuable method for SEM as they encode directed relationships. Therefore, a data-driven method like Bayesian networks may identify the optimal structure to test in an SEM. The directed relationships found in Bayesian networks help identify the predictor and response relationships in an SEM. The structure of the SEM is often hypothesized a priori, based on evidence from previous literature. Additionally, exploratory factor analysis is another data-driven method to identify a structure to test (Liew et al., 2023a; Marcot & Penman, 2019; Pearl, 2009).

The complexity principle of the network theory, according to Borsboom (2017), may be assessed empirically by comparing an LVM to a network model with latent variables using items of an assessment as nodes in the network. If the LVM does not fulfil the local independence assumption, a network may be fitted in addition to the LVM, which is an integration of the two approaches. Here we take the associations between latent variables and items, and the directed associations between items, and include these in the model in lavaan. We postulate that network methods are adequate to generate an interpretable model with a good fit to the data when combined with an a priori LVM based on the literature.

Given the increasing literature on symptom networks and the arguments made by symptom network theorists, efforts have been made to compare the model fit of LVM and network models in the study of psychometric data (Kan et al., 2020). Kan et al. (2020) proposed a method to directly compare partial correlation networks to the structures hypothesized in LVMs. In addition to Kan et al. (2020) and McFarland (2020) researchers have compared the fit statistics of network models and LVM (Christensen et al., 2019; Kan et al., 2020; Moriana et al., 2022; Moriconi et al., 2025; Schmank et al., 2019). Arguably, fit statistics, while informative as to which model fits the data best, do not lead to a rejection of models and are not hypothesis tests of model fit (Barrett, 2007).

Research needs to be undertaken to examine whether the model should include dependency between items of an assessment, as network theory proposes. Although Kan et al. (2020) and McFarland (2020), aim to provide evidence in favor of network models, likelihood ratio tests are more suited to test this hypothesis formally. Hence, we can directly compare whether the proposed LVM has a poorer fit than an integration between the two models using a hypothesis test. While networks and SEMs are used together in other disciplines (Díez-Mesa et al., 2018; Li et al., 2018), we are not aware of any research with people diagnosed with schizophrenia (PDS) that has subjected the complexity principle of the network theory of mental disorders to a hypothesis test, using SEM and likelihood ratio tests (Buchwald et al., 2024). The network model with latent variables represents an integration of both the network and LVM. To the best of the authors' knowledge, there has been no empirical comparison to date between a network model, an LVM model, and an integration of these two models in PDS (Buchwald et al., 2024). We therefore hypothesize that items interact, as proposed by the complexity principle in the theory by Borsboom (2017), therefore, the LVM with item interactions fits better than a latent variable alone. Additionally, we hypothesize that a network model with latent variables has a better fit than a network model without latent variables.

6.3 Method

6.3.1 Participant characteristics

The first dataset considered is from the NAPLS3 study conducted by the University of California San Francisco (Addington et al., 2022), where we obtained the data from the National Institute of Health data repository (National Institute of Mental Health, 2024a). The NAPLS3 study (Addington et al., 2022) is a consortium of nine programs that follow people at ultra-high-risk of schizophrenia over a two-year period and aims to assess the predictors of transition to schizophrenia. This dataset was retrieved from the National Institute of Mental Health (2024b). The sample included participants from health care providers, educators, social services, and self-referrals. In addition to the exclusion criteria documented in Addington et al. (2022), participants who did not complete all items on the Scale of Psychosis Risk Symptoms (SOPS) were excluded. A total of 795 participants fully completed the SOPS, and when participants had undertaken repeated measures on the SOPS during the longitudinal study, we selected the latest observation. Table 8 provides the descriptive statistics for people who participated in the NAPLS3 study. Most participants were Male (427; 53.7%) and identified as White (European American; 479; 60.3%). Other ethnic groups in this study include participants who identify as Asian (99; 12.5%), Black (African American; 95; 12.0%), or American Indian and Alaska Native (17, 2.1%). This study contained a cohort with a mean age of less than 20 years (M = 18.7; SD = 4.1). Only a few individuals had a diagnosis of a psychotic disorder at the end of the study (64; 8.1%). The descriptive statistics for participants who completed the PANSS in the CATIE study (N = 1,446) can be found in Table 18 in the Supplementary Materials Descriptive Statistics for the CATIE Study section (Appendix C3).

Table 8. Demographics or the NAPLS3 study

Demographic	*N* (*M*)	% (*SD*)	Missing
Age	(18.7)	(4.1)	
Sex			
Male	427	53.7	
Female	368	46.3	
Ethnicity			1
White or European American	479	60.3	
Asian	99	12.5	
Black or African American	95	12.0	
American Indian/Alaska Native	17	2.1	
Other	104	13.1	
Immigration status			4
Born in USA or Canada (not 1st or 2nd generation)	602	76.1	
2nd generation migrant (born in USA or Canada)	99	12.5	
Subject and parents born abroad	90	11.4	
Diagnosis (SCID-5, latest assessment)			
Schizophrenia	30	3.8	
Schizoaffective disorder	12	1.5	
Schizophreniform	4	0.5	
Other psychotic disorder	18	2.3	

Note. N = Sample size; M = Mean; SD = Standard deviation; SCID-5 = Structed clinical interview for the DSM-5; SOPS = Scale for the assessment of prodromal symptoms; SOFA = Social and Occupational Functional Assessment Scale of the DSM-5.

6.3.2 Measures and covariates

The SOPS (Miller et al., 2002) is a 19-item assessment used to quantify severe schizophrenia-like symptoms and to identify if a person has brief intermittent psychotic syndrome, attenuated positive symptom syndrome, and genetic risk and functional decline psychosis risk syndrome. The SOPS has four subscales: positive, negative, disorganized, and general (Miller et al., 1999).

The items are ranked on a scale from zero to six, and a score of six on some items of the SOPS means the participant met one criterion for current psychosis. Miller et al. (2002) found interrater reliability for diagnoses derived from the SOPS was excellent (Kappa=.81). Woods et al. (2019) reviewed the SOPS and reported excellent interrater reliability estimates across studies and strong predictive, convergent, and discriminant validity across studies.

The PANSS (Kay et al., 1987) was developed to assess the severity of positive and negative symptoms of schizophrenia and their contribution to global psychopathology. The PANSS has three subscales: positive, negative, and general (Kay et al., 1987). Kay et al. (1987) reported that the PANSS has acceptable to good reliability across the positive and negative subscales of the PANSS, which are positively correlated to the Brief Psychiatric Rating Scale and Manifest Affect Rating Scale subscales. Since then, it has been the subject of many systematic reviews and meta-analyses that identify its utility for use with PDS.

6.3.3 Data diagnosis

The SOPS and PANSS items were left unstandardized. We assumed that the responses to the SOPS and PANSS were continuous to implement a maximum likelihood SEM in the R package lavaan (Rosseel, 2012) and because there were many seemingly equidistant levels in the SOPS and PANSS items. To account for any non-normality of the error terms, we used robust standard errors using the "MLR" option in the R package lavaan (version 0.6-16;Rosseel, 2012).

6.3.4 Analysis

Analysis was completed in R version 4.3.2 (R Core Team, 2024). Given a heuristic based on a sample size to parameter ratio of 20 to 1 (Kline, 2023), the subscales general and disorganized from the SOPS in the analysis of the NAPLS3 study were excluded to simplify the model further. The general subscale from the PANSS was also not included. Estimating the power of these models using parametric methods is challenging, as the models are complex and a joint distribution must be identified. Many rules of thumb estimates for sample sizes have been proposed and disputed (Kline, 2023). We aimed to be conservative in the complexity of the network. Given the heuristic of 20 participants per parameter, our resultant networks should have approximately 35 parameters to be estimated for the models in the NAPLS study and 63 parameters for models in the CATIE study. Hence, adding the factor and items representing the subscales general and disorganised would lead to insufficient power to fit and estimate the models. These latent variables were therefore excluded from our models. Our latent variable structure aligns with the assessment manuals of these assessments for positive and negative symptom dimensions (Kay et al., 1987; Miller et al., 2002).

We used a similar concept to cross-validation to avoid unfairly comparing the model generated on the data (network model) to a model not generated on the data (LVM). We used a random training sample of size 100 for the NAPLS study and one of size 180 for the CATIE study (approximately 12.5%) to generate the network model structure. This sample size was chosen to ensure the structural equation model has a sufficient sample size to fit the required number of parameters. We then implemented this structure in an SEM on the remaining data to estimate the parameters. This split represents one-eighth of the data and allows for the parameters to be estimated in the SEM when using the test sample. This is not cross-validation in the usual sense, as we are not predicting values in the test dataset. We could not use split-half or k-fold cross-validation as the sample size in the test sample was insufficient to estimate the parameters of an SEM. This strategy allows the network structure to be generated on an out-of-bag sample to make a fair comparison to the LVM approach, which was also not generated on the data. We repeated this five times on different training and test datasets for both the NAPLS-3 and CATIE studies to ensure the results can be replicated. Multiple testing is useful to avoid the training sample being unusual with respect to the test dataset. No participant was included more than once across training samples.

Regarding the NAPLS3 dataset, the network model was a reconstructed network model on 11 items of the SOPS, representing items from the positive and negative subscales (network model). We added a covariance term between LVMs, which was significant for each LVM in the test datasets. We also combined the edges found in the network model (between items) and LVM (between items and latent variables) and named this the integrated model. We repeated this five times for five training and test samples for the NAPLS3 study. Given this, we constructed 15 SEMs on five test datasets for each model (network model, LVM, and integrated model) for the NAPLS3 study.

Similarly, for the CATIE dataset, the network model is a reconstructed network model of 14 items of the PANSS representing the positive and negative symptom subscales. Again, we added a covariance term between latent variables as this was significant for each LVM in the test datasets for the CATIE dataset. Lastly, the integrated model combines the LVM and network model, where relationships between latent variables and items in the LVM and the relationships between items in the network model were included in the integrated model. We repeated this process for five training and test datasets. Given this, we constructed 15 SEMs representing five test samples for each model for the CATIE study.

All Bayesian network models were implemented using the hill climbing algorithm in the package bnlearn version 4.9.4 (Scutari & Denis, 2021). We also used the package lavaan version 0.6-17 (Rosseel, 2012) to implement the SEMs. We selected the hill climbing algorithm in the package bnlearn (Scutari & Denis, 2021) for the Bayesian network, as it can use BIC scores to optimize the network. We did not specify priors or hyperparameters. We used maximum likelihood estimation of the parameters to estimate the model fit. We obtained the comparative fit index (CFI), Tucker-Lewis Index (TLI), and root mean square error of approximation (RMSEA). We also evaluated the fit of the model-implied variance-covariance matrix to the observed variance-covariance matrix using a chi-square test of model fit. Additionally, we extracted the Akaike information criterion (AIC), BIC, and the log-likelihood for each model from fitted SEMs using the lavaan package (Rosseel, 2012). For CFI and TLI, scores range between zero and one, where higher scores indicate that the model fits the data better, with scores above .95 being acceptable (Hu & Bentler, 1999). Accordingly, RMSEA has values between zero and one, where lower values indicate a better model. RMSEA values should be below approximately .06 to suggest a satisfactory model fit (Hu & Bentler, 1999). We then compared the LVM and integrated model for both the NAPLS3 and CATIE data, using likelihood ratio tests as the LVM is included within the integrated model. The summary statistics for SOPS and the PANSS can be found in Tables 19 and 20 in the Supplementary Materials for the NAPLS3 and CATIE study, respectively (Appendix C3). Lastly, we conducted a unique variable analysis from the R package EGAnet (Golino & Christensen, 2025), and included in the results whether the observed variables are independent. This serves as an indication that the assumption of local independence is violated according to the method by Christensen et al. (2023). These authors use the weighted topological overlap method to determine independence between observed variables, where any values above 0.25 indicate local dependence between items (Christensen et al., 2023). Although a Gaussian graphical model was estimated to identify local independence, this was used to assess the local independence assumption of the LVM. More information on this method to reject local independence can be found in Christensen et al. (2023). This study was not preregistered, and all code used to produce the results of this data can be found in: https://github.com/KhanBuchwald/Evidence_for_the_Network_Theory_of_Mental_Disorders.

6.4 Results

Table 9 provides the model fit statistics for the 30 models mentioned in the Analysis subsection. The results in Table 9 suggest that the integrated models better fit the data than the LVMs in the NAPLS3 and CATIE studies when comparing CFI, TLI, and RMSEA. The integrated models fit the data adequately, even when obtaining the structure of the BN on a small sample size. The LVM had a relatively poor fit to the NAPLS3 and CATIE study data for the CFI, TLI, and RMSEA indices. The network models had better BIC, AIC, and log-likelihood scores than the LVMs and integrated models in all samples across the NAPLS3 and CATIE studies. However, the network and integrated models represent fundamentally different concepts; one contains latent variables, while the other does not. Therefore, a comparison should not be made between these models using likelihood-based statistics. In a chi-square test of model fit, the model implied variance-covariance matrix and the observed variance-covariance matrix were significantly different from each other in every network model (***p*** = .001), LVM model (***p*** < .001), and integrated model (***p*** < .001) in the NAPLS3 study and the CATIE study. The statistical significance suggests that the models may not fully account for the observed covariance structure in the data. All models from the test dataset are considered to violate local independence, using the weight topological overlap statistic as the criterion. Two integrated models had estimated negative variance in the model, suggesting the model is underpowered or mis-specified.

Table 9. Fit Statistics for Each SEM and BN.

Study	Model	Sample	*CFI*	*TLI*	*RMSEA*	*Chi Sq.*	*df*	*p*	*BIC*	*AIC*	*Log Likelihood*	*Local Independence*
NAPLS3	Network model	1	0.925	0.883	0.090	230.5	35	<.001	23668	23532	-11736	
NAPLS3	Network model	2	0.862	0.795	0.118	396.5	37	<.001	23815	23687	-11816	
NAPLS3	Network model	3	0.839	0.773	0.127	473.3	39	<.001	24062	23944	-11946	
NAPLS3	Network model	4	0.888	0.829	0.108	329.5	36	<.001	23721	23589	-11766	
NAPLS3	Network model	5	0.929	0.843	0.103	208.7	25	<.001	23732	23550	-11735	
NAPLS3	LVM model	1	0.884	0.852	0.101	345.5	43	<.001	26460	26356	-13155	False
NAPLS3	LVM model	2	0.872	0.837	0.106	376.3	43	<.001	26496	26392	-13173	False
NAPLS3	LVM model	3	0.878	0.844	0.105	372.4	43	<.001	26414	26310	-13132	False
NAPLS3	LVM model	4	0.877	0.843	0.104	364.6	43	<.001	26411	26306	-13130	False
NAPLS3	LVM model	5	0.871	0.834	0.106	376.6	43	<.001	26483	26379	-13166	False
NAPLS3	Integrated model	1	0.987	0.970	0.045	58.5	24	<.001	26298	26107	-13011	
NAPLS3	Integrated model	2	0.974	0.944	0.062	95.1	26	<.001	26326	26145	-13032	
NAPLS3	Integrated model	3	0.975	0.951	0.059	95.2	28	<.001	26235	26062	-12993	
NAPLS3	Integrated model	4	0.975	0.950	0.059	91.8	27	<.001	26242	26065	-12994	
NAPLS3	Integrated model	5*	0.956	0.914	0.076	140.9	28	<.001	26346	26173	-13049	
CATIE	Network model	1	0.885	0.822	0.092	693.0	59	<.001	50921	50690	-25300	
CATIE	Network model	2	0.904	0.854	0.084	587.5	59	<.001	46240	46019	-22967	
CATIE	Network model	3	0.909	0.866	0.079	551.1	62	<.001	50613	50397	-25156	
CATIE	Network model	4	0.892	0.839	0.087	649.3	61	<.001	51062	50841	-25378	
CATIE	Network model	5	0.910	0.870	0.079	556.7	63	<.001	50452	50241	-25079	
CATIE	LVM model	1	0.730	0.677	0.124	1557.6	76	<.001	55840	55690	-27816	False
CATIE	LVM model	2	0.743	0.692	0.122	1496.5	76	<.001	55775	55626	-27784	False
CATIE	LVM model	3	0.732	0.680	0.122	1510.1	76	<.001	55918	55769	-27855	False
CATIE	LVM model	4	0.737	0.685	0.122	1511.7	76	<.001	56032	55883	-27912	False
CATIE	LVM model	5	0.723	0.669	0.125	1590.7	76	<.001	55922	55773	-27858	False
CATIE	Integrated model	1	0.950	0.916	0.063	328.6	54	<.001	54768	54506	-27202	
CATIE	Integrated model	2	0.978	0.955	0.047	168.3	45	<.001	54668	54360	-27120	
CATIE	Integrated model	3*	0.948	0.905	0.066	329.6	50	<.001	54923	54640	-27265	
CATIE	Integrated model	4	0.963	0.936	0.055	251.9	52	<.001	54944	54671	-27283	
CATIE	Integrated model	5	0.946	0.908	0.066	351.7	54	<.001	54841	54578	-27238	

Note. LVM = Latent variable model; N = Sample size; CFI = Comparative fit index; TLI = Tucker-Lewis index; RMSEA = Root mean square error of approximation; Chi sq. = Chi-square test statistic; df = Degrees of freedom; p = p-value; BIC = Bayesian information criterion; AIC = Akaike information criterion;*: This model had estimated negative variances.

Table 10 presents the results of the likelihood ratio tests between the integrated models and the LVMs. The degrees of freedom in Table 10 represent the difference between the number of unique pieces of information and the number of estimated parameters. Hence, the model with fewer degrees of freedom is more complex. The results suggest that for each random sample, the integrated model had a significantly better fit than the LVM (***p*** <.001) in every sample and for both datasets. The statistical significance indicates that the model fit is significantly better in the integrated model after considering the difference in the number of parameters of the two models.

Table 10. Likelihood Ratio Test of LVM and Integrated Model for Each Sample.

Study	Model one	Model two	Sample	*df Model 1*	*df Model 2*	*Chi Sq. diff*	*df diff*	P^1
NAPLS3	LVM model	Integrated model	1	43	24	221.1	19	<.001
NAPLS3	LVM model	Integrated model	2	43	26	217.8	17	<.001
NAPLS3	LVM model	Integrated model	3	43	28	216.1	15	<.001
NAPLS3	LVM model	Integrated model	4	43	27	199.5	16	<.001
NAPLS3	LVM model	Integrated model	5*	43	28	155.2	15	<.001
CATIE	LVM model	Integrated model	1	76	54	950.9	22	<.001
CATIE	LVM model	Integrated model	2	76	45	1151.1	31	<.001
CATIE	LVM model	Integrated model	3*	76	50	865.7	26	<.001
CATIE	LVM model	Integrated model	4	76	52	1042.4	24	<.001
CATIE	LVM model	Integrated model	5	76	54	956.7	22	<.001

Note. LVM = Latent variable model; df = Degrees of freedom; p = p-value; 1: Using the Satorra and Bentler approximation; *: This model had estimated negative variances; degrees of freedom represent the difference between the number of unique pieces of information minus the number of parameters, as more complex models have fewer degrees of freedom.

The structural equation model in Figure 17 presents the best-fitting model according to CFI, TLI, and RMSEA and represents an integrated model from the NAPLS3 dataset. The model, which includes the relationships between items and the latent variables and the relationships between items identified by the network model, is presented to give a visual view of the integrated models reconstructed in this study. Significance values between latent variables and items have been omitted from this Figure. All other figures are provided in the Supplementary Materials Model Structures section (Appendix C3).

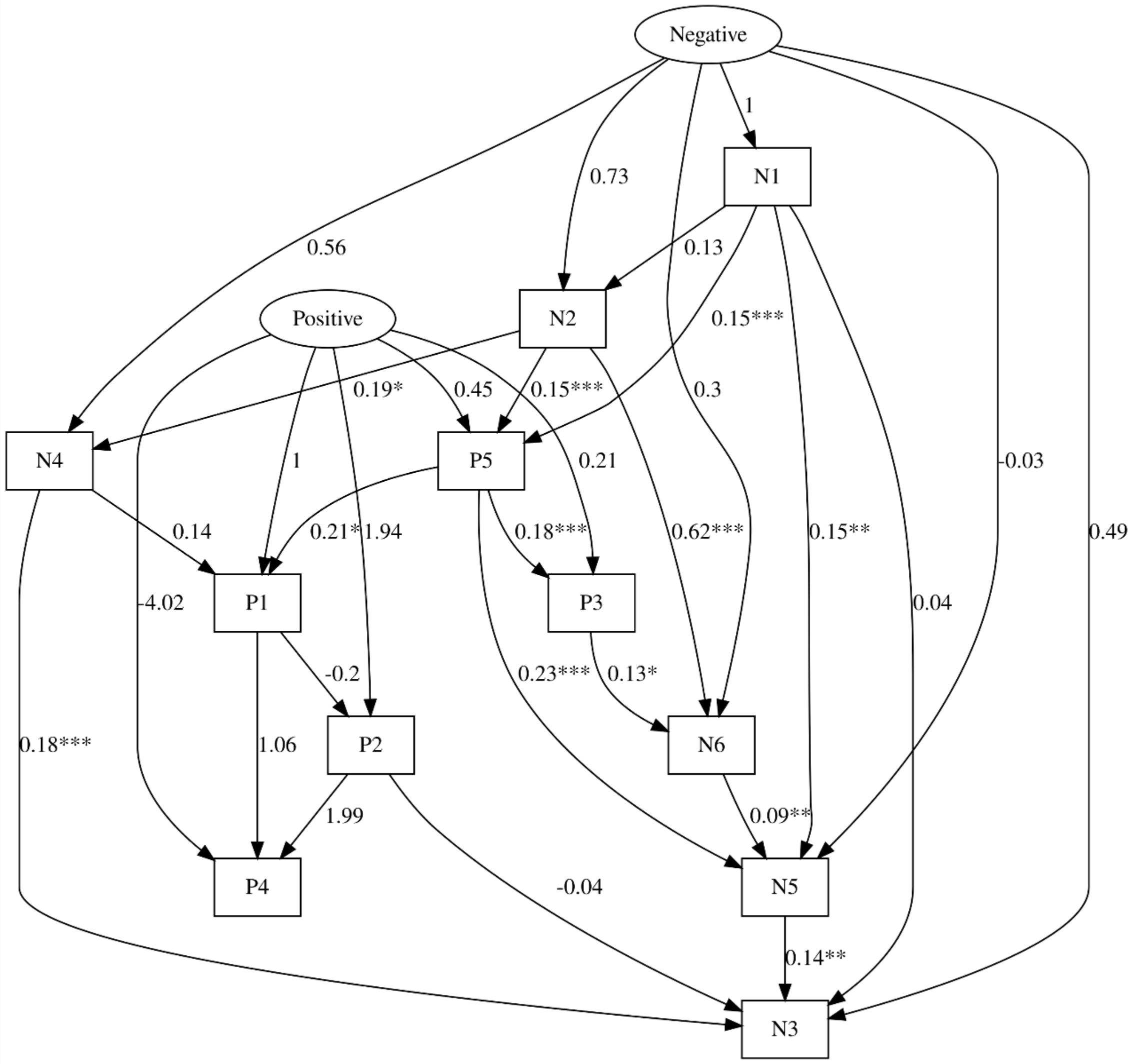

Figure 17. Structural Equation Model Diagram of Best-Fitting Model.

Note. Positive = Latent variable for the positive symptoms subscale; negative = Latent variable for the negative symptoms subscale; P1 = Unusual thought content/delusional ideas; P2 = Suspicious/persecutory ideas; P3 = Grandiose ideas; P4 = Perceptual abnormalities/hallucinations; P5 = Disorganized communication; N1 = Social anhedonia; N2 = Avolition; N3 = Expression of emotion; N4 = Experience of emotions and self; N5 = Ideational richness; N6 = Occupational functioning; Edge wights = Unstandardized regression coefficients; * = Significant; ** = Moderately significant; *** = Highly significant.Discussion

We aimed to assess the complexity principle of Borsboom (2017) and identify whether we could integrate the LVM and network model to obtain a better-fitting model. This study compared models of the theorized relationships between items of the SOPS in people at ultra-high risk of schizophrenia based on models from the network theory of mental disorders and the LVM approach. This is replicated for items of the PANSS with participants with chronic schizophrenia. Our research provides empirical support for directed acyclic graphs with latent variables as adequate models of the underlying model of the responses to items of the SOPS and PANSS, given the LVM structure. Adding associations between items found in a network model and the associations between the latent variables and the items found in the LVM model significantly improved the fit over the LVM model alone in the NAPLS3 study. This significance adds partial empirical support to the complexity principle of the theory by Borsboom (2017), as items representing symptoms or observations should have associations with each other. This finding, however, rests on the assumption that the local independence assumption was not met with the a priori LVM. We also found that including latent variables (as prescribed under the LVM) improved the fit statistics CFI, TLI, and RMSEA over the network model without latent variables. This finding suggests that network models with latent variables can improve the fit of a LVM and network models without latent variables, which may be used in future research where these models have suboptimal fit.

The network model with latent variables integrates the two modeling approaches and fits better than the network model and the LVM alone. The notion that items interact, as Borsboom (2017) proposed, is supported by these findings. We also confirmed these results in a second empirical assessment of the PANSS data from the CATIE pharmaceutical trial. Hence, we provide empirical evidence to support the validity of the complexity principle of the network theory of mental disorders as proposed by Borsboom (2017), when the LVM is suboptimal in PDS with a chronic condition and in people at ultra-high risk of schizophrenia on the PANSS and SOPS assessments, respectively.

Borsboom and Cramer (2013), Borsboom (2017), Bringmann et al. (2022), and Cramer et al. (2010) advocated for the advancement of the theory that psychological disorders are embedded in a network of symptoms. Additionally, Epskamp and Borsboom published previously on network models with latent variables (Epskamp et al., 2017). Adding latent variables to networks is not a novel method used in our study (Epskamp et al., 2017; Pearl, 1995). Other research comparing the LVM and network model tends to identify that the network models generally have a better fit to the data (Christensen et al., 2019; Kan et al., 2020; Moriana et al., 2022; Moriconi et al., 2025), even when the underlying factor structure has been well-researched (Schmank et al., 2019). This may partially be due to the use of sum scores to measure latent variables, as opposed to using the factors from the principal components analysis, which could be problematic (McNeish & Wolf, 2020). We found a good fit even when generating the network on a small sample size of 100, potentially because networks are data-driven models compared to our LVMs (Liew et al., 2023b).

Other researchers have identified that although these two approaches are different conceptually, and many arguments have been debated on both sides (Bringmann & Eronen, 2018), these models can be complementary. Bringmann and Eronen (2018) identify that if variable A and Variable B have a common cause (latent) variable C, then this common cause may explain the covariance of variable A and variable B, but not all covariance. This is essentially what is found in our empirical study, where the LVM does not explain all the covariance structure found in the observed responses to the items of the SOPS and PANSS. This may be inherent in the calculation of sub-scores to represent latent variables. It is unclear the extent to which LVMs proposed in the wider psychometric literature have a suboptimal fit, where relationships between observed values can be included to improve the model, as identified by the network theory of mental disorders.

Although we found a significantly better fit for a network model with latent variables, the LVM may still be superior when modelling some phenomena, or another latent variable structure may be better for the PANSS and SOPS (Kay et al., 1987; Miller et al., 2002). We used latent variables as documented by Kay et al. (1987) and Miller et al. (2002), although this does not appear to be the optimal LVM for these data or these assessments. These authors proposed the latent variables a priori instead of specifying them using methods such as principal components analysis. Hence, although we found the integrated model fitted better, and in this case, items can interact, this does not refute other LVMs that could equally well fit these data.

Network models and LVM may be used to explore statistics that are applicable in different contexts. Here, the proposed LVM can be used to identify severity scores based on latent variables or cut-off values as indicators or diagnostic tools, depending on the assessment's psychometric properties. In addition to this, network statistics can be conducted on the network model itself. Network statistics have been explored in depth by other researchers, including introducing probability queries to the network by treating it as an expert system, centrality statistics, and edge statistics (Briganti et al., 2023; Bringmann et al., 2019). Hence, both models offer different solutions to the analysis of psychopathology. Future research could examine whether additional statistics can be drawn from integrative network and LVM models beyond what is provided by both approaches.

6.4.1 Limitations

Our study has several limitations. First, we used ordinal data when obtaining the multivariate normal likelihood estimates. We used robust standard errors to reduce the effect of potential violations of test assumptions (Williams, 2021). Secondly, the implied variance-covariance structure significantly differed from the observed variance-covariance structure for all models, indicating that our identified models were not entirely faithful to the data. This suggests that although we found that the network models have a better fit, other models may better represent the responses to the SOPS and PANSS items. Some of the models did not converge and may suggest the model is over-parameterized, and a simpler model, such as an LVM or network model, may be better for simplicity. Estimating the power of the model would have allowed the identification of a suitable level of complexity to be modelled, however parametric estimates of power are intractable and Monte Carlo approaches rely heavily on specifying the sampling distribution (Wolf et al., 2013). Hence, the heuristic of 20 participants per parameter was used despite many authors noting that this may not be the preferred approach (Hoyle & Gottfredson, 2015; Kline, 2023; Wolf et al., 2013). Estimated negative variances may have occurred due to a lack of power to fit the models. Lastly, some integrative models' coefficients have estimated negative variance despite having a better fit than the LVM and network model. Both of these considerations may be due to a lack of power in estimating many coefficients in the model. In addition to this, we used the PANSS to assess negative symptoms in PDS, and there has been some concern about the validity of the PANSS to assess negative symptoms, as the concept of negative symptoms has changed considerably since the development of the PANSS (Kumari et al., 2017). Newer scales, such as the Clinical Assessment Interview for Negative Symptoms and the Brief Negative Symptom Scale, may be preferred to assess negative symptoms due to their reliability and validity to assess the current understanding of negative symptoms of schizophrenia (Kumari et al., 2017). However, this study is based on the CATIE trial, which did not include these newer assessments in the study (Stroup et al., 2003).

6.4.2 Conclusions

The network models in the present study that included latent variables derived from the literature showed adequate fit, superior to the LVM that did not allow interactions between items. The finding that responses to items of the SOPS and PANSS interact is notable in our study, as this is prohibited in LVMs due to all information already being explained by the latent variables (Fabrigar et al., 1999). However, for the LVM selected based on the authors of the SOPS and PANSS (Kay et al., 1987; Miller et al., 2002), we found that integrating the network model and LVM fit the data the best. Hence, in a sample of people at ultra-high risk of schizophrenia and PDS, responses to items interact or are associated with the responses on other items. This provides partial empirical support for principle 1 of the network theory of mental disorders (Borsboom, 2017) when the assumption of local independence is violated. The integrated model can be used if the LVM has a poor fit to the data to improve the model fit and generate statistics from both the LVM and the network model.

Chapter 7 Discussion and Conclusions

The literature reviews, the three studies of SNs, and the discussion section incorporate various contributions to the understanding of SNs and schizophrenia. Each chapter is presented to meet the aims and objectives of this thesis. Firstly, the introduction in Chapter 1 provides a concise overview of schizophrenia, SNs, and the aims and objectives of this thesis. Secondly, the literature reviews in Chapters 2 and 3 are proposed to provide a more detailed overview of schizophrenia and the SN approach, respectively, as they apply to this thesis. Thirdly, the systematic review in Chapter 4 successfully identified which domain of health is most central across SN studies of schizophrenia and identified gaps in the literature of SNs of schizophrenia. Fourth, the SN in Chapter 5 aimed to fit a BN to the cognitive, clinical, QOL, and demographic characteristics of schizophrenia in order to make inferences about the relationship between cognition and other variables. Fifth, the model comparison study of Chapter 6 aimed to test the complexity principle theorised by Borsboom (2017) by combining an LVM and edges in a network model and conducting a likelihood ratio test between integrated models and nested LVMs. Finally, the discussion to follow aims to propose a clinical profile using SNs and explore the primacy of cognition in schizophrenia. The discussion section is structured into five parts. I first provide a summary of the main findings. I then propose the importance of cognition and processing speed in schizophrenia, and propose extending the utility of SNs for a clinical profile. Following this, a brief overview of the limitations of the methods and design of the studies in this thesis is provided, along with directions for future research. Finally, a summative conclusion is presented, concluding the body of the thesis.

7.1 Summary of thesis and manuscripts

Each research component and the remaining contents of this manuscript supported the aims and objectives of this thesis. The literature reviews, although not exhaustive, provide context for the concepts of schizophrenia, SNs, and network analysis. The first study in Chapter 4, Centrality Statistics of Symptom Networks of Schizophrenia: A Systematic Review, identified what areas of SNs of schizophrenia have not been assessed, and this gap was filled in the following research on cognition in schizophrenia. The results also provided consistent themes. Cognition and functioning were most central in nearly all the networks that included assessments of these components. However, given other publications, the results are well-integrated with the literature on cognition in schizophrenia (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). Given the selection criteria, articles that did not mention a diagnosis of schizophrenia were excluded, which may have reduced the overall number of publications included, and several key publications could not be included (Isvoranu et al., 2020; Isvoranu et al., 2016). The themes and gaps in the literature identified in this study, as presented in the supplementary materials of this thesis (a primary aim of this thesis), highlight that cognition may be useful in additional research when implementing SNs of schizophrenia.

The second study utilised the general results and gaps identified in the systematic review to implement a study that assesses the role of cognition in the SNs of schizophrenia. Other research has examined cognition in schizophrenia (Buchwald et al., 2024). However, based on my systematic review (Buchwald et al., 2024), no research on BNs has examined the directed relationships of cognition to other measures of health, such as QOL, clinical correlates, and sociodemographics in PDS (Abplanalp et al., 2023; Buchwald et al., 2024). Hence, a primary aim of this research was to look explicitly at the role of cognition. The results suggested that processing speed was a predictor variable of other components of cognition, negative symptoms, and QOL. This supports other research that identifies processing speed as most impaired and may be the primary cognitive impairment in schizophrenia (Dickinson et al., 2007; Schaefer et al., 2013), although less research is documented on which component of the MATRICS is most important for schizophrenia (Horan et al., 2022). Interestingly, positive symptoms were conditionally independent of cognitive processes. This independence or conditional independence is in agreement with other research (Dupuy et al., 2022; Rek-Owodziń et al., 2022; Ventura et al., 2010; Weinberger & Harrison, 2011).

The final study aimed to test the complexity principle of the NTMD, which posits that items or observed variables interact in a psychopathology network (Borsboom, 2017). The study was designed to determine whether an LVM, with the positive and negative symptom structure prescribed by the literature, should include associations between items. In a traditional LVM context, an LVM may be fully explained only by associations between items and latent variables. The goal when proposing an LVM is to make items conditionally independent given their association with latent variables (Borsboom et al., 2003). However, in psychology, this is often not the outcome of a proposed LVM. I found, by implementing the positive and negative symptom structure of the PANSS (Kay et al., 1987) and SOPS (Miller et al., 2002), that the LVM had a poor fit to the data, and adding edges between items significantly improved the model's fit. This was used to provide partial support for the complexity principle of mental disorders (Borsboom, 2017). This is partial support due to the sample and assessments considered; replication of this result is needed. This research, the literature reviews in Chapters 2 and 3, the systematic review in Chapter 4, and the SN of cognition in Chapter 5, allowed me to fulfil the final aims and objectives of this thesis: to explore the theoretical status of the primacy of cognition in schizophrenia and to propose new applications of SNs.

7.2 Synthesis and propositions

7.2.1 On the primacy of processing speed and cognition in schizophrenia

Some of the implications of this thesis can be identified through using SNs to explain psychopathology and the role of cognition in schizophrenia. I found that variables representing cognition featured as central nodes in networks more than positive, negative, and depressive symptoms. This provides support for the notion that schizophrenia is, in essence, a disorder of cognition (Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). This study was conducted in which, for the first time, cognition, sociodemographics, QOL, and clinical variables were included in a directed network of schizophrenia. Information processing speed is a predictor variable of all other cognitive processes in the directed network. This suggests that other cognitive processes depend on processing speed rather than vice versa, although the direction of the relationship may not be compelled in the network.

Research suggests cognition is a consistent predictor of later global levels of functioning in schizophrenia, even after 10 years, although there may be moderator variables associated with this relationship (Engen et al., 2022; Kharawala et al., 2022). Global levels of functioning were also central nodes in the PLS networks in the systematic review (Buchwald et al., 2024). The evidence suggests that cognitive functioning is one of the best prognostic factors to predict the general outcomes and functioning of PLS (Davies & Greenwood, 2020). The results also suggested that processing speed was the only component of the MATRICS that predicted QOL. My results suggest that cognition should be incorporated into all networks that directly relate to the clinical aspects of schizophrenia. Omitting cognition from the network may result in a biased network, as my results suggest that cognitive processes are essential variables to control for their effect (Briganti et al., 2023; Marcot, 2017).

When viewing cognition from a complex systems approach, a cognitive process is not independent from other cognitive processes, as demonstrated in my study in Chapter 5. Cognitive processes are likely interrelated, have dependencies, and cannot be treated in isolation. Chapter 5 highlights the natural dependency between cognitive functions, which can be observed in SN models. Scores on assessments of one cognitive process are likely to have dependencies or associated relationships with scores on assessments of other cognitive processes. An example that cognitive functions are interrelated in schizophrenia is the research on top-down and bottom-up cognitive processes of schizophrenia (Javitt, 2009). Other studies suggest that, in general, changes on one node (symptom) in a network usually do not happen in practice due to the complex interrelationships between variables and the common therapeutic effects (Bringmann et al., 2019). Despite interrelationships and the lack of isolation of cognitive processes, it is unclear whether any single cognitive process is more important.

There is no consensus in the broader literature on which cognitive functions are more important in the presentation or outcomes of schizophrenia, and whether cognitive impairment is a specific or general impairment (Best & Bowie, 2017; Green et al., 2015; Horan et al., 2022; Medalia & Choi, 2009; Miyamoto et al., 2012; Schaefer et al., 2013). Despite the lack of consensus on importance, there are cognitive processes that are more impaired than others in schizophrenia. In schizophrenia, processing speed is often most impaired, followed by working memory, perceptual organisation, and verbal abilities in people who have not had symptom remission (Bombassaro et al., 2023; Dickinson et al., 2007; Schaefer et al., 2013). According to the resultant network in Chapter 5, the network is approximately organised around neuropsychological variables, with the highest level of impairment serving as predictor variables and those with the lowest level of impairment as response variables (Schaefer et al., 2013). Processing speed is often sensitive to changes in functional and anatomical neurology, whereas verbal abilities tend to be robust to such changes, a phenomenon observed in other neurological conditions, as well as schizophrenia (Lezak et al., 2012; Schaefer et al., 2013). The level of impairment and the potential mediating effect of processing speed may suggest that processing speed is the prime cognitive impairment in schizophrenia.

Processing speed may serve as a substrate for higher-order cognitive processes. A study by Alloza et al. (2016) suggests that processing speed partially mediates the relationship between white matter abnormalities and general intelligence in schizophrenia, and this may be the pathway to the general cognitive impairment of schizophrenia. Additionally, there is evidence that processing speed has a higher weight in contributing to general intelligence than other cognitive components in schizophrenia (Dickinson et al., 2008). One study found that processing speed mediates the impairment in executive functioning, particularly shifting tasks, which has been identified as being almost entirely associated with processing speed (Thuaire et al., 2022). According to Sheppard and Vernon (2008), the association between processing speed and general intelligence is stronger when performing more complex tasks. Another study found that impairments in processing speed are more pronounced than hypothesised under the accelerated ageing hypothesis, and additional factors, such as task strategy, may be central to processing speed impairments (Mathias et al., 2017). Although impairments in processing speed may be central and severe in PLS, processing speed may become an important feature in schizophrenia if it impairs functioning and outcomes over the course of the syndrome.

Because cognitive functioning is crucial in PLS, greater impairments in processing speed may impact areas of functioning, activities of daily living, and other outcomes in PLS. Evidence suggests that processing speed in schizophrenia may be more crucial for overall levels of functioning (Davies & Greenwood, 2020; Halverson et al., 2019), social functioning (Javed & Charles, 2018; Lahera et al., 2017), life satisfaction (Gutiérrez-Rojas et al., 2021), and, similar to my study in Chapter 5, QOL (Rekhi et al., 2023). Despite processing speed influencing these outcomes, cognition is seen to be independent or conditionally independent of positive symptoms (Rek-Owodziń et al., 2022; Ventura et al., 2010; Weinberger & Harrison, 2011), as also demonstrated in my study. Because processing speed and cognition in general have better predictive validity for these outcomes, and long-term outcomes or disability of schizophrenia (Harvey et al., 2019), cognition may have primacy over positive and negative symptoms, and processing speed may have primacy over other cognitive functions.

Although no consensus has been reached, the primacy of processing speed has been proposed in several other studies, including another recent study on network analysis (Abplanalp et al., 2023). Abplanalp et al. (2023) also identified that processing speed was a predictor variable for both social and non-social cognitive processes. In another study using a partial correlation network of cognition, psychopathology, and motor functions in schizophrenia, processing speed was closely associated and central to many other cognitive processes (Moura et al., 2021). This finding was also replicated in a later study by Moura et al. (2022). Given this, other authors have suggested that processing speed may underlie other cognitive processes (Abplanalp et al., 2023; Ojeda et al., 2012). Processing speed may be the central cognitive deficit for PLS, and once controlled for, group differences between PLS and HC may attenuate (Dickinson et al., 2007; Knowles et al., 2010; Ojeda et al., 2012).

Given that processing speed is most impaired in schizophrenia, that processing speed predicts and moderates other cognitive functions, and that functioning and outcomes of schizophrenia depend strongly on processing speed, the proposal that processing speed is the central cognitive function of schizophrenia is forwarded in this thesis (Abplanalp et al., 2023; Dickinson et al., 2007; Knowles et al., 2010; Ojeda et al., 2012). The following conjectures, based on this research and the general literature, are made in this thesis:

1. Processing speed is the largest cognitive impairment in schizophrenia.
2. Other cognitive functions depend primarily on processing speed.
3. Processing speed has a direct association with outcomes in schizophrenia, including functioning, QOL, and well-being.
4. Given these conjectures, processing speed is the prime cognitive impairment.

In the research by Heinrichs (2005), the authors suggested the primacy of cognition in schizophrenia, and in this thesis, I support the work by Abplanalp et al. (2023) on the notion of the primacy of processing speed as the prime cognitive impairment of schizophrenia. Processing speed can be included in a network alongside other indicators of cognition; it may even be necessary to include processing speed in SNs of schizophrenia because of its importance

(Briganti et al., 2023; Marcot, 2017). Measures of processing speed may also be used in clinical contexts to identify prognosis or functioning in PLS. SNs are rather new, and it may be possible to use processing speed in repeated measures of an individual if cognition or mental acuity is important to that individual. This thesis now focuses on developing a framework of SN for clinical applications, and processing speed may be a variable that could be included in these tools for their application to PLS.

7.2.2 On symptom networks of schizophrenia and mental illness

Although the primacy of processing speed conjecture is proposed, considerable research is needed to validate this, and it may take a long period before applied implications are realised. Alternatively, a clinical profile may be a more immediate application of SNs. In addition to the primacy of processing speed, a clinical profile can be constructed, and this thesis proposes the following method. A clinical profile is developed based on one individual’s longitudinal data and on measures that are important to the individual and the clinician. No prior template is used in a clinical profile. Assessments could be administered that reflect health needs rather than those specific to a mental disorder, such as schizophrenia. Once assessments have been conducted, the structure, parameters, symptom centrality, probability queries, and clustering can be used to inform clinicians about information pertinent to the individual, and this could be used to determine factors in which these elements are sensitive to change (Bringmann, 2021; Nelson et al., 2017). The network approach may be one solution to reintegrate symptoms or experiences into a broader context of influencing factors. Additionally, QOL, functioning, and well-being could be seen as nodes that mark abnormality or therapeutic goals, as opposed to the presence or absence of symptoms. From this, a personalised treatment plan can be established, with dynamic routine data collected over time to inform an individual's progress (Bringmann, 2021; Nelson et al., 2017). A clinical profile template to identify key areas to intervene on is given below.

1) Standard assessments with predictive validity for schizophrenia and assessments representing the person's needs (or symptoms to be addressed) are administered.
2) Assessments are repeated over time.
3) A BN is reconstructed on this longitudinal data.
4) Properties of the network are identified and utilised to gain insight into the complex relationships between symptoms or needs in PLS.
5) Latent variables given by the assessment developers can be included to provide severity scores.
6) The structure, parameters, symptom centrality, probability queries, and clustering are obtained.

7) Given the network's properties, nodes or variables are then nominated to be the target of an intervention, according to the client's needs.
8) Following an intervention, the network is updated with new data to incorporate changes to its structure or parameters.

The repeated assessments may need to be collected through ecological momentary assessment methods and introduce a dynamic model of the relationships to account for time dependencies. The number of assessments may include multiple assessments per day over months. The number of repeated assessments is not defined in BNs, and generally, the more data that is collected, the more complex the network can be and the less likely the network will contain false-positive and false-negative edges (Zuk et al., 2012). Ad-hoc sample size estimates of 20 participants per parameter have been proposed for SCMs, but this may not be an effective way to estimate sample size (Kline, 2023). There are methods available for BNs for sparse data, however (Scutari & Denis, 2021). Nevertheless, data could be collected multiple times a day over weeks or months.

In addition to this, given evidence from my study, it is essential to include latent variables in the model, which may predict responses in assessment variables. Including latent variables for an integrated model will likely improve the model's fit to the data while adding practical benefits (Kline, 2023). These hidden variables can be specified, named, and used as wellness measures. As it is assumed that latent variables cause observable variables, intervening on an observable variable represents an intervention on a latent variable (van Bork et al., 2021). The latent variables must be specified rather than data-driven, although model fit statistics can be produced on the imposed structure of the latent and observed variables (Kline, 2023). The advantages of using SCMs on structures found using a reconstructed BN are that it is a method which allows latent variables to be specified in the network.

Intervening on the network may focus on clusters of nodes or relationships between nodes, although it is likely that an intervention has an effect on the network as a whole, because of dependence structures and common factors associated with therapy (Bringmann et al., 2019; Schumacher et al., 2024). Intervening on an element of the network is likely to have more global than local effects on the network. The network following therapy may be used to identify whether the treatment has been successful. This treatment is more likely to be psychosocial than medical, unless positive symptoms, anxiety, depression, or other symptoms are the goal of treatment and can be treated with medication. In terms of aiming to intervene on one node, probability queries in BNs may help clinicians identify how intervening in one experience may be associated with a change in the expression of other experiences, such as QOL (Briganti et al., 2023). Networks can also be used to predict what may happen if there are changes to the network components (Heckerman, 1998). For example, a prediction could be made about the response of a person's QOL with schizophrenia after an intervention on processing speed using cognitive remediation. The person can identify key health domains to target, such as positive symptoms, cognition, and resilience, and data can be collected longitudinally through psychological assessments. Additionally, the researcher can identify symptoms that connect conditions or symptom clusters, named bridge symptoms (Jones et al., 2021a). Intervening on bridge symptoms, for example, could sever the connections between the expression of schizophrenia and depression (Jones et al., 2021a). However, the treatment goals do not necessarily need to be based on clinical symptoms.

An example of how a clinical profile is provided is next. An individual and clinician may identify that social skills, satisfactory employment, cognition, and QOL are important to address, with QOL being the most important consideration. Assessments for social skills, employment needs, cognition, and QOL are administered multiple times per day over several months using ecological momentary assessments. A dynamic BN is fitted using the subscales of these assessments. Like in Chapter 5, if QOL is dependent on employment, then the clinician could design a social work package to help the person obtain meaningful employment (Bouwmans et al., 2015; Patmisari et al., 2024). Like in Chapter 5, if the QOL is dependent on processing speed, cognitive remediation may be necessary for the individual (Vita et al., 2024). If QOL is dependent on social skills, social skills training may be implemented (Öngün et al., 2022). It may be better to intervene on multiple aspects of the person to facilitate better outcomes (Petkari et al., 2024), especially given the interdependency of variables in a network (Schumacher et al., 2024). Assessments can continue throughout the intervention, and the network may be refitted using the new data to determine if the relationships have changed or if further interventions are appropriate for the individual.

Using empirical data to optimise or predict outcomes, this method allows BNs to be used for precision medicine in evidence-based assessment and treatment. Previous research suggests that centrality statistics may be useful for personalised treatments (Cusack et al., 2025; Levinson et al., 2021), and I propose that it can also be based on conditional probability queries and shared treatment objectives found between the clinician and the client. The use of the term precision medicine herein represents differences or interventions tailored at the person level. Directed networks may help clinicians identify the dependency relationships between symptoms. In my study, I identified that processing speed was associated with general psychopathology in the PANSS and QOL. For a person living with schizophrenia, delusions or alogia may be the most central experience in the network. Hence, interventions could target that symptom and associated symptoms in the network. Alternatively, QOL may be featured as a key variable to intervene on. This may indicate that global functioning or QOL may be a better general target for treatment than simply focusing on positive symptoms.

Transitioning from symptom reduction to QOL and well-being outcomes could be suggested as a focal point of the use of a clinical profile and treatment in general. As suggested by van Os et al. (2019), services may transition in focus from symptom reduction to prioritising connectedness, empowerment, identity, resilience, meaning, hope, and optimism. Here, a meaningful life may be the core element in the recovery process (van Os et al., 2019). Wellbeing, global functioning, or QOL may be part of a more comprehensive network of influencing factors instead of the presence or absence of one or more symptoms (Pardeller et al., 2020). SN and integrated networks may be useful in transitioning from symptom reduction to broader health outcomes. This may benefit individuals who focus on meeting needs beyond just symptom reduction, such as social, cultural, occupational, well-being, or spiritual needs. Psychiatry has, for long periods, been organised so that conditions are diagnosable entities where practitioners provide evidence-based practice of symptom reduction at the group level (van Os et al., 2019). Marked by an inability to cure mental disorders like schizophrenia, the symptom reduction model may be disconnected from people's core psychological needs (van Os et al., 2019).

Functional precision medicine using integrated models and SNs may result in more effective management of schizophrenia and even identify risks and outcomes of schizophrenia (Manchia et al., 2020). Using machine learning in SNs may help as a predictive tool to optimise treatment and predict outcomes, leading to personalised trajectories of treatments based on individual needs (Manchia et al., 2020). Dynamic networks have already been conducted using ecological momentary assessment data from an individual with schizophrenia (Bak et al., 2016), and this illustrates one way in which clinicians can design a treatment plan with individuals that can be monitored and updated within a person to identify possible experiences to intervene on and outcome variables to measure (Nelson et al., 2017). Monitoring and predicting outcomes on a subset of variables that are important to a PLS may lead to a more holistic approach to treating mental illness, taking into consideration a broader and more complex interplay of clients' needs. As long as the concept can be assessed using methods or tools with good psychometric properties, a focus on clients' needs can be easily implemented in BN, which includes a dimension of time, representing an individual's personalised and dynamic model of health. There is an array of psychological interventions that can be implemented to address the various needs of individuals (Davidson et al., 2009; Fava & Tomba, 2009; Prochaska & Norcross, 2024), which could focus on elements of the network that the client and clinician identify as therapeutically important. This represents a reciprocal relationship between client and clinician, where empirical evidence and precision medicine are at the forefront of improving outcomes for PLS.

7.3 Limitations

The research in this thesis has several limitations due to the methodological or conceptual stance taken. Each study included in this thesis had specific limitations that may affect the outcomes reported. In the systematic review in Chapter 4, the most important limitation is that I excluded studies that included psychotic disorders other than schizophrenia, schizophreniform, and schizoaffective disorders. Several studies that motivated the systematic review were then unfortunately excluded (Isvoranu, van Borkulo, et al., 2017; Boyette et al., 2020). In terms of Chapter 5, it was not possible to identify whether processing speed is the predictor of all other cognitive processes in the population. Additionally, I labelled processing speed as the central cognitive impairment because it was the primary predictor variable. However, it was not most central on betweenness and closeness measures of centrality. It was highest in terms of degree, however. Regarding the research in Chapter 6, some networks were over-parameterised with two latent variables, given the sample size; therefore, I could not include a third latent variable for general psychopathology. The model would require a larger sample size to estimate the parameters in the SEM.

For limitations across studies, in chapters 5 and 6, I did not assess the assumptions of all regressions, which would add rigour in future studies. Furthermore, in chapters 5 and 6, I used the CATIE study, which may be less relevant than newer datasets for this thesis. Additionally, I did not use longitudinal data in chapters 5 and 6, where longitudinal data may have improved my ability to make inferences from a BN. Furthermore, I did not have the ability to infer causality on cross-sectional, non-experimental data I carried out the analysis on, despite using SEMs conducted in chapters 5 and 6. It is also not possible to identify if the reconstructed network proposed is the best-fitting network for the population.

In terms of broader limitations of this thesis, this thesis is primarily on Bayesian SNs of schizophrenia. Despite this, there were minimal clinical inferences made for schizophrenia in Chapter 6. Another limitation of this thesis is that I could not share the datasets used for the studies in this thesis because of contractual requirements. Sharing data would have made replication of the studies in this thesis straightforward. Another key limitation is that since writing this thesis, the Food and Drug Administration has approved a drug for schizophrenia that may have moderate effectiveness in treating cognition in schizophrenia (Bukhari et al., 2025; Torjesen, 2024). This drug was approved on the 26th of September 2024, and the evidence for the pharmacological treatment of cognition was not described in this thesis (U.S. Food and Drug Administration, 2025).

7.4 Directions for future research

This thesis has been written to fulfil the requirements of the Doctor of Philosophy degree, and throughout the degree, three key potential research ideas have been identified that may be useful in future research on SNs or SNs of PLS. This includes reviewing the published systematic review included in this thesis in Chapter 4 (Buchwald et al., 2024) to identify whether processing speed is more central than other cognitive processes in the selected studies, an SN of people ultra-high-risk of schizophrenia in those who transition or do not transition to the experience of florid symptoms of schizophrenia, and a new diagnostic approach using SN.

Firstly, in this thesis is a proposition of the primacy of processing speed over other cognitive processes, in congruence with other research in this area (Abplanalp et al., 2023; Bowie & Harvey, 2006; Buchwald et al., 2024; Green & Harvey, 2014; Heinrichs, 2005; Kahn & Keefe, 2013; Kharawala et al., 2022). The systematic review published and included in this thesis did not look explicitly at which cognitive process was most central across the studies that included various cognitive processes in their SN. Future research could implement a systematic review of SNs of schizophrenia that includes components of cognition to explicitly compare processing speed to other cognitive functions. This would assist with the verification that processing speed is the prime cognitive impairment in PLS.

The second proposal for future research is to conduct a BN on people who are ultra-high risk of schizophrenia, who do or do not transition to an identified schizophrenia diagnosis. Several key datasets, including the NAPLS 3 study (Addington et al., 2022) and the CAARMS study (Nelson et al., 2013; Yung et al., 2005), may be useful to identify predictors of the transition to schizophrenia. BNs are applicable in this regard because the orientation of some predictor and response relationships is determined using data-driven mechanisms (Pearl, 1985; Scutari & Denis, 2021). Rather than specifying hypotheses between predictors and diagnosis a priori, BNs may be better at learning more complex relationships between predictors of diagnosis. Treating the BN as an expert system may help determine the reduction in the probability of diagnosis given an event. The event may be a psychotherapeutic intervention or the presence of a risk factor. Diagnosis of schizophrenia is dichotomous and hence some available software may need to be adapted to fit logistic regressions (Rosseel, 2012; Scutari, 2017). Alternatively, mixed graphical models may be used, but the orientation of nodes as predictor and response variables can be ambiguous (Haslbeck & Waldorp, 2015).

The last proposal for research in future investigations is the use of SNs as diagnostic tools. There has been a lengthy critique of the diagnostic approach using the medical model as a framework for psychopathology, where signs and symptoms are either present or absent within an individual, and several criteria must be met for a diagnosis (Lahey et al., 2022). This diagnostic approach, adopted in the DSM-5 (American Psychiatric Association, 2022) and ICD-11 (World Health Organization, 2019), represents a knowledge-derived rule-based system, and initially, BNs were developed to utilise probability inferences to make decisions, an alternative to knowledge-derived rule-based systems (Pearl, 2018). This diagnostic process may be applied through systems of symptoms recognised to underlie a condition. This diagnostic tool may utilise the dimensional nature of symptoms and the complex interrelationships between symptoms, integrating an LVM and SN, as conducted in Chapter 6. This would be an extension of the dimensional approach to psychopathology (Widiger & Samuel, 2005). Cut-off values or the fit of the model, dependence relationships between nodes (dependency, conditional independence), the centrality of nodes (betweenness, closeness, strength), or clustering may be proposed as indicators of a diagnosis. Because this proposal is new, limited research has identified it as a proposed alternative to diagnostic manuals. Consequently, a framework has not been established. Although it may be theoretically possible, the effectiveness of this approach has not been tested to determine whether it provides better applied outcomes overall, in terms of its diagnostic efficacy. This approach to diagnosis would likely require a substantial international investment to test its feasibility and efficacy.

7.5 Conclusion

Schizophrenia is a heterogeneous syndrome that disrupts functioning across a broad range of domains. Many PLS experience positive, negative, and disorganised symptoms, and cognitive and functional impairments for decades of their lives (Charlson et al., 2018). Innovations in theoretical and applied research on schizophrenia are currently being developed to improve outcomes of the schizophrenia syndrome, including the development of novel statistical methods such as SNs. SNs may have strong utility to model symptoms of schizophrenia due to the heterogeneity and complexity in the aetiology, presentations, and outcomes of PLS (Isvoranu et al., 2018). Network methods may be useful for modelling complex relationships between clinical variables, cognitive processes, functioning, QOL, well-being, and other variables pertinent to PLS. Given the applicability of SN to PLS, this thesis generally aimed to provide research on SNs of schizophrenia to improve the understanding of the syndrome and support later research to improve outcomes of PLS.

Several specific aims of this thesis were proposed. This thesis aimed to: survey current and past literature on schizophrenia and SNs; provide a systematic review of SNs of PDS, looking at the common themes and gaps in the literature; conduct a SN of cognitive, clinical, and QOL variables in PDS; provide evidence for the complexity principle of the NTMD, by comparing a LVM to an integrated network and LVM (Borsboom, 2017); to identify the importance of specific cognitive processes by extending on previous research (Abplanalp et al., 2023); and expand on novel applications of using SNs as a clinical tool (Bringmann, 2021). This research supports a broader body of evidence of schizophrenia and SNs.

This thesis identified three major outcomes. The systematic review found that cognition and functioning are central to schizophrenia. This supports the notion that schizophrenia is a disorder of cognition (Heinrichs, 2005; Kahn & Keefe, 2013). In the second study, I found that processing speed was a predictor of other cognitive processes, negative symptoms, and QOL. This supports a similar outcome found by Abplanalp et al. (2023), who identified that processing speed may be the most important cognitive impairment in schizophrenia. In the third study, the model fit statistics of an integrated LVM and network model were found to fit better than the fit of a LVM alone. The integrated model also fit better than the network model, as indicated by several model fit statistics. This suggests that introducing edges in an LVM improves model fit and provides partial support for the complexity principle proposed by Borsboom (2017). It also suggests that adding latent variables may be key when conducting an SN (Briganti et al., 2023; Scutari & Denis, 2021).

The three studies provide three different approaches to the study of SN and schizophrenia. This evidence was synthesised with broader evidence of SNs and schizophrenia, identifying two propositions. The first proposition of this thesis expands on the primacy of cognition in schizophrenia (Heinrichs, 2005; Kahn & Keefe, 2013) and proposes that processing speed is the prime cognitive impairment, in agreement with the findings by Abplanalp et al. (2023). This thesis proposes that processing speed is the most severe cognitive impairment of schizophrenia, that other cognitive functions depend the most on processing speed, and processing speed has a direct association with outcomes of schizophrenia, more than other cognitive functions. These conjectures align with earlier evidence of schizophrenia (Abplanalp et al., 2023; Davies & Greenwood, 2020; Dickinson et al., 2007; Gutiérrez-Rojas et al., 2021; Halverson et al., 2019; Javed & Charles, 2018; Lahera et al., 2017; Rekhi et al., 2023; Schaefer et al., 2013). Secondly, some studies have employed ecological momentary assessment to investigate symptoms in PDS (Bak et al., 2016). I propose, in line with the arguments by Bringmann (2021) and the research by Bak et al. (2016), a process to utilise SNs as a clinical profile. The measures in this clinical profile include assessments deemed important to both the client and the clinician. Interventions can then be developed that are tailored to the individual's needs, using evidence-based psychotherapy and data-driven SNs to guide intervention points. The clinical profile aims to be an adjunct assessment tool for the treatment of schizophrenia and other mental disorders, and may emphasise a transition from a symptom reduction model to a well-being approach to the implementation of interventions (van Os et al., 2019). The social, cognitive, affective, neuropsychological, and clinical complexity of mental disorders like schizophrenia can be explicitly introduced into a tailored treatment regime.

This thesis highlights the need for an integrative and complex understanding of the schizophrenia syndrome, and that cognition and processing speed are central in schizophrenia. The SN is designed to accommodate the complex interplay between cognition, symptomatology, functional, and QOL outcomes. This thesis and earlier propositions (Abplanalp & Green, 2022; Bringmann, 2021) aim to improve the understanding of schizophrenia, and the use of SNs may support better outcomes of schizophrenia in the future. This thesis demonstrates that a complex systems approach, a holistic or integrated approach, can be used to identify new discoveries using this methodological approach.

Despite rapid advances in research and methodology, the development of innovative technology in the treatment and management of schizophrenia has not reached fruition yet, and older models of health predominate in the treatment models. Given an accumulation of research, the integration of robust, innovative methods in practice may, in time, introduce new perspectives, tools, and treatment opportunities for people experiencing severe mental disorders, such as schizophrenia. This era of new technologies is needed to revolutionise the care of the schizophrenia syndrome, since the development of antipsychotic medicines and community care (Shrivastava & Johnston, 2010). Viewing schizophrenia as a complex system of symptoms, a system of experiences, not as a static and discrete construct, is one step in advancing the research for people with schizophrenia. Being cognisant of the experiences of schizophrenia means understanding that people with schizophrenia can experience symptoms and dysfunction for decades. It is hoped that this thesis leads to outcomes that change the experiences of people with schizophrenia forever, a change in life that occurs, perhaps, for a second time.

References

Abplanalp, S. J., & Green, M. F. (2022). Symptom structure in schizophrenia: Implications of latent variable modeling vs network analysis. *Schizophrenia Bulletin*, *48*(3), 538-543. https://doi.org/10.1093/schbul/sbac020

Abplanalp, S. J., Lee, J., Horan, W. P., Kern, R. S., Penn, D. L., & Green, M. F. (2023). A Bayesian network approach to social and nonsocial cognition in schizophrenia: Are some domains more fundamental than others? *Schizophrenia Bulletin*, *49*(4), 997-1006. https://doi.org/10.1093/schbul/sbad012

Addington, D., Addington, J., & Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: The Calgary Depression Scale. *The British Journal of Psychiatry*, *163*(S22), 39-44. https://doi.org/10.1192/S0007125000292581

Addington, J., & Addington, D. (1991). Positive and negative symptoms of schizophrenia: Their course and relationship over time. *Schizophrenia Research*, *5*(1), 51-59. https://doi.org/10.1016/0920-9964(91)90053-T

Addington, J., Addington, D., & Maticka-Tyndale, E. (1991). Cognitive functioning and positive and negative symptoms in schizophrenia. *Schizophrenia Research*, *5*(2), 123-134. https://doi.org/10.1016/0920-9964(91)90039-T

Addington, J., Liu, L., Brummitt, K., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., McGlashan, T. H., & Perkins, D. O. (2022). North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. *Schizophrenia Research*, *243*, 262-267. https://doi.org/10.1016/j.schres.2020.04.010

Ajnakina, O., Stubbs, B., Francis, E., Gaughran, F., David, A. S., Murray, R. M., & Lally, J. (2020). Hospitalisation and length of hospital stay following first-episode psychosis: Systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*, *50*(6), 991-1001. https://doi.org/10.1017/S0033291719000904

Al-Issa, I. (1995). The illusion of reality or the reality of illusion: Hallucinations and culture. *The British Journal of Psychiatry*, *166*(3), 368-373. https://doi.org/10.1192/bjp.166.3.368

Aleman, A., & Larøi, F. (2008). *Hallucinations: The science of idiosyncratic perception*. American Psychological Association. https://doi.org/10.1037/11751-000

Alloza, C., Cox, S. R., Duff, B., Semple, S. I., Bastin, M. E., Whalley, H. C., & Lawrie, S. M. (2016). Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia. *Psychiatry Research: Neuroimaging*, *254*, 26-33. https://doi.org/10.1016/j.pscychresns.2016.05.008

Altamura, C., Fagiolini, A., Galderisi, S., Rocca, P., & Rossi, A. (2014). Schizophrenia today: Epidemiology, diagnosis, course and models of care. *Journal of Psychopathology*, *20*, 223-243. https://old.jpsychopathol.it/wp-content/uploads/2015/07/01_schizofrenia-inglese1.pdf

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). https://psychiatryonline.org/doi/10.1176/ajp.152.8.1228

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

American Psychiatric Association. (2022). *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.). https://doi.org/10.1176/appi.books.9780890425787

American Psychological Association. (2020). *Publication manual of the American Psychological Association* (7th ed.). American Psychological Association. https://doi.org/10.1037/0000165-000

Amore, M., Murri, M. B., Calcagno, P., Rocca, P., Rossi, A., Aguglia, E., Bellomo, A., Blasi, G., Carpiniello, B., & Cuomo, A. (2020). The association between insight and depressive symptoms in schizophrenia: Undirected and Bayesian network analyses. *European Psychiatry*, *63*(1), 1-9. https://doi.org/10.1192/j.eurpsy.2020.45

an der Heiden, W., Leber, A., & Häfner, H. (2016). Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(5), 387-396. https://doi.org/10.1007/s00406-016-0697-2

Anand, M., Gonzalez, A., Guichard, F., Kolasa, J., & Parrott, L. (2010). Ecological systems as complex systems: Challenges for an emerging science. *Diversity*, *2*(3), 395-410. https://doi.org/10.3390/d2030395

Andreasen, N. C., & Olsen, S. (1982). Negative v positive schizophrenia: Definition and validation. *Archives of General Psychiatry*, *39*(7), 789-794. https://doi.org/10.1001/archpsyc.1982.04290070025006

Angelin-Bonnet, O., Biggs, P. J., & Vignes, M. (2019). Gene regulatory networks: A primer in biological processes and statistical modelling. In G. Sanguinetti & V. A. Huynh-Thu (Eds.), *Gene regulatory networks: Methods and protocols* (pp. 347-383). Springer New York. https://doi.org/10.1007/978-1-4939-8882-2_15

Anzellotti, F., Onofrj, V., Maruotti, V., Ricciardi, L., Franciotti, R., Bonanni, L., Thomas, A., & Onofrj, M. (2011). Autoscopic phenomena: Case report and review of literature. *Behavioral and Brain Functions*, *7*(1), 1-11. https://doi.org/10.1186/1744-9081-7-2

Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., & Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort. *Schizophrenia Research*, *168*(1-2), 84-91. https://doi.org/10.1016/j.schres.2015.07.021

Awad, A. G. (1993). Subjective response to neuroleptics in schizophrenia. *Schizophrenia Bulletin*, *19*(3), 609-618. https://doi.org/10.1093/schbul/19.3.609

Baba, Y., Nemoto, T., Tsujino, N., Yamaguchi, T., Katagiri, N., & Mizuno, M. (2017). Stigma toward psychosis and its formulation process: Prejudice and discrimination against early stages of schizophrenia. *Comprehensive Psychiatry*, *73*, 181-186. https://doi.org/10.1016/j.comppsych.2016.11.005

Badal, V. D., Parrish, E. M., Holden, J. L., Depp, C. A., & Granholm, E. (2021). Dynamic contextual influences on social motivation and behavior in schizophrenia: A case-control network analysis. *NPJ Schizophrenia*, *7*(1), 1-9. https://doi.org/10.1038/s41537-021-00189-6

Bagney, A., Dompablo, M., Santabárbara, J., Moreno-Ortega, M., Lobo, A., Jimenez-Arriero, M.-A., Palomo, T., & Rodriguez-Jimenez, R. (2015). Are negative symptoms really related to cognition in schizophrenia? *Psychiatry Research*, *230*(2), 377-382. https://doi.org/10.1016/j.psychres.2015.09.022

Bailey, T., Alvarez-Jimenez, M., Garcia-Sanchez, A. M., Hulbert, C., Barlow, E., & Bendall, S. (2018). Childhood trauma is associated with severity of hallucinations and delusions in psychotic disorders: A systematic review and meta-analysis. *Schizophrenia Bulletin*, *44*(5), 1111-1122. https://doi.org/10.1093/schbul/sbx161

Bak, M., Drukker, M., Hasmi, L., & Van Jim, O. S. (2016). An n=1 clinical network analysis of symptoms and treatment in psychosis. *PLOS ONE*, *11*(9), 1-15. https://doi.org/10.1371/journal.pone.0162811

Barch, D. M., Karcher, N., & Moran, E. (2022). Reinventing schizophrenia – Embracing complexity and complication. *Schizophrenia Research*, *242*, 7-11. https://doi.org/10.1016/j.schres.2021.11.037

Barrett, P. (2007). Structural equation modelling: Adjudging model fit. *Personality and Individual Differences*, *42*(5), 815-824. https://doi.org/10.1016/j.paid.2006.09.018

Bell, M., Milstein, R., Beam-Goulet, J., Lysaker, P., & Cicchetti, D. (1992). The Positive and Negative Syndrome Scale and the Brief Psychiatric Rating Scale: Reliability, comparability, and predictive validity. *The Journal of Nervous and Mental Disease*, *180*(11), 723-728. https://journals.lww.com/jonmd/abstract/1992/11000/the_positive_and_negative_syndrome_scale_and_the.7.aspx

Bell, M. D., Lysaker, P. H., Milstein, R. M., & Beam-Goulet, J. L. (1994). Concurrent validity of the cognitive component of schizophrenia: Relationship of PANSS scores to neuropsychological assessments. *Psychiatry Research*, *54*(1), 51-58. https://doi.org/10.1016/0165-1781(94)90064-7

Benfer, N., Bardeen, J. R., Cero, I., Kramer, L. B., Whiteman, S. E., Rogers, T. A., Silverstein, M. W., & Weathers, F. W. (2018). Network models of posttraumatic stress symptoms across trauma types. *Journal of Anxiety Disorders*, *58*, 70-77. https://doi.org/10.1016/j.janxdis.2018.07.004

Benrimoh, D., Dlugunovych, V., Wright, A. C., Phalen, P., Funaro, M. C., Ferrara, M., Powers III, A. R., Woods, S. W., Guloksuz, S., & Yung, A. R. (2024). On the proportion of patients who experience a prodrome prior to psychosis onset: A systematic review and meta-analysis. *Molecular Psychiatry*, *29*, 1361–1381. https://doi.org/10.1038/s41380-024-02415-w

Berta, A., Miguel Ángel, C., Clara, G.-S., & Rubén, H. (2022). A bibliometric analysis of 10 years of research on symptom networks in psychopathology and mental health. *Psychiatry Research*, *308*, 1-9. https://doi.org/10.1016/j.psychres.2021.114380

Besag, J. (1974). Spatial interaction and the statistical analysis of lattice systems. *Journal of the Royal Statistical Society: Series B (Methodological)*, *36*(2), 192-225. https://doi.org/10.1111/j.2517-6161.1974.tb00999.x

Best, M. W., & Bowie, C. R. (2017). A review of cognitive remediation approaches for schizophrenia: From top-down to bottom-up, brain training to psychotherapy. *Expert Review of Neurotherapeutics*, *17*(7), 713-723. https://doi.org/10.1080/14737175.2017.1331128

Biedermann, F., & Fleischhacker, W. W. (2016). Psychotic disorders in DSM-5 and ICD-11. *CNS Spectrums*, *21*(4), 349-354. https://doi.org/10.1017/S1092852916000316

Birkeland, M. S., Greene, T., & Spiller, T. R. (2020). The network approach to posttraumatic stress disorder: A systematic review. *European Journal of Psychotraumatology*, *11*(1), 1-14. https://doi.org/10.1080/20008198.2019.1700614

Bishop, R. C. (2011). Metaphysical and epistemological issues in complex systems. In C. Hooker (Ed.), *Philosophy of complex systems* (Vol. 10, pp. 105-136). North-Holland. https://doi.org/10.1016/B978-0-444-52076-0.50003-1

Bleuler, E. (1908). Die Prognose der Dementia praecox (Schizophreniegruppe) [The prognosis of dementia praecox (schizophrenia group)]. *Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin*, *31*, 436-480. https://cir.nii.ac.jp/crid/1570854175999818112

Boldi, P., & Vigna, S. (2014). Axioms for centrality. *Internet Mathematics*, *10*(3-4), 222-262. https://doi.org/10.1080/15427951.2013.865686

Bombassaro, T., Carrilho, C. G., Peixoto, C., Alves, G. S., Kahn, J. P., Nardi, A. E., & Veras, A. B. (2023). Cognition in schizophrenia: A systematic review of Wechsler Adult Intelligence Scale studies. *The Primary Care Companion for CNS Disorders*, *25*(5), 22r03456. https://doi.org/10.4088/PCC.22r03456

Bonacich, P., & Lu, P. (2012). *Introduction to mathematical sociology*. Princeton University Press. https://doi.org/10.1515/9781400842452-015

Borsboom, D. (2008a). Latent variable theory. *Measurement: Interdisciplinary Research and Perspectives*, *6*(1-2), 25-53. https://doi.org/10.1080/15366360802035497

Borsboom, D. (2008b). Psychometric perspectives on diagnostic systems. *Journal of Clinical Psychology*, *64*(9), 1089-1108. https://doi.org/10.1002/jclp.20503

Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, *16*(1), 5-13. https://doi.org/10.1002/wps.20375

Borsboom, D., & Cramer, A. O. (2013). Network analysis: An integrative approach to the structure of psychopathology. *Annual Review of Clinical Psychology*, *9*, 91-121. https://doi.org/10.1146/annurev-clinpsy-050212-185608

Borsboom, D., Fried, E. I., Epskamp, S., Waldorp, L. J., van Borkulo, C. D., van der Maas, H. L., & Cramer, A. O. (2017). False alarm? A comprehensive reanalysis of "Evidence that psychopathology symptom networks have limited replicability" by Forbes, Wright, Markon, and Krueger (2017). *Journal of Abnormal Psychology*, *126*(7). https://doi.org/10.1037/abn0000276

Borsboom, D., Mellenbergh, G. J., & Van Heerden, J. (2003). The theoretical status of latent variables. *Psychological Review*, *110*(2), 203-219. https://doi.org/10.1037/0033-295X.110.2.203

Bouwmans, C., Caroline, d. S., L., M. C., & and Hakkaart-van Roijen, L. (2015). Employment and the associated impact on quality of life in people diagnosed with schizophrenia.

Neuropsychiatric Disease and Treatment, *11*, 2125-2142. https://doi.org/10.2147/NDT.S83546

Bowie, C. R., & Harvey, P. D. (2006). Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatric Disease and Treatment*, *2*(4), 531-536. https://doi.org/10.2147/nedt.S24531

Brandt, J. (1991). The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. *The Clinical Neuropsychologist*, *5*(2), 125-142. https://doi.org/10.1080/13854049108403297

Brandt, L., Henssler, J., Müller, M., Wall, S., Gabel, D., & Heinz, A. (2019). Risk of psychosis among refugees: A systematic review and meta-analysis. *JAMA Psychiatry*, *76*(11), 1133-1140. https://doi.org/10.1001/jamapsychiatry.2019.1937

Brasso, C., Bellino, S., Bozzatello, P., Del Favero, E., Montemagni, C., & Rocca, P. (2023). Inter-relationships among psychopathology, cognition, and real-life functioning in early and late phase schizophrenia: A network analysis approach. *Schizophrenia Research*, *256*, 8-16. https://doi.org/10.1016/j.schres.2023.04.011

Briganti, G., Scutari, M., & McNally, R. J. (2023). A tutorial on Bayesian networks for psychopathology researchers. *Psychological Methods*, *28*(4), 947-961. https://doi.org/10.1037/met0000479

Bringmann, L. F. (2021). Person-specific networks in psychopathology: Past, present, and future. *Current Opinion in Psychology*, *41*, 59-64. https://doi.org/10.1016/j.copsyc.2021.03.004

Bringmann, L. F., Albers, C., Bockting, C., Borsboom, D., Ceulemans, E., Cramer, A., Epskamp, S., Eronen, M. I., Hamaker, E., & Kuppens, P. (2022). Psychopathological networks: Theory, methods and practice. *Behaviour Research and Therapy*, *149*, 1-15. https://doi.org/10.1016/j.brat.2021.104011

Bringmann, L. F., Elmer, T., Epskamp, S., Krause, R. W., Schoch, D., Wichers, M., Wigman, J. T., & Snippe, E. (2019). What do centrality measures measure in psychological networks? *Journal of Abnormal Psychology*, *128*(8), 892-903. https://doi.org/10.1037/abn0000446

Bringmann, L. F., & Eronen, M. I. (2018). Don't blame the model: Reconsidering the network approach to psychopathology. *Psychological Review*, *125*(4), 606-615. https://doi.org/10.1037/rev0000108

Brown, R. (2001). Australian Indigenous mental health. *Australian and New Zealand Journal of Mental Health Nursing*, *10*(1), 33-41. https://doi.org/10.1046/j.1440-0979.2001.00189.x

Brusco, M. J., Steinley, D., Hoffman, M., Davis-Stober, C., & Wasserman, S. (2019). On Ising models and algorithms for the construction of symptom networks in psychopathological research. *Psychological Methods*, *24*(6), 735-753. https://doi.org/10.1037/met0000207

Buchanan, R. W., & Carpenter, W. T. (1994). Domains of psychopathology: An approach to the reduction of heterogeneity in schizophrenia. *The Journal of Nervous and Mental Disease*, *182*(4), 193-204. https://doi.org/10.1097/00005053-199404000-00001

Buchwald, K., Narayanan, A., Siegert, R. J., Vignes, M., Arrowsmith, K., & Sandham, M. (2024). Centrality statistics of symptom networks of schizophrenia: A systematic review. *Psychological Medicine*, *54*(6), 1061-1073. https://doi.org/10.1017/S003329172300363X

Bukhari, S. M. R., Btool, S., Abbas, J., Hussain, A., Mehdi, H., & Raza, M. (2025). Cobenfy (xanomeline-trospium): A breakthrough FDA-approved therapy redefining schizophrenia treatment. *Annals of Medicine and Surgery*, 1-5. https://doi.org/10.1097/MS9.0000000000003309

Callaghan, R. C., Cunningham, J. K., Allebeck, P., Arenovich, T., Sajeev, G., Remington, G., Boileau, I., & Kish, S. J. (2012). Methamphetamine use and schizophrenia: A population-based cohort study in California. *American Journal of Psychiatry*, *169*(4), 389-396. https://doi.org/10.1176/appi.ajp.2011.10070937

Cantor-Graae, E., & Selten, J.-P. (2005). Schizophrenia and migration: A meta-analysis and review. *American Journal of Psychiatry*, *162*(1), 12-24. https://doi.org/10.1176/appi.ajp.162.1.12

Carbon, M., & Correll, C. U. (2014). Thinking and acting beyond the positive: The role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrums*, *19*(S1), 35-53. https://doi.org/10.1017/S1092852914000601
Carpenter, W. T., Jr. (2007). Schizophrenia: Disease, syndrome, or dimensions? *Family Process*, *46*(2), 199-206. https://doi.org/10.1111/j.1545-5300.2007.00204.x
Castillejos, M., Martín-Pérez, C., & Moreno-Küstner, B. (2018). A systematic review and meta-analysis of the incidence of psychotic disorders: The distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level. *Psychological Medicine*, *48*(13), 2101-2115. https://doi.org/10.1017/S0033291718000235
Cella, M., Preti, A., Edwards, C., Dow, T., & Wykes, T. (2017). Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis. *Clinical Psychology Review*, *52*, 43-51. https://doi.org/10.1016/j.cpr.2016.11.009
Charernboon, T. (2021). Interplay among positive and negative symptoms, neurocognition, social cognition, and functional outcome in clinically stable patients with schizophrenia: A network analysis. *F1000Research*, *10*, 1-21. https://doi.org/10.12688/f1000research.74385.3
Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., McGrath, J. J., & Whiteford, H. A. (2018). Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophrenia Bulletin*, *44*(6), 1195-1203. https://doi.org/10.1093/schbul/sby058
Cheng, J., Li, T., Levina, E., & Zhu, J. (2017). High-dimensional mixed graphical models. *Journal of Computational and Graphical Statistics*, *26*(2), 367-378. https://doi.org/10.1080/10618600.2016.1237362
Cheng, S. C., & Schepp, K. G. (2016). Early intervention in schizophrenia: A literature review. *Archives of Psychiatric Nursing*, *30*(6), 774-781. https://doi.org/10.1016/j.apnu.2016.02.009
Chickering, D. M. (2002). Learning equivalence classes of Bayesian-network structures. *The Journal of Machine Learning Research*, *2*(3), 445-498. https://doi.org/10.1162/153244302760200696
Choi, J., Yoon, H.-J., Park, J. H., Nakagami, Y., Kubota, C., Inada, T., Kato, T. A., Yang, S.-Y., Lin, S.-K., & Chong, M.-Y. (2022). Network analysis-based disentanglement of the symptom heterogeneity in Asian patients with schizophrenia: Findings from the research on Asian psychotropic prescription patterns for antipsychotics. *Journal of Personalized Medicine*, *12*(1), 1-13. https://doi.org/10.3390/jpm12010033
Christensen, A. P., Garrido, L. E., & Golino, H. (2023). Unique variable analysis: A network psychometrics method to detect local dependence. *Multivariate Behavioral Research*, *58*(6), 1165-1182. https://doi.org/10.1080/00273171.2023.2194606
Christensen, A. P., Gross, G. M., Golino, H. F., Silvia, P. J., & Kwapil, T. R. (2019). Exploratory graph analysis of the Multidimensional Schizotypy Scale. *Schizophrenia Research*, *206*, 43-51. https://doi.org/10.1016/j.schres.2018.12.018
Chung, M. K. (2019). *Brain network analysis*. Cambridge University Press. https://doi.org/10.1017/9781316882610
Claeskens, G., & Hjort, N. L. (2012). *Model selection and model averaging*. Cambridge University Press. https://doi.org/10.1017/CBO9780511790485
Clemmensen, L., Vernal, D. L., & Steinhausen, H.-C. (2012). A systematic review of the long-term outcome of early onset schizophrenia. *BMC Psychiatry*, *12*, 1-16. https://doi.org/10.1186/1471-244X-12-150
Contreras, A., Nieto, I., Valiente, C., Espinosa, R., & Vazquez, C. (2019). The study of psychopathology from the network analysis perspective: A systematic review. *Psychotherapy and Psychosomatics*, *88*(2), 71-83. https://doi.org/10.1159/000497425
Cornblatt, B. A., Risch, N. J., Faris, G., Friedman, D., & Erlenmeyer-Kimling, L. (1988). The Continuous Performance Test, Identical Pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Research*, *26*(2), 223-238. https://doi.org/10.1016/0165-1781(88)90076-5
Correll, C. U., Abi-Dargham, A., & Howes, O. (2022). Emerging treatments in schizophrenia. *The Journal of Clinical Psychiatry*, *83*(1), 1-13. https://doi.org/10.4088/JCP.SU21024IP1

Correll, C. U., & Howes, O. D. (2021). Treatment-resistant schizophrenia: Definition, predictors, and therapy options. *The Journal of Clinical Psychiatry*, *82*(5), 1-9. https://doi.org/10.4088/JCP.MY20096AH1C

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric Disease and Treatment*, *16*, 519-534. https://doi.org/10.2147/NDT.S225643

Cortes-Briones, J. A., Tapia-Rivas, N. I., D'Souza, D. C., & Estevez, P. A. (2022). Going deep into schizophrenia with artificial intelligence. *Schizophrenia Research*, *245*, 122-140. https://doi.org/10.1016/j.schres.2021.05.018

Cotter, J., Zabel, E., French, P., & Yung, A. R. (2017). Prolonged duration of untreated psychosis: A problem that needs addressing. *Early Intervention in Psychiatry*, *11*(3), 263-268. https://doi.org/10.1111/eip.12308

Cramer, A. O., Waldorp, L. J., Van Der Maas, H. L., & Borsboom, D. (2010). Comorbidity: A network perspective. *Behavioral and Brain Sciences*, *33*(2-3), 137-150. https://doi.org/10.1017/S0140525X09991567

Crane, H., & Dempsey, W. (2021). A statistical framework for modern network science. *Statistical Science*, *36*(1), 51-67. https://doi.org/10.1214/19-STS759

Crawford, W., & Lamarre Jean, E. (2021). *Structural equation modelling*. Oxford University Press. https://doi.org/10.1093/acrefore/9780190224851.013.232

Cross, G. R., & Jain, A. K. (1983). Markov random field texture models. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *1*, 25-39. https://doi.org/10.1109/TPAMI.1983.4767341

Cunningham, T., Hoy, K., & Shannon, C. (2016). Does childhood bullying lead to the development of psychotic symptoms? A meta-analysis and review of prospective studies. *Psychosis*, *8*(1), 48-59. https://doi.org/10.1080/17522439.2015.1053969

Cusack, C. E., Sandoval-Araujo, L. E., Hernández, J. C., Pennesi, J.-L., Lazarus, G., Levinson, C. A., & Fisher, A. J. (2025). What's strength centrality got to do with it? Examining the stability of central symptoms across symptom ensembles and time in idiographic networks. *Journal of Psychopathology and Clinical Science*. Advance online publication. https://doi.org/10.1037/abn0001005

Cuthbert, B. N., & Morris, S. E. (2021). Evolving concepts of the schizophrenia spectrum: A research domain criteria perspective. *Frontiers in Psychiatry*, *12*, 1-6. https://doi.org/10.3389/fpsyt.2021.641319

Dal Santo, F., Fonseca-Pedrero, E., García-Portilla, M. P., González-Blanco, L., Sáiz, P. A., Galderisi, S., Giordano, G. M., & Bobes, J. (2022). Searching for bridges between psychopathology and real-world functioning in first-episode psychosis: A network analysis from the OPTiMiSE trial. *European Psychiatry*, *65*(1), 1-10. https://doi.org/10.1192/j.eurpsy.2022.25

Dash, D., & Cooper, G. F. (2004). Model averaging for prediction with discrete Bayesian networks. *Journal of Machine Learning Research*, *5*, 1177-1203. https://jmlr.org/papers/volume5/dash04a/dash04a.pdf

Davidson, L., Rowe, M., Tondora, J., O'Connell, M. J., & Lawless, M. S. (2009). *A practical guide to recovery-oriented practice: Tools for transforming mental health care*. Oxford University Press New York. https://global.oup.com/academic/product/a-practical-guide-to-recovery-oriented-practice-9780195304770

Davies, C., Segre, G., Estradé, A., Radua, J., De Micheli, A., Provenzani, U., Oliver, D., de Pablo, G. S., Ramella-Cravaro, V., & Besozzi, M. (2020). Prenatal and perinatal risk and protective factors for psychosis: A systematic review and meta-analysis. *The Lancet Psychiatry*, *7*(5), 399-410. https://doi.org/10.1016/S2215-0366(20)30057-2

Davies, G., & Greenwood, K. (2020). A meta-analytic review of the relationship between neurocognition, metacognition and functional outcome in schizophrenia. *Journal of Mental Health*, *29*(5), 496-505. https://doi.org/10.1080/09638237.2018.1521930

De Carvalho, J., & Chima, F. O. (2014). Applications of structural equation modeling in social sciences research. *American International Journal of Contemporary Research*, *4*(1), 6-11. https://api.semanticscholar.org/CorpusID:30164675

de Leede-Smith, S., & Barkus, E. (2013). A comprehensive review of auditory verbal hallucinations: Lifetime prevalence, correlates and mechanisms in healthy and clinical individuals. *Frontiers in Human Neuroscience*, *7*, 1-25. https://doi.org/10.3389/fnhum.2013.00367

Dempster, A. P. (1972). Covariance selection. *Biometrics*, *28*(1), 157-175. https://doi.org/10.2307/2528966

Demyttenaere, K., Anthonis, E., Acsai, K., & Correll, C. U. (2022a). Depressive symptoms and PANSS symptom dimensions in patients with predominant negative symptom schizophrenia: A network analysis. *Frontiers in Psychiatry*, *13*, 1-8. https://doi.org/10.3389/fpsyt.2022.795866

Demyttenaere, K., Leenaerts, N., Acsai, K., Sebe, B., Laszlovszky, I., Barabássy, Á., Fonticoli, L., Szatmári, B., Earley, W., Németh, G., & Correll, C. U. (2022b). Disentangling the symptoms of schizophrenia: Network analysis in acute phase patients and in patients with predominant negative symptoms. *European Psychiatry*, *65*(1), 1-10, Article e18. https://doi.org/10.1192/j.eurpsy.2021.2241

Devoe, D. J., Farris, M. S., Townes, P., & Addington, J. (2019). Attenuated psychotic symptom interventions in youth at risk of psychosis: A systematic review and meta-analysis. *Early Intervention in Psychiatry*, *13*(1), 3-17. https://doi.org/10.1111/eip.12677

Devoe, D. J., Farris, M. S., Townes, P., & Addington, J. (2020). Interventions and transition in youth at risk of psychosis: A systematic review and meta-analyses. *The Journal of Clinical Psychiatry*, *81*(3), 1-13. https://doi.org/10.4088/JCP.17r12053

Dickinson, D., Ragland, J. D., Gold, J. M., & Gur, R. C. (2008). General and specific cognitive deficits in schizophrenia: Goliath defeats David? *Biological Psychiatry*, *64*(9), 823-827. https://doi.org/10.1016/j.biopsych.2008.04.005

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry*, *64*(5), 532-542. https://doi.org/10.1001/archpsyc.64.5.532

Díez-Mesa, F., de Oña, R., & de Oña, J. (2018). Bayesian networks and structural equation modelling to develop service quality models: Metro of Seville case study. *Transportation Research Part A: Policy and Practice*, *118*, 1-13. https://doi.org/10.1016/j.tra.2018.08.012

Dollfus, S., Petit, M., Lesieur, P., & Menard, J. (1991). Principal-component analysis of PANSS and SANS-SAPS global ratings in schizophrenic patients. *European Psychiatry*, *6*(5), 251-259. https://doi.org/10.1017/S0924933800003886

Dominguez Mde, G., Viechtbauer, W., Simons, C. J., van Os, J., & Krabbendam, L. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin*, *135*(1), 157-171. https://doi.org/10.1037/a0014415

Dong, M., Lu, L., Zhang, L., Zhang, Y.-S., Ng, C. H., Ungvari, G. S., Li, G., Meng, X., Wang, G., & Xiang, Y.-T. (2019). Quality of life in schizophrenia: A meta-analysis of comparative studies. *Psychiatric Quarterly*, *90*(3), 519-532. https://doi.org/10.1007/s11126-019-09633-4

Driver, D. I., Thomas, S., Gogtay, N., & Rapoport, J. L. (2020). Childhood-onset schizophrenia and early-onset schizophrenia spectrum disorders: An update. *Child and Adolescent Psychiatric Clinics*, *29*(1), 71-90. https://doi.org/10.1016/j.chc.2019.08.017

Dupuy, M., Abdallah, M., Swendsen, J., N'kaoua, B., Chanraud, S., Schweitzer, P., Fatseas, M., Serre, F., Barse, E., & Auriacombe, M. (2022). Real-time cognitive performance and positive symptom expression in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *272*, 415-425. https://doi.org/10.1007/s00406-021-01296-2

Durie, M. (1994). *Whaiora: Māori health development*. Oxford University Press. https://natlib.govt.nz/records/22131975

Durie, M. (2004). An indigenous model of health promotion. *Health Promotion Journal of Australia*, *15*(3), 181-185. https://doi.org/10.1071/HE04181

Eaton, W. W., Thara, R., Federman, B., Melton, B., & Liang, K.-y. (1995). Structure and course of positive and negative symptoms in schizophrenia. *Archives of General Psychiatry*, *52*(2), 127-134. https://doi.org/10.1001/archpsyc.1995.03950140045005

Engen, M. J., Vaskinn, A., Melle, I., Færden, A., Lyngstad, S. H., Flaaten, C. B., Widing, L. H., Wold, K. F., Åsbø, G., & Haatveit, B. (2022). Cognitive and global functioning in patients with first-episode psychosis stratified by level of negative symptoms. A 10-year follow-up study. *Frontiers in Psychiatry*, *13*, 1-13. https://doi.org/10.3389/fpsyt.2022.841057

Epskamp, S., Borsboom, D., & Fried, E. I. (2018a). Estimating psychological networks and their accuracy: A tutorial paper. *Behavior Research Methods*, *50*, 195-212. https://doi.org/10.3758/s13428-017-0862-1

Epskamp, S., Cramer, A. O., Waldorp, L. J., Schmittmann, V. D., & Borsboom, D. (2012). Qgraph: Network visualizations of relationships in psychometric data. *Journal of Statistical Software*, *48*(4), 1-18. https://doi.org/10.18637/jss.v048.i04

Epskamp, S., & Fried, E. I. (2018). A tutorial on regularized partial correlation networks. *Psychological Methods*, *23*(4), 617-634. https://doi.org/10.1037/met0000167

Epskamp, S., Rhemtulla, M., & Borsboom, D. (2017). Generalized network psychometrics: Combining network and latent variable models. *Psychometrika*, *82*, 904-927. https://doi.org/10.1007/s11336-017-9557-x

Epskamp, S., Waldorp, L. J., Mõttus, R., & Borsboom, D. (2018b). The Gaussian graphical model in cross-sectional and time-series data. *Multivariate Behavioral Research*, *53*(4), 453-480. https://doi.org/10.1080/00273171.2018.1454823

Esfahlani, F. Z., Sayama, H., Visser, K. F., & Strauss, G. P. (2017). Sensitivity of the Positive and Negative Syndrome Scale (PANSS) in detecting treatment effects via network analysis. *Innovations in Clinical Neuroscience*, *14*(11-12), 59-67. https://pmc.ncbi.nlm.nih.gov/articles/PMC5788252/

Esfahlani, F. Z., Visser, K., Strauss, G. P., & Sayama, H. (2018). A network-based classification framework for predicting treatment response of schizophrenia patients. *Expert Systems with Applications*, *109*, 152-161. https://doi.org/10.1016/j.eswa.2018.05.005

Estrada, E. (2024). What is a complex system, after all? *Foundations of Science*, *29*(4), 1143-1170. https://doi.org/10.1007/s10699-023-09917-w

Eunho, Y., Yulia, B., Pradeep, R., Genevera, A., & Zhandong, L. (2014). Mixed graphical models via exponential families. *Proceedings of the Seventeenth International Conference on Artificial Intelligence and Statistics*, *Iceland*. *33*, 1042-1050. https://proceedings.mlr.press/v33/yang14a.html

Fabrigar, L. R., Wegener, D. T., MacCallum, R. C., & Strahan, E. J. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods*, *4*(3), 272-299. https://doi.org/10.1037/1082-989X.4.3.272

Fan, W., & Davidson, I. (2007). On sample selection bias and its efficient correction via model averaging and unlabeled examples. *Proceedings of the 2007 SIAM International Conference on Data Mining*, *USA*. 320-331. https://doi.org/10.1137/1.9781611972771.29

Fava, G. A., & Tomba, E. (2009). Increasing psychological well-being and resilience by psychotherapeutic methods. *Journal of Personality*, *77*(6), 1903-1934. https://doi.org/10.1111/j.1467-6494.2009.00604.x

Feyaerts, J., Henriksen, M. G., Vanheule, S., Myin-Germeys, I., & Sass, L. A. (2021). Delusions beyond beliefs: A critical overview of diagnostic, aetiological, and therapeutic schizophrenia research from a clinical-phenomenological perspective. *The Lancet Psychiatry*, *8*(3), 237-249. https://doi.org/10.1016/S2215-0366(20)30460-0

Finnemann, A., Borsboom, D., Epskamp, S., & van der Maas, H. L. (2021). The theoretical and statistical Ising model: A practical guide in R. *Psych*, *3*(4), 593-617. https://doi.org/10.3390/psych3040039

Fišar, Z. (2023). Biological hypotheses, risk factors, and biomarkers of schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *120*, 1-18. https://doi.org/10.1016/j.pnpbp.2022.110626

Forbes, M. K., Wright, A. G., Markon, K. E., & Krueger, R. F. (2017). Evidence that psychopathology symptom networks have limited replicability. *Journal of Abnormal Psychology*, *126*(7), 969-988. https://doi.org/10.1037/abn0000276

Forbes, M. K., Wright, A. G., Markon, K. E., & Krueger, R. F. (2021). Quantifying the reliability and replicability of psychopathology network characteristics. *Multivariate Behavioral Research*, *56*(2), 224-242. https://doi.org/10.1080/00273171.2019.1616526

Fosse, R., Joseph, J., & Jones, M. (2016). Schizophrenia: A critical view on genetic effects. *Psychosis*, *8*(1), 72-84. https://doi.org/10.1080/17522439.2015.1081269

Fovet, T., Yger, P., Lopes, R., de Pierrefeu, A., Duchesnay, E., Houenou, J., Thomas, P., Szaffarczyk, S., Domenech, P., & Jardri, R. (2022). Decoding activity in Broca's area predicts the occurrence of auditory hallucinations across subjects. *Biological Psychiatry*, *91*(2), 194-201. https://doi.org/10.1016/j.biopsych.2021.08.024

Fowles, D. C. (1992). Schizophrenia: Diathesis-stress revisited. *Annual Review of Psychology*, *43*(1), 303-336. https://doi.org/10.1146/annurev.ps.43.020192.001511

Franco, V. R., Barros, G. W., & Jiménez, M. (2024). A generalized approach for Bayesian Gaussian graphical models. *Advances. in/Psychology*, *2*, 1-25. https://doi.org/10.56296/aip00022

Fried, E. I., Eidhof, M. B., Palic, S., Costantini, G., Huisman-van Dijk, H. M., Bockting, C. L. H., Engelhard, I., Armour, C., Nielsen, A. B. S., & Karstoft, K.-I. (2018). Replicability and generalizability of posttraumatic stress disorder (PTSD) networks: A cross-cultural multisite study of PTSD symptoms in four trauma patient samples. *Clinical Psychological Science*, *6*(3), 335-351. https://doi.org/10.1177/2167702617745092

Fried, E. I., Epskamp, S., Nesse, R. M., Tuerlinckx, F., & Borsboom, D. (2016). What are 'good' depression symptoms? Comparing the centrality of DSM and non-DSM symptoms of depression in a network analysis. *Journal of Affective Disorders*, *189*, 314-320. https://doi.org/10.1016/j.jad.2015.09.005

Fried, E. I., van Borkulo, C. D., Cramer, A. O., Boschloo, L., Schoevers, R. A., & Borsboom, D. (2017). Mental disorders as networks of problems: A review of recent insights. *Social Psychiatry and Psychiatric Epidemiology*, *52*(1), 1-10. https://doi.org/10.1007/s00127-016-1319-z

Fried, E. I., van Borkulo, C. D., & Epskamp, S. (2021). On the importance of estimating parameter uncertainty in network psychometrics: A response to Forbes et al.(2019). *Multivariate Behavioral Research*, *56*(2), 243-248. https://doi.org/10.1080/00273171.2020.1746903

Friedman, N., Nachman, I., & Pe'er, D. (2013). *Learning Bayesian network structure from massive datasets: The" sparse candidate" algorithm.* arXiv. https://doi.org/10.48550/arXiv.1301.6696

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome. *Clinical Neuroscience*, *3*(2), 89-97. https://fil.ion.ucl.ac.uk/~karl/Schizophrenia%20a%20disconnection%20syndrome.pdf

Frith, C. (1994). Theory of mind in schizophrenia. In A. S. David & J. C. Cutting (Eds.), *The neuropsychology of schizophrenia* (pp. 147-161). Lawrence Erlbaum Associates, Inc. https://doi.org/10.1016/j.mppsy.2008.07.016

Funkhouser, C. J., Correa, K. A., Gorka, S. M., Nelson, B. D., Phan, K. L., & Shankman, S. A. (2020). The replicability and generalizability of internalizing symptom networks across five samples. *Journal of Abnormal Psychology*, *129*(2), 191-203. https://doi.org/10.1037/abn0000496

Fusar-Poli, P., Estradé, A., Stanghellini, G., Venables, J., Onwumere, J., Messas, G., Gilardi, L., Nelson, B., Patel, V., & Bonoldi, I. (2022). The lived experience of psychosis: A bottom-up review co-written by experts by experience and academics. *World Psychiatry*, *21*(2), 168-188. https://doi.org/10.1002/wps.20959

Gaebel, W., & Kerst, A. (2019). The debate about renaming schizophrenia: A new name would not resolve the stigma. *Epidemiology and Psychiatric Sciences*, *28*(3), 258-261. https://doi.org/10.1017/S2045796018000513

Gaebel, W., Kerst, A., & Stricker, J. (2020). Classification and diagnosis of schizophrenia or other primary psychotic disorders: Changes from ICD-10 to ICD-11 and implementation in clinical practice. *Psychiatria Danubina*, *32*(3-4), 320-324. https://doi.org/10.24869/psyd.2020.320

Galbraith, N. (2021). Delusions and pathologies of belief: Making sense of conspiracy beliefs via the psychosis continuum. In V. Cardella & A. Gangemi (Eds.), *Psychopathology and Philosophy of Mind* (pp. 117-144). Routledge. https://doi.org/10.4324/9781003009856

Galderisi, S., Kaiser, S., Bitter, I., Nordentoft, M., Mucci, A., Sabé, M., Giordano, G. M., Nielsen, M. Ø., Glenthøj, L. B., Pezzella, P., Falkai, P., Dollfus, S., & Gaebel, W. (2021). EPA guidance on treatment of negative symptoms in schizophrenia. *European Psychiatry*, *64*(1), 1-15. https://doi.org/10.1192/j.eurpsy.2021.13

Galderisi, S., Rucci, P., Kirkpatrick, B., Mucci, A., Gibertoni, D., Rocca, P., Rossi, A., Bertolino, A., Strauss, G. P., & Aguglia, E. (2018). Interplay among psychopathologic variables, personal resources, context-related factors, and real-life functioning in individuals with schizophrenia: A network analysis. *JAMA Psychiatry*, *75*(4), 396–404. https://doi.org/10.1001/jamapsychiatry.2017.4607

Galderisi, S., Rucci, P., Mucci, A., Rossi, A., Rocca, P., Bertolino, A., Aguglia, E., Amore, M., Bellomo, A., & Bozzatello, P. (2020). The interplay among psychopathology, personal resources, context-related factors and real-life functioning in schizophrenia: Stability in relationships after 4 years and differences in network structure between recovered and non-recovered patients. *World Psychiatry*, *19*(1), 81-91. https://doi.org/10.1002/wps.20700

Gejman, P. V., Sanders, A. R., & Duan, J. (2010). The role of genetics in the etiology of schizophrenia. *Psychiatric Clinics*, *33*(1), 35-66. https://doi.org/10.1016/j.psc.2009.12.003

Gejman, P. V., Sanders, A. R., & Kendler, K. S. (2011). Genetics of schizophrenia: New findings and challenges. *Annual Review of Genomics and Human Genetics*, *12*, 121-144. https://doi.org/10.1146/annurev-genom-082410-101459

George, M., Maheshwari, S., Chandran, S., Manohar, J. S., & Rao, T. S. (2017). Understanding the schizophrenia prodrome. *Indian Journal of Psychiatry*, *59*(4), 505-509. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_464_17

Ghanem, M., Evangeli-Dawson, C., & Georgiades, A. (2023). The role of culture on the phenomenology of hallucinations and delusions, explanatory models, and help-seeking attitudes: A narrative review. *Early Intervention in Psychiatry*, *17*(9), 843-863. https://doi.org/10.1111/eip.13449

Goekoop, R., & Goekoop, J. G. (2014). A network view on psychiatric disorders: Network clusters of symptoms as elementary syndromes of psychopathology. *PLOS ONE*, *9*(11), 1-47. https://doi.org/10.1371/journal.pone.0112734

Goetz, C. J., Mushquash, C. J., & Maranzan, K. A. (2023). An integrative review of barriers and facilitators associated with mental health help seeking among indigenous populations. *Psychiatric Services*, *74*(3), 272-281. https://doi.org/10.1176/appi.ps.202100503

Gold, J. M., Carpenter, C., Randolph, C., Goldberg, T. E., & Weinberger, D. R. (1997). Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of General Psychiatry*, *54*(2), 159-165. https://doi.org/10.1001/archpsyc.1997.01830140071013

Gold, J. M., & Luck, S. J. (2022). Working memory in people with schizophrenia. In D. M. Barch & J. W. Young (Eds.), *Cognitive functioning in schizophrenia: Leveraging the RDoC framework* (pp. 137-152). Springer. https://doi.org/10.1007/978-3-031-26441-2

Gold, J. M., Randolph, C., Carpenter, C. J., Goldberg, T. E., & Weinberger, D. R. (1992). Forms of memory failure in schizophrenia. *Journal of Abnormal Psychology*, *101*(3), 487-494. https://doi.org/10.1037//0021-843X.101.3.487

Golino, H., & Christensen, A. (2025). *EGAnet: Exploratory graph analysis – a framework for estimating the number of dimensions in multivariate data using network psychometrics* (Version R package version 2.1.1). https://doi.org/10.32614/CRAN.package.EGAnet

Gottesman, I. I. (1991). *Schizophrenia genesis: The origins of madness*. W H Freeman/Times Books/ Henry Holt & Co. https://psycnet.apa.org/record/1990-98902-000

Gottesman, I. I., Laursen, T. M., Bertelsen, A., & Mortensen, P. B. (2010). Severe mental disorders in offspring with 2 psychiatrically ill parents. *Archives of General Psychiatry*, *67*(3), 252-257. https://doi.org/10.1001/archgenpsychiatry.2010.1

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia Research: Cognition*, *1*(1), 1-9. https://doi.org/10.1016/j.scog.2014.02.001

Green, M. F., Horan, W. P., & Lee, J. (2015). Social cognition in schizophrenia. *Nature Reviews Neuroscience*, *16*, 620-631. https://doi.org/10.1038/nrn4005

Griffiths, S. L., Lalousis, P. A., Wood, S. J., & Upthegrove, R. (2022). Heterogeneity in treatment outcomes and incomplete recovery in first episode psychosis: Does one size fit all? *Translational Psychiatry*, *12*(1), 1-6. https://doi.org/10.1038/s41398-022-02256-7

Gutiérrez-Rojas, L., González-Domenech, P. J., Junquera, G., Halverson, T. F., & Lahera, G. (2021). Functioning and happiness in people with schizophrenia: Analyzing the role of cognitive impairment. *International Journal of Environmental Research and Public Health*, *18*(14), 1-14. https://doi.org/10.3390/ijerph18147706

Guy, W. (1976). *ECDEU Assessment manual for psychopharmacology*. U.S. Dept. of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse, and Mental health Administration. https://psycnet.apa.org/buy/PE

Guyon, H., Falissard, B., & Kop, J.-L. (2017). Modeling psychological attributes in psychology–an epistemological discussion: Network analysis vs. latent variables. *Frontiers in Psychology*, *8*, 1-10. https://doi.org/10.3389/fpsyg.2017.00798

Häfner, H. (2019). From onset and prodromal stage to a life-long course of schizophrenia and its symptom dimensions: How sex, age, and other risk factors influence incidence and course of illness. *Psychiatry Journal*, *2019*, 1-15. https://doi.org/10.1155/2019/9804836

Haig, B. D., & Evers, C. (2015). *Realist inquiry in social science*. Sage Publications. https://uk.sagepub.com/en-gb/eur/realist-inquiry-in-social-science/book239560#description

Hair, J. F., Hult, G. T. M., Ringle, C. M., Sarstedt, M., Danks, N. P., & Ray, S. (2021). *Partial least squares structural equation modeling (PLS-SEM) using R: A workbook*. Springer International Publishing. https://doi.org/10.1007/978-3-030-80519-7_1

Hajdúk, M., Klein, H. S., Harvey, P. D., Penn, D. L., & Pinkham, A. E. (2019). Paranoia and interpersonal functioning across the continuum from healthy to pathological - network analysis. *The British Journal of Clinical Psychology*, *58*(1), 19-34. https://doi.org/10.1111/bjc.12199

Halverson, T. F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A.-K., & Penn, D. L. (2019). Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. *Neuroscience & Biobehavioral Reviews*, *105*, 212-219. https://doi.org/10.1016/j.neubiorev.2019.07.020

Harrington, L., Siegert, R. J., & McClure, J. (2005). Theory of mind in schizophrenia: A critical review. *Cognitive Neuropsychiatry*, *10*(4), 249-286. https://doi.org/10.1080/13546800444000056

Hart, M., & Lewine, R. R. (2017). Rethinking thought disorder. *Schizophrenia Bulletin*, *43*(3), 514-522. https://doi.org/10.1093/schbul/sbx003

Hartley, S., Barrowclough, C., & Haddock, G. (2013). Anxiety and depression in psychosis: A systematic review of associations with positive psychotic symptoms. *Acta Psychiatrica Scandinavica*, *128*(5), 327-346. https://doi.org/10.1111/acps.12080

Harvey, P. D., Koren, D., Reichenberg, A., & Bowie, C. R. (2006). Negative symptoms and cognitive deficits: What is the nature of their relationship? *Schizophrenia Bulletin*, *32*(2), 250-258. https://doi.org/10.1093/schbul/sbj011

Harvey, P. D., Strassnig, M. T., & Silberstein, J. (2019). Prediction of disability in schizophrenia: Symptoms, cognition, and self-assessment. *Journal of Experimental Psychopathology*, *10*(3), 1-20. https://doi.org/10.1177/2043808719865693

Haslbeck, J., & Waldorp, L. J. (2015). *Mgm: Estimating time-varying mixed graphical models in high-dimensional data.* arXiv. https://doi.org/10.48550/arXiv.1510.06871

Hasson-Ohayon, I., Goldzweig, G., Lavi-Rotenberg, A., Luther, L., & Lysaker, P. H. (2018). The centrality of cognitive symptoms and metacognition within the interacting network of symptoms, neurocognition, social cognition and metacognition in schizophrenia. *Schizophrenia Research*, *202*, 260-266. https://doi.org/10.1016/j.schres.2018.07.007

Heck, R. H. (1998). Fator analysis exploratory and confirmatory approaches. In G. A. Marcoulides (Ed.), *Modern methods for business research* (pp. 177-216). https://doi.org/10.4324/9781410604385-7

Heckerman, D. (1998). A tutorial on learning with Bayesian networks. In M. I. Jordan (Ed.), *Learning in Graphical Models* (pp. 301-354). https://doi.org/10.1007/978-94-011-5014-9_11

Hegarty, S. (2005, April 8). Glimpsing inside a beautiful mind. *The Irish Times*. https://www.irishtimes.com/

Heilbronner, U., Samara, M., Leucht, S., Falkai, P., & Schulze, T. G. (2016). The longitudinal course of schizophrenia across the lifespan: Clinical, cognitive, and neurobiological aspects. *Harvard Review of Psychiatry*, *24*(2), 118-128. https://doi.org/10.1097/HRP.0000000000000092

Heinrichs, D. W., Hanlon, T. E., & Carpenter, W. T., Jr. (1984). The Quality of Life Scale: An instrument for rating the schizophrenic deficit syndrome. *Schizophrenia Bulletin*, *10*(3), 388-398. https://doi.org/10.1093/schbul/10.3.388

Heinrichs, R. W. (2005). The primacy of cognition in schizophrenia. *American Psychologist*, *60*(3), 229-242. https://doi.org/10.1037/0003-066X.60.3.229

Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. *American Heart Journal*, *150*(6), 1115-1121. https://doi.org/10.1016/j.ahj.2005.02.007

Henssler, J., Brandt, L., Müller, M., Liu, S., Montag, C., Sterzer, P., & Heinz, A. (2020). Migration and schizophrenia: Meta-analysis and explanatory framework. *European Archives of Psychiatry and Clinical Neuroscience*, *270*, 325-335. https://doi.org/10.1007/s00406-019-01028-7

Hevey, D. (2018). Network analysis: A brief overview and tutorial. *Health Psychology and Behavioral Medicine*, *6*(1), 301-328. https://doi.org/10.1080/21642850.2018.1521283

Hogan, T. P., Awad, A., & Eastwood, R. (1983). A self-report scale predictive of drug compliance in schizophrenics: Reliability and discriminative validity. *Psychological Medicine*, *13*(1), 177-183. https://www.doi.org/10.1017/S0033291700050182

Holm, M., Taipale, H., Tanskanen, A., Tiihonen, J., & Mitterdorfer-Rutz, E. (2021). Employment among people with schizophrenia or bipolar disorder: A population-based study using nationwide registers. *Acta Psychiatrica Scandinavica*, *143*(1), 61-71. https://doi.org/10.1111/acps.13254

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics*, *6*(2), 65-70. https://jstor.org/stable/4615733

Hopkins, S. C., Tomioka, S., Ogirala, A., Loebel, A., Koblan, K. S., & Marder, S. R. (2022). Assessment of negative symptoms in clinical trials of acute schizophrenia: Test of a novel enrichment strategy. *Schizophrenia Bulletin Open*, *3*(1), 1-11. https://doi.org/10.1093/schizbullopen/sgac027

Horan, W. P., Catalano, L. T., & Green, M. F. (2022). An update on treatment of cognitive impairment associated with schizophrenia. In D. M. Barch & J. W. Young (Eds.), *Cognitive functioning in schizophrenia: Leveraging the RDoC framework* (pp. 407-436). Springer. https://doi.org/10.1007/978-3-031-26441-2

Howes, O., McCutcheon, R., & Stone, J. (2015). Glutamate and dopamine in schizophrenia: An update for the 21st century. *Journal of Psychopharmacology*, *29*(2), 97-115. https://doi.org/10.1177/0269881114563634

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III—the final common pathway. *Schizophrenia Bulletin*, *35*(3), 549-562. https://doi.org/10.1093/schbul/sbp006

Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biological Psychiatry*, *81*(1), 9-20. https://doi.org/10.1016/j.biopsych.2016.07.014

Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. *The Lancet*, *383*(9929), 1677-1687. https://doi.org/10.1016/S0140-6736(13)62036-X

Hoyle, R. H., & Gottfredson, N. C. (2015). Sample size considerations in prevention research applications of multilevel modeling and structural equation modeling. *Prevention Science*, *16*(7), 987-996. https://doi.org/10.1007/s11121-014-0489-8

Hu, H.-X., Lau, W. Y. S., Ma, E. P. Y., Hung, K. S. Y., Chen, S.-Y., Cheng, K.-S., Cheung, E. F. C., Lui, S. S. Y., & Chan, R. C. K. (2022). The important role of motivation and pleasure deficits on social functioning in patients with schizophrenia: A network analysis. *Schizophrenia Bulletin*, *48*(4), 860-870. https://doi.org/10.1093/schbul/sbac017

Hu, L. t., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, *6*(1), 1-55. https://doi.org/10.1080/10705519909540118

Ickstadt, K., Bornkamp, B., Grzegorczyk, M., Wieczorek, J., Sheriff, M. R., Grecco, H. E., & Zamir, E. (2011). Nonparametric Bayesian networks. In J. M. Bernardo, M. J. Bayarri, J. O. Berger, A. P. Dawid, D. Heckerman, A. F. M. Smith, & M. West (Eds.), *Bayesian statistics* (pp. 283-316). Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199694587.003.0010

Isohanni, M., Miettunen, J., & Penttilä, M. (2020). Life span development of schizophrenia: Symptoms, clinical course, and outcomes. In C. A. Tamminga, E. Ivleva, U. Reininghaus, & J. van Os (Eds.), *Psychotic disorders: Comprehensive conceptualization and treatments* (pp. 143-151). Oxford University Press. https://doi.org/10.1093/med/9780190653279.003.0017

Isvoranu, A.-M., Boyette, L.-L., Guloksuz, S., & Borsboom, D. (2018). Chapter G1. Symptom network models of psychosis. In C. A. Tamminga, E. Ivleva, U. Reininghaus, & J. van Os (Eds.), *Dimensions of Psychosis* (pp. 70-78). Oxford University Press. https://doi.org/10.17605/OSF.IO/NK8YV

Isvoranu, A.-M., & Epskamp, S. (2023). Which estimation method to choose in network psychometrics? Deriving guidelines for applied researchers. *Psychological Methods*, *28*(4), 925-946. https://doi.org/10.1037/met0000439

Isvoranu, A.-M., Epskamp, S., & Cheung, M. W.-L. (2021). Network models of posttraumatic stress disorder: A meta-analysis. *Journal of Abnormal Psychology*, *130*(8), 841-861. https://doi.org/10.1037/abn0000704

Isvoranu, A.-M., Epskamp, S., Waldorp, L., & Borsboom, D. (2022). *Network psychometrics with R: A guide for behavioral and social scientists*. Routledge. https://doi.org/10.4324/9781003111238

Isvoranu, A.-M., Guloksuz, S., Epskamp, S., van Os, J., & Borsboom, D. (2020). Toward incorporating genetic risk scores into symptom networks of psychosis. *Psychological Medicine*, *50*(4), 636-643. https://doi.org/10.1017/S003329171900045X

Isvoranu, A.-M., van Borkulo, C. D., Boyette, L.-L., Wigman, J. T. W., Vinkers, C. H., Borsboom, D., & Investigators, G. (2016). A network approach to psychosis: Pathways between childhood trauma and psychotic symptoms. *Schizophrenia Bulletin*, *43*(1), 187-196. https://doi.org/10.1093/schbul/sbw055

Janoutová, J., Janácková, P., Sery, O., Zeman, T., Ambroz, P., Kovalová, M., Varechova, K., Hosák, L., Jirik, V., & Janout, V. (2016). Epidemiology and risk factors of schizophrenia. *Neuroendocrinology Letters*, *37*(1), 1-8. https://nel.edu/userfiles/articlesnew/NEL370116R01.pdf

Jardri, R., Pouchet, A., Pins, D., & Thomas, P. (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: A coordinate-based meta-analysis. *American Journal of Psychiatry*, *168*(1), 73-81. https://doi.org/10.1176/appi.ajp.2010.09101522

Jauhar, S., Johnstone, M., & McKenna, P. J. (2022). Schizophrenia. *The Lancet*, *399*(10323), 473-486. https://doi.org/10.1016/S0140-6736(21)01730-X

Jauhar, S., McKenna, P., Radua, J., Fung, E., Salvador, R., & Laws, K. (2014). Cognitive–behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *The British Journal of Psychiatry*, *204*(1), 20-29. https://doi.org/10.1192/bjp.bp.112.116285

Javed, A., & Charles, A. (2018). The importance of social cognition in improving functional outcomes in schizophrenia. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00157

Javitt, D. C. (2009). When doors of perception close: Bottom-up models of disrupted cognition in schizophrenia. *Annual Review of Clinical Psychology*, *5*, 249-275. https://doi.org/10.1146/annurev.clinpsy.032408.153502

Javitt, D. C. (2023). Cognitive impairment associated with schizophrenia: From pathophysiology to treatment. *Annual Review of Pharmacology and Toxicology*, *63*, 119-141. https://doi.org/10.1146/annurev-pharmtox-051921-093250

Jones, P. J., Heeren, A., & McNally, R. J. (2017). Commentary: A network theory of mental disorders. *Frontiers in Psychology*, *8*, 1-3. https://doi.org/10.1002/wps.20375

Jones, P. J., Ma, R., & McNally, R. J. (2021a). Bridge centrality: A network approach to understanding comorbidity. *Multivariate Behavioral Research*, *56*(2), 353-367. https://doi.org/10.1080/00273171.2019.1614898

Jones, P. J., Williams, D. R., & McNally, R. J. (2021b). Sampling variability is not nonreplication: A Bayesian reanalysis of Forbes, Wright, Markon, and Krueger. *Multivariate Behavioral Research*, *56*(2), 249-255. https://doi.org/10.1080/00273171.2020.1797460

Jones, S. R., & Fernyhough, C. (2007). A new look at the neural diathesis–stress model of schizophrenia: The primacy of social-evaluative and uncontrollable situations. *Schizophrenia Bulletin*, *33*(5), 1171-1177. https://doi.org/10.1093/schbul/sbl058

Jordan, D. G., Winer, E. S., & Salem, T. (2020). The current status of temporal network analysis for clinical science: Considerations as the paradigm shifts? *Journal of Clinical Psychology*, *76*(9), 1591-1612. https://doi.org/10.1002/jclp.22957

Jordan, G., MacDonald, K., Pope, M. A., Schorr, E., Malla, A. K., & Iyer, S. N. (2018). Positive changes experienced after a first episode of psychosis: A systematic review. *Psychiatric Services*, *69*(1), 84-99. https://doi.org/10.1176/appi.ps.201600586

Juola, P., Miettunen, J., Veijola, J., Isohanni, M., & Jääskeläinen, E. (2013). Predictors of short– and long-term clinical outcome in schizophrenic psychosis–the Northern Finland 1966 Birth Cohort study. *European Psychiatry*, *28*(5), 263-268. https://doi.org/10.1016/j.eurpsy.2011.11.001

Kahn, R. S. (2020). On the origins of schizophrenia. *American Journal of Psychiatry*, *177*(4), 291-297. https://doi.org/10.1176/appi.ajp.2020.20020147

Kahn, R. S., & Keefe, R. S. (2013). Schizophrenia is a cognitive illness: Time for a change in focus. *JAMA Psychiatry*, *70*(10), 1107-1112. https://doi.org/10.1001/jamapsychiatry.2013.155

Kaite, C. P., Karanikola, M., Merkouris, A., & Papathanassoglou, E. D. (2015). "An ongoing struggle with the self and illness": A meta-synthesis of the studies of the lived experience of severe mental illness. *Archives of Psychiatric Nursing*, *29*(6), 458-473. https://doi.org/10.1016/j.apnu.2015.06.012

Kalisch, M., & Bühlman, P. (2007). Estimating high-dimensional directed acyclic graphs with the PC-algorithm. *Journal of Machine Learning Research*, *8*(3). https://www.jmlr.org/papers/volume8/kalisch07a/kalisch07a.pdf

Kan, K.-J., de Jonge, H., van der Maas, H. L. J., Levine, S. Z., & Epskamp, S. (2020). How to compare psychometric factor and network models. *Journal of Intelligence*, *8*(4), 1-10. https://doi.org/10.3390/jintelligence8040035

Kane, J. M., & Correll, C. U. (2010). Past and present progress in the pharmacologic treatment of schizophrenia. *The Journal of Clinical Psychiatry*, *71*(9), 1115-1124. https://doi.org/10.4088/JCP.10r06264yel

Katschnig, H. (2018). Psychiatry's contribution to the public stereotype of schizophrenia: Historical considerations. *Journal of Evaluation in Clinical Practice*, *24*(5), 1093-1100. https://doi.org/10.1111/jep.13011

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261-276. https://doi.org/10.1093/schbul/13.2.261

Keefe, R. (2014). The longitudinal course of cognitive impairment in schizophrenia: An examination of data from premorbid through posttreatment phases of illness. *Journal of Clinical Psychiatry*, *75*, 8-13. https://doi.org/10.4088/JCP.13065su1.02

Keefe, R. S., Bilder, R. M., Harvey, P. D., Davis, S. M., Palmer, B. W., Gold, J. M., Meltzer, H. Y., Green, M. F., Miller, D. D., & Canive, J. M. (2006). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology*, *31*(9), 2033-2046. https://doi.org/10.1038/sj.npp.1301072

Keefe, R. S., & Harvey, P. D. (2012). Cognitive impairment in schizophrenia. In M. Geyer & G. Gross (Eds.), *Novel Antischizophrenia Treatments. Handbook of Experimental Pharmacology* (pp. 11-37). Springer. https://doi.org/10.1007/978-3-642-25758-2_2

Keefe, R. S., Mohs, R. C., Bilder, R. M., Harvey, P. D., Green, M. F., Meltzer, H. Y., Gold, J. M., & Sano, M. (2003). Neurocognitive assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project schizophrenia trial: Development, methodology, and rationale. *Schizophrenia Bulletin*, *29*(1), 45-55. https://doi.org/10.1093/oxfordjournals.schbul.a006990

Kendell, R. E. (1987). Diagnosis and classification of functional psychoses. *British Medical Bulletin*, *43*(3), 499-513. https://doi.org/10.1093/oxfordjournals.bmb.a072198

Khalesi, E., & Khalesi, E. (2024). Schizophrenia cureness and gene therapy. *Advances in Neurology and Neuroscience*, *7*(2), 1-5. https://opastpublishers.com/open-access-articles/schizophrenia-cureness-and-gene-therapy.pdf

Khalil, M., Hollander, P., Raucher-Chéné, D., Lepage, M., & Lavigne, K. M. (2022). Structural brain correlates of cognitive function in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews*, *132*, 37-49. https://doi.org/10.1016/j.neubiorev.2021.11.034

Kharawala, S., Hastedt, C., Podhorna, J., Shukla, H., Kappelhoff, B., & Harvey, P. D. (2022). The relationship between cognition and functioning in schizophrenia: A semi-systematic review. *Schizophrenia Research: Cognition*, *27*, 1-16. https://doi.org/10.1016/j.scog.2021.100217

Kiburi, S. K., Molebatsi, K., Ntlantsana, V., & Lynskey, M. T. (2021). Cannabis use in adolescence and risk of psychosis: Are there factors that moderate this relationship? A systematic review and meta-analysis. *Substance Abuse*, *42*(4), 527-542. https://doi.org/10.1080/08897077.2021.1876200

Kiraz, S., & Demir, E. (2021). Global scientific outputs of schizophrenia publications from 1975 to 2020: A bibliometric analysis. *Psychiatric Quarterly*, *92*(4), 1725-1744. https://doi.org/10.1007/s11126-021-09937-4

Kline, R. B. (2023). *Principles and practice of structural equation modeling* (4th ed.). Guilford Press. https://guilford.com/books/Principles-and-Practice-of-Structural-Equation-Modeling/Rex-Kline/9781462551910

Klingberg, S., Wittorf, A., & Wiedemann, G. (2006). Disorganization and cognitive impairment in schizophrenia: Independent symptom dimensions? *European Archives of Psychiatry and Clinical Neuroscience*, *256*, 532-540. https://doi.org/10.1007/s00406-006-0704-0

Knowles, E. E. M., David, A. S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: Reexamining the evidence. *American Journal of Psychiatry*, *167*(7), 828-835. https://doi.org/10.1176/appi.ajp.2010.09070937

Korb, K. B., & Nicholson, A. E. (2008). The causal interpretation of Bayesian networks. In D. E. Holmes & L. C. Jain (Eds.), *Innovations in Bayesian networks. Studies in Computational Intelligence* (pp. 83-116). Springer. https://doi.org/10.1007/978-3-540-85066-3_4

Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis. *Schizophrenia Research*, *161*(2-3), 143-149. https://doi.org/10.1016/j.schres.2014.11.026

Kraepelin, E. (1913). *Psychiatrie: Ein Lehrbuch für studierende und Ärzte [Psychiatry: A textbook for students and doctors]* (8th ed.). Verlag von Johann Ambrosius Barth. https://archive.org/details/psychiatrieeinle04krae

Kumari, S., Malik, M., Florival, C., Manalai, P., & Sonje, S. (2017). An assessment of five (PANSS, SAPS, SANS, NSA-16, CGI-SCH) commonly used symptoms rating scales in schizophrenia and comparison to newer scales (CAINS, BNSS). *Journal of Addiction Research & Therapy*, *8*(3), 1-14. https://doi.org/10.4172/2155-6105.1000324

Ladyman, J., Lambert, J., & Wiesner, K. (2013). What is a complex system? *European Journal for Philosophy of Science*, *3*(1), 33-67. https://philsci-archive.pitt.edu/9044/4/LLWultimate.pdf

Lahera, G., Ruiz, A., Brañas, A., Vicens, M., & Orozco, A. (2017). Reaction time, processing speed and sustained attention in schizophrenia: Impact on social functioning. *Revista de Psiquiatría y Salud Mental*, *10*(4), 197-205. https://doi.org/10.1016/j.rpsmen.2017.10.006

Laing, R. D., & Esterson, A. (1964). *Sanity, madness and the family*. Tavistock Publications.

Lako, I. M., Bruggeman, R., Knegtering, H., Wiersma, D., Schoevers, R., Slooff, C., & Taxis, K. (2012). A systematic review of instruments to measure depressive symptoms in patients with schizophrenia. *Journal of Affective Disorders*, *140*(1), 38-47. https://doi.org/10.1016/j.jad.2011.10.014

Lally, J., Ajnakina, O., Stubbs, B., Cullinane, M., Murphy, K. C., Gaughran, F., & Murray, R. M. (2017). Remission and recovery from first-episode psychosis in adults: Systematic review and meta-analysis of long-term outcome studies. *The British Journal of Psychiatry*, *211*(6), 350-358. https://doi.org/10.1192/bjp.bp.117.201475

Lambert, C., Da Silva, S., Ceniti, A. K., Rizvi, S. J., Foussias, G., & Kennedy, S. H. (2018). Anhedonia in depression and schizophrenia: A transdiagnostic challenge. *CNS Neuroscience & Therapeutics*, *24*(7), 615-623. https://doi.org/10.1111/cns.12854

Langdon, R., Siegert, R. J., McClure, J., & Harrington, L. (2005). Schizophrenia, theory of mind, and persecutory delusions. *Cognitive Neuropsychiatry*, *10*(2), 87-104. https://doi.org/10.1080/13546800344000327

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Archives of General Psychiatry*, *68*(6), 555-561. https://doi.org/10.1001/archgenpsychiatry.2011.5

Larøi, F., Luhrmann, T. M., Bell, V., Christian , W. A., Jr, Deshpande, S., Fernyhough, C., Jenkins, J., & Woods, A. (2014). Culture and hallucinations: Overview and future directions. *Schizophrenia Bulletin*, *40*(Suppl. 4), S213-S220. https://doi.org/10.1093/schbul/sbu012

Laurens, K. R., Luo, L., Matheson, S. L., Carr, V. J., Raudino, A., Harris, F., & Green, M. J. (2015). Common or distinct pathways to psychosis? A systematic review of evidence from prospective studies for developmental risk factors and antecedents of the schizophrenia spectrum disorders and affective psychoses. *BMC Psychiatry*, *15*, 1-20. https://doi.org/10.1186/s12888-015-0562-2

Lauritzen, S. L. (1996). *Graphical models*. Clarendon Press. https://global.oup.com/academic/product/graphical-models-9780198522195?cc=nz&lang=en&

Lauritzen, S. L., & Wermuth, N. (1989). Graphical models for associations between variables, some of which are qualitative and some quantitative. *The Annals of Statistics*, *17*(1), 31-57. https://doi.org/10.1214/aos/1176347003

Laursen, T. M., Munk-Olsen, T., & Vestergaard, M. (2012). Life expectancy and cardiovascular mortality in persons with schizophrenia. *Current Opinion in Psychiatry*, *25*(2), 83-88. https://doi.org/10.1097/YCO.0b013e32835035ca

Lavallee, L. F., & Poole, J. M. (2010). Beyond recovery: Colonization, health and healing for Indigenous people in Canada. *International Journal of Mental Health and Addiction*, *8*, 271-281. https://doi.org/10.1007/s11469-009-9239-8

Law, M., Stewart, C., Pollock, N., Letts, L., Bosch, J., & Westmorland, M. (1998). McMaster critical review form-Quantitative studies. https://mcgill.ca/cpengine/files/cpengine/quanreview_form1.doc

Laws, K. R., Darlington, N., Kondel, T. K., McKenna, P. J., & Jauhar, S. (2018). Cognitive behavioural therapy for schizophrenia-outcomes for functioning, distress and quality of life: A meta-analysis. *BMC Psychology*, *6*(32), 1-10. https://doi.org/10.1186/s40359-018-0243-2

Lee, E. E., Liu, J., Tu, X., Palmer, B. W., Eyler, L. T., & Jeste, D. V. (2018). A widening longevity gap between people with schizophrenia and general population: A literature review and call for action. *Schizophrenia Research*, *196*, 9-13. https://doi.org/10.1016/j.schres.2017.09.005

Lejeune, J. A., Northrop, A., & Kurtz, M. M. (2021). A meta-analysis of cognitive remediation for schizophrenia: Efficacy and the role of participant and treatment factors. *Schizophrenia Bulletin*, *47*(4), 997-1006. https://doi.org/10.1093/schbul/sbab022

Lett, T. A., Voineskos, A. N., Kennedy, J. L., Levine, B., & Daskalakis, Z. J. (2014). Treating working memory deficits in schizophrenia: A review of the neurobiology. *Biological Psychiatry*, *75*(5), 361-370. https://doi.org/10.1016/j.biopsych.2013.07.026

Levine, S. Z., & Leucht, S. (2016). Identifying a system of predominant negative symptoms: Network analysis of three randomized clinical trials. *Schizophrenia Research*, *178*(1-3), 17-22. https://doi.org/10.1016/j.schres.2016.09.002

Levinson, C. A., Hunt, R. A., Keshishian, A. C., Brown, M. L., Vanzhula, I., Christian, C., Brosof, L. C., & Williams, B. M. (2021). Using individual networks to identify treatment targets for eating disorder treatment: A proof-of-concept study and initial data. *Journal of Eating Disorders*, *9*(1), 1-18. https://doi.org/10.1186/s40337-021-00504-7

Lewis, D. A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. *Annual Review of Neuroscience*, *25*, 409-432. https://doi.org/10.1146/annurev.neuro.25.112701.142754

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). Oxford University Press. https://global.oup.com/academic/product/neuropsychological-assessment-9780195395525

Li, C., & Mahadevan, S. (2018). Efficient approximate inference in Bayesian networks with continuous variables. *Reliability Engineering & System Safety*, *169*, 269-280. https://doi.org/10.1016/j.ress.2017.08.017

Li, W., Zhang, Q., Tang, Y., Park, S.-C., Park, Y., Yang, S.-Y., Chen, L.-Y., Lin, S.-K., Najoan, E., & Kallivayalil, R. A. (2022). Network analysis of psychiatric symptoms in schizophrenia: Findings from the research on Asian Psychotropic Prescription Patterns for Antipsychotics (REAP-AP). *Asian Journal of Psychiatry*, *75*, 1-8. https://doi.org/10.1016/j.ajp.2022.103200

Li, X., Zhang, Y., Guo, F., Gao, X., & Wang, Y. (2018). Predicting the effect of land use and climate change on stream macroinvertebrates based on the linkage between structural equation modeling and Bayesian network. *Ecological Indicators*, *85*, 820-831. https://doi.org/10.1016/j.ecolind.2017.11.044

Liddle, P. F., Barnes, T. R., Morris, D., & Haque, S. (1989). Three syndromes in chronic schizophrenia. *The British Journal of Psychiatry*, *155*(S7), 119-122. https://doi.org/10.1192/S0007125000291642

Liew, B., Hartvigsen, J., Scutari, M., & Kongsted, A. (2023a). Data-driven pathway analysis of physical and psychological factors in low back pain. *Journal of Clinical Epidemiology*, *153*, 55-77. https://doi.org/10.1016/j.jclinepi.2022.11.010

Liew, B., Palacios-Ceña, M., Scutari, M., Fuensalida-Novo, S., Guerrero-Peral, A., Ordás-Bandera, C., Pareja, J. A., & Fernández-de-las-Peñas, C. (2023b). Path analysis models integrating psychological, psycho-physical and clinical variables in individuals with tension-type headache. *The Journal of Pain*, *24*(3), 426-436. https://doi.org/10.1016/j.jpain.2022.10.003

Little Bear, L. (2000). Jagged worldviews colliding. In M. Battiste (Ed.), *Reclaiming Indigenous voice and vision* (pp. 77-85). University of British Columbia Press. https://doi.org/10.59962/9780774853170-009

Lo, L., Kaur, R., Meiser, B., & Green, M. (2020). Risk of schizophrenia in relatives of individuals affected by schizophrenia: A meta-analysis. *Psychiatry Research*, *286*, 1-10. https://doi.org/10.1016/j.psychres.2020.112852

Lu, E. Y., Cheng, A. S. K., Tsang, H. W. H., Chen, J., Leung, S., Yip, A., Lin, J. J., Lam, Z. V., Zhang, W., Zhao, M., & Ma, N. (2022). Psychoeducation, motivational interviewing, cognitive remediation training, and/or social skills training in combination for psychosocial functioning of patients with schizophrenia spectrum disorders: A systematic review and meta-analysis of randomized controlled trials. *Frontiers in Psychiatry*, *13*, 1-17. https://doi.org/10.3389/fpsyt.2022.899840

Lutgens, D., Gariepy, G., & Malla, A. (2017). Psychological and psychosocial interventions for negative symptoms in psychosis: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *210*(5), 324-332. https://doi.org/10.1192/bjp.bp.116.197103

Ma, M., Shi, Z., Chen, Y., & Ma, X. (2023). Recovery journey of people with a lived experience of schizophrenia: A qualitative study of experiences. *BMC Psychiatry*, *23*, 1-13. https://doi.org/10.1186/s12888-023-04862-1

Mainzer, K. (2007). The emergence of mind and brain: An evolutionary, computational, and philosophical approach. In R. Banerjee & B. K. Chakrabarti (Eds.), *Progress in Brain Research* (Vol. 168, pp. 115-132). Elsevier. https://doi.org/10.1016/S0079-6123(07)68010-8

Malgaroli, M., Calderon, A., & Bonanno, G. A. (2021). Networks of major depressive disorder: A systematic review. *Clinical Psychology Review*, *85*, 1-14. https://doi.org/10.1016/j.cpr.2021.102000

Manchia, M., Pisanu, C., Squassina, A., & Carpiniello, B. (2020). Challenges and future prospects of precision medicine in psychiatry. *Pharmacogenomics and Personalized Medicine*, *13*, 127-140. https://doi.org/10.2147/PGPM.S198225

Mannarini, S., Taccini, F., Sato, I., & Rossi, A. A. (2022). Understanding stigma toward schizophrenia. *Psychiatry Research*, *318*, 1-10. https://doi.org/10.1016/j.psychres.2022.114970

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, *42*(5), 1262-1269. https://doi.org/10.1093/schbul/sbw003

Marcot, B. G. (2017). Common quandaries and their practical solutions in Bayesian network modeling. *Ecological Modelling*, *358*, 1-9. https://doi.org/10.1016/j.ecolmodel.2017.05.011

Marcot, B. G., & Penman, T. D. (2019). Advances in Bayesian network modelling: Integration of modelling technologies. *Environmental Modelling & Software*, *111*, 386-393. https://doi.org/10.1016/j.envsoft.2018.09.016

Marder, S. R., & Fenton, W. (2004). Measurement and Treatment Research to Improve Cognition in Schizophrenia: NIMH MATRICS initiative to support the development of agents for improving cognition in schizophrenia. *Schizophrenia Research*, *72*(1), 5-9. https://doi.org/10.1016/j.schres.2004.09.010

Margaritis, D. (2003). *Learning Bayesian network model structure from data* (Publication No. CMU-CS-03-153) [Doctoral dissertation, Mellon University]. CMU School of Computer Science. https://www.cs.cmu.edu/~dmarg/Papers/PhD-Thesis-Margaritis.pdf

Marsh, H. W., Morin, A. J. S., Parker, P. D., & Kaur, G. (2014). Exploratory structural equation modeling: An integration of the best features of exploratory and confirmatory actor analysis. *Annual Review of Clinical Psychology*, *10*, 85-110. https://doi.org/10.1146/annurev-clinpsy-032813-153700

Martínez, A. L., Brea, J., Rico, S., De los Frailes, M. T., & Loza, M. I. (2021). Cognitive deficit in schizophrenia: From etiology to novel treatments. *International Journal of Molecular Sciences*, *22*(18), 1-22. https://doi.org/10.3390/ijms22189905

Mathias, S. R., Knowles, E. E. M., Barrett, J., Leach, O., Buccheri, S., Beetham, T., Blangero, J., Poldrack, R. A., & Glahn, D. C. (2017). The processing-speed impairment in psychosis is more than just accelerated aging. *Schizophrenia Bulletin*, *43*(4), 814-823. https://doi.org/10.1093/schbul/sbw168

McCarthy-Jones, S., Smailes, D., Corvin, A., Gill, M., Morris, D. W., Dinan, T. G., Murphy, K. C., Waddington, J. L., Bank, A. S. R., & Donohoe, G. (2017). Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. *Psychiatry Research*, *252*, 154-160. https://doi.org/10.1016/j.psychres.2017.01.102

McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, dopamine and the striatum: From biology to symptoms. *Trends in Neurosciences*, *42*(3), 205-220. https://www.doi.org/10.1016/j.tins.2018.12.004

McCutcheon, R. A., Keefe, R. S., & McGuire, P. K. (2023). Cognitive impairment in schizophrenia: Aetiology, pathophysiology, and treatment. *Molecular Psychiatry*, *28*, 1-17. https://doi.org/10.1038/s41380-023-01949-9

McEvoy, J. P., Apperson, L. J., Appelbaum, P. S., Ortlip, P., Brecosky, J., Hammill, K., Geller, J. L., & Roth, L. (1989). Insight in schizophrenia. Its relationship to acute psychopathology. *The Journal of Nervous and Mental Disease*, *177*(1), 43-47. https://doi.org/10.1097/00005053-198901000-00007

McFarland, D. (2020). The effects of using partial or uncorrected correlation matrices when comparing network and latent variable models. *Journal of Intelligence*, *8*(1), 1-6. https://doi.org/10.3390/jintelligence8010007

McGlashan, T. H., Miller, T. J., Woods, S. W., Hoffman, R. E., & Davidson, L. (2001). Instrument for the assessment of prodromal symptoms and states. In T. Miller, S. A. Mednick, T. H. McGlashan, J. Libiger, & J. O. Johannessen (Eds.), *Early intervention in psychotic disorders* (pp. 135-149). Springer Netherlands. https://doi.org/10.1007/978-94-010-0892-1_7

McGorry, P. D., Mei, C., Hartmann, J., Yung, A. R., & Nelson, B. (2021). Intervention strategies for ultra-high risk for psychosis: Progress in delaying the onset and reducing the impact of first-episode psychosis. *Schizophrenia Research*, *228*, 344-356. https://doi.org/10.1016/j.schres.2020.12.026

McGorry, P. D., Nelson, B., Amminger, G. P., Bechdolf, A., Francey, S. M., Berger, G., Riecher-Rössler, A., Klosterkötter, J., Ruhrmann, S., & Schultze-Lutter, F. (2009). Intervention in individuals at ultra high risk for psychosis: A review and future directions. *The Journal of Clinical Psychiatry*, *70*(9), 1206-1212. https://doi.org/10.4088/JCP.08r04472

McNally, R., Mair, P., Mugno, B., & Riemann, B. (2017). Co-morbid obsessive–compulsive disorder and depression: A Bayesian network approach. *Psychological Medicine*, *47*(7), 1204-1214. https://doi.org/10.1017/S0033291716003287

McNally, R. J. (2016). Can network analysis transform psychopathology? *Behaviour Research and Therapy*, *86*, 95-104. https://doi.org/10.1016/j.brat.2016.06.006

McNeish, D., & Wolf, M. G. (2020). Thinking twice about sum scores. *Behavior Research Methods*, *52*, 2287-2305. https://doi.org/10.3758/s13428-020-01398-0

Medalia, A., & Choi, J. (2009). Cognitive remediation in schizophrenia. *Neuropsychology Review*, *19*, 353-364. https://doi.org/10.1007/s11065-009-9097-y

Mei, C., van der Gaag, M., Nelson, B., Smit, F., Yuen, H. P., Berger, M., Krcmar, M., French, P., Amminger, G. P., & Bechdolf, A. (2021). Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. *Clinical Psychology Review*, *86*, 1-16. https://doi.org/10.1016/j.cpr.2021.102005

Mihajlovic, V., & Petkovic, M. (2001). Dynamic Bayesian networks: A state of the art. *Europhysics Letters*, *34*, 1-37. https://research.utwente.nl/files/27679465/0000006a.pdf

Mihaljević-Peleš, A., Bajs Janović, M., Šagud, M., Živković, M., Janović, Š., & Jevtović, S. (2019). Cognitive deficit in schizophrenia: An overview. *Psychiatria Danubina*, *31*(suppl 2), 139-142. https://hrcak.srce.hr/file/382035

Milgram, S. (1967). The small world problem. *Psychology Today*, *2*(1), 60-67. http://snap.stanford.edu/class/cs224w-readings/milgram67smallworld.pdf

Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K., & Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: Preliminary evidence of interrater reliability and predictive validity. *American Journal of Psychiatry*, *159*(5), 863-865. https://doi.org/10.1176/appi.ajp.159.5.863

Miller, T. J., McGlashan, T. H., Woods, S. W., Stein, K., Driesen, N., Corcoran, C. M., Hoffman, R., & Davidson, L. (1999). Symptom assessment in schizophrenic prodromal states. *Psychiatric Quarterly*, *70*(4), 273-287. https://doi.org/10.1023/A:1022034115078

Miyamoto, S., Miyake, N., Jarskog, L., Fleischhacker, W., & Lieberman, J. (2012). Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and future therapeutic agents. *Molecular Psychiatry*, *17*(12), 1206-1227. https://doi.org/10.1038/mp.2012.47

Modinos, G., & McGuire, P. (2015). The prodromal phase of psychosis. *Current Opinion in Neurobiology*, *30*, 100-105. https://doi.org/10.1016/j.conb.2014.11.003

Moffa, G., Kuipers, J., Carrà, G., Crocamo, C., Kuipers, E., Angermeyer, M., Brugha, T., Toumi, M., & Bebbington, P. (2021). Longitudinal symptomatic interactions in long-standing schizophrenia: A novel five-point analysis based on directed acyclic graphs. *Psychological Medicine*, *53*(4), 1371-1378. https://doi.org/10.1017/S0033291721002920

Mohr, P. E., Cheng, C. M., Claxton, K., Conley, R. R., Feldman, J. J., Hargreaves, W. A., Lehman, A. F., Lenert, L. A., Mahmoud, R., & Marder, S. R. (2004). The heterogeneity of schizophrenia in disease states. *Schizophrenia Research*, *71*(1), 83-95. https://doi.org/10.1016/j.schres.2003.11.008

Mollon, J., & Reichenberg, A. (2018). Cognitive development prior to onset of psychosis. *Psychological Medicine*, *48*(3), 392-403. https://doi.org/10.1017/S0033291717001970

Montagnese, M., Leptourgos, P., Fernyhough, C., Waters, F., Larøi, F., Jardri, R., McCarthy-Jones, S., Thomas, N., Dudley, R., & Taylor, J.-P. (2021). A review of multimodal hallucinations: Categorization, assessment, theoretical perspectives, and clinical recommendations. *Schizophrenia Bulletin*, *47*(1), 237-248. https://doi.org/10.1093/schbul/sbaa101

Monteleone, P., Cascino, G., Monteleone, A. M., Rocca, P., Rossi, A., Bertolino, A., Aguglia, E., Amore, M., Collantoni, E., Corrivetti, G., Cuomo, A., Bellomo, A., D'Ambrosio, E., Dell'Osso, L., Frascarelli, M., Giordano, G. M., Giuliani, L., Marchesi, C., Montemagni, C., . . . Maj, M. (2021). Prevalence of antipsychotic-induced extrapyramidal symptoms and their association with neurocognition and social cognition in outpatients with schizophrenia in the "real-life". *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *109*, 1-8. https://doi.org/10.1016/j.pnpbp.2021.110250

Monteleone, P., Cascino, G., Rossi, A., Rocca, P., Bertolino, A., Aguglia, E., Amore, M., Andriola, I., Bellomo, A., & Biondi, M. (2022). Evolution of antipsychotic-induced extrapyramidal symptoms in patients with schizophrenia in the real-life: A 4-year follow-up naturalistic study. *Schizophrenia Research*, *248*, 279-286. https://doi.org/10.1016/j.schres.2022.08.015

Moraffah, R., Sheth, P., Karami, M., Bhattacharya, A., Wang, Q., Tahir, A., Raglin, A., & Liu, H. (2021). Causal inference for time series analysis: Problems, methods and evaluation. *Knowledge and Information Systems*, *63*, 3041-3085. https://doi.org/10.1007/s10115-021-01621-0

Moreno-Kustner, B., Martin, C., & Pastor, L. (2018). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLOS ONE*, *13*(4), 1-25. https://doi.org/10.1371/journal.pone.0195687

Morgan, S. L., & Winship, C. (2014). *Counterfactuals and causal inference: Methods and principles for social research*. Cambridge University Press. https://doi.org/10.1017/CBO9781107587991

Moriana, J. A., Jurado-González, F. J., García-Torres, F., Contreras, A., Muñoz-Navarro, R., González-Blanch, C., Medrano, L. A., Ruiz-Rodríguez, P., & Cano-Vindel, A. (2022). Exploring the structure of the GAD-7 scale in primary care patients with emotional disorders: A network analysis approach. *Journal of Clinical Psychology*, *78*(2), 283-297. https://doi.org/10.1002/jclp.23217

Moriconi, V., Menéndez, A., Neimeyer, R. A., & Moggia, D. (2025). Adaptation of the Spanish Grief and Meaning Reconstruction Inventory: An initial validation and network analysis. *Journal of Death and Dying*, *90*(3), 1229-1249. https://doi.org/10.1177/00302228221118169

Morrison, P. D., & Murray, R. (2009). From real-world events to psychosis: The emerging neuropharmacology of delusions. *Schizophrenia Bulletin*, *35*(4), 668-674. https://doi.org/10.1093/schbul/sbp049

Mosolov, S. N., & Yaltonskaya, P. A. (2022). Primary and secondary negative symptoms in schizophrenia. *Frontiers in Psychiatry*, *12*, 1-12. https://doi.org/10.3389/fpsyt.2021.766692

Moura, B. M., Isvoranu, A.-M., Kovacs, V., Van Rooijen, G., Van Amelsvoort, T., Simons, C. J. P., Bartels-Velthuis, A. A., Bakker, P. R., Marcelis, M., De Haan, L., & Schirmbeck, F. (2022). The puzzle of functional recovery in schizophrenia-spectrum disorders—replicating a network analysis study. *Schizophrenia Bulletin*, *48*(4), 871-880. https://doi.org/10.1093/schbul/sbac018

Moura, B. M., van Rooijen, G., Schirmbeck, F., Wigman, J. T. W., Risk, G., investigators, O. o. P., Madeira, L., Harten, P. v., van Os, J., Bakker, P. R., & Marcelis, M. (2021). A network of psychopathological, cognitive, and motor symptoms in schizophrenia spectrum disorders. *Schizophrenia Bulletin*, *47*(4), 915-926. https://doi.org/10.1093/schbul/sbab002

Moustafa, A. A., Garami, J. K., Mahlberg, J., Golembieski, J., Keri, S., Misiak, B., & Frydecka, D. (2016). Cognitive function in schizophrenia: Conflicting findings and future directions. *Reviews in the Neurosciences*, *27*(4), 435-448. https://doi.org/10.1515/revneuro-2015-0060

Mumford, J. A., & Ramsey, J. D. (2014). Bayesian networks for fMRI: A primer. *Neuroimage*, *86*, 573-582. https://doi.org/10.1016/j.neuroimage.2013.10.020

Murphy, K., & Mian, S. (1999). *Modelling gene expression data using dynamic Bayesian networks*. University of California. https://cbio.mines-paristech.fr/~jvert/svn/bibli/local/Murphy1999Modelling.pdf

Murray, R. M., Bhavsar, V., Tripoli, G., & Howes, O. (2017). 30 years on: How the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophrenia Bulletin*, *43*(6), 1190-1196. https://doi.org/10.1093/schbul/sbx121

Murray, R. M., & Lewis, S. W. (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journal*, *295*(6600), 681-682. https://doi.org/10.1136/bmj.295.6600.681

Nagarajan, R., Scutari, M., & Lèbre, S. (2013). *Bayesian networks in R: With applications in systems biology*. Springer. https://doi.org/10.1007/978-1-4614-6446-4

Napal, O., Ojeda, N., Sánchez, P., Elizagarate, E., Pena, J., Ezcurra, J., & Gutiérrez, M. (2012). The course of schizophrenia and its impact on cognition: A review of literature. *Actas Espanolas de Psiquiatria*, *40*(4), 198-220. https://actaspsiquiatria.es/index.php/actas/article/view/456

National Institute of Mental Health. (2024a). *Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)* [Dataset]. National Institute of Mental Health Data Archive. https://nda.nih.gov/edit_collection.html?id=2081

National Institute of Mental Health. (2024b). *North American Prodromal Longitudinal Study 3 (NAPLS3)* [Dataset]. National Institute of Mental Health Data Archive. https://nda.nih.gov/edit_collection.html?id=2275

Nelson, B., McGorry, P. D., Wichers, M., Wigman, J. T., & Hartmann, J. A. (2017). Moving from static to dynamic models of the onset of mental disorder: A review. *JAMA Psychiatry*, *74*(5), 528-534. https://doi.org/10.1001/jamapsychiatry.2017.0001

Nelson, B., Yuen, H. P., Wood, S. J., Lin, A., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Simmons, M., Foley, D. L., & Brewer, W. J. (2013). Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: The PACE 400 study. *JAMA Psychiatry*, *70*(8), 793-802. https://doi.org/10.1001/jamapsychiatry.2013.1270

Nelson, S. E., & Wilson, K. (2017). The mental health of Indigenous peoples in Canada: A critical review of research. *Social Science & Medicine*, *176*, 93-112. https://doi.org/10.1016/j.socscimed.2017.01.021

Norman, R. M., & Malla, A. K. (2001). Duration of untreated psychosis: A critical examination of the concept and its importance. *Psychological Medicine*, *31*(3), 381-400. https://doi.org/10.1017/S0033291701003488

Novick, D., Montgomery, W., Cheng, Y., Moneta, V., & Haro, J. (2015). Impact of negative symptoms on quality of life in patients with schizophrenia. *Value in Health*, *18*(7), A836-A837. https://doi.org/10.1016/j.jval.2015.09.351

Nowak, I., Sabariego, C., Świtaj, P., & Anczewska, M. (2016). Disability and recovery in schizophrenia: A systematic review of cognitive behavioral therapy interventions. *BMC Psychiatry*, *16*, 1-15. https://doi.org/10.1186/s12888-016-0912-8

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*(1), 29-39. https://doi.org/10.1016/j.schres.2004.09.007

Nuijten, M., Deserno, M., Cramer, A., & Borsboom, D. (2016). Mental disorders as complex networks: An introduction and overview of a network approach to psychopathology. *Clinical Neuropsychiatry*, *13*(4/5), 68-76. http://clinicalneuropsychiatry.org/pdf/borsbooml.pdf

O'Leary, D. S., Flaum, M., Kesler, M. L., Flashman, L. A., Arndt, S., & Andreasen, N. C. (2000). Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(1), 4-15. https://doi.org/10.1176/jnp.12.1.4

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment*, *2012*, 1-9. https://doi.org/10.1155/2012/916198

Ojeda, N., Peña, J., Schretlen, D. J., Sánchez, P., Aretouli, E., Elizagárate, E., Ezcurra, J., & Gutiérrez, M. (2012). Hierarchical structure of the cognitive processes in schizophrenia:

The fundamental role of processing speed. *Schizophrenia Research*, *135*(1), 72-78. https://doi.org/10.1016/j.schres.2011.12.004
Olsen, K., & Rosenbaum, B. (2006). Prospective investigations of the prodromal state of schizophrenia: Review of studies. *Acta Psychiatrica Scandinavica*, *113*(4), 247-272. https://doi.org/10.1111/j.1600-0447.2005.00697.x
Öngün, E., Ünsal, G., & Karaca, S. (2022). Meta-analysis of the effect of psychosocial skills training on the quality of life of people with schizophrenia. *Perspectives in Psychiatric Care*, *58*(4), 2272-2285. https://doi.org/10.1111/ppc.13057
OpenAI. (2025). *ChatGPT* (Version o3) [Large language model]. https://chat.openai.com
Orcan, F. (2018). Exploratory and confirmatory factor analysis: Which one to use first? *Journal of Measurement and Evaluation in Education and Psychology*, *9*(4), 414-421. https://doi.org/10.21031/epod.394323
Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry*, *4*, 1-15. https://doi.org/10.3389/fpsyt.2013.00035
Oude Maatman, F. (2020). Reformulating the network theory of mental disorders: Folk psychology as a factor, not a fact. *Theory & Psychology*, *30*(5), 703-722. https://doi.org/10.1177/095935432092146
Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*, 1-9. https://doi.org/10.1136/bmj.n71
Pardeller, S., Kemmler, G., Hoertnagl, C. M., & Hofer, A. (2020). Associations between resilience and quality of life in patients experiencing a depressive episode. *Psychiatry Research*, *292*, 1-6. https://doi.org/10.1016/j.psychres.2020.113353
Park, S. C., Kim, K., Jang, O. J., Yoon, H. J., Jang, S. H., Kim, S. W., Lee, B. J., Park, J. H., Lee, K. U., & Choi, J. (2020). Network analysis of language disorganization in patients with schizophrenia. *Yonsei Medical Journal*, *61*(8), 726-730. https://doi.org/10.3349/ymj.2020.61.8.726
Patmisari, E., Huang, Y., Orr, M., Govindasamy, S., Hielscher, E., & McLaren, H. (2024). Supported employment interventions with people who have severe mental illness: Systematic mixed-methods umbrella review. *PLOS ONE*, *19*(6), 1-36. https://doi.org/10.1371/journal.pone.0304527
Pearl, J. (1982). Reverend Bayes on inference engines: A distributed hierarchical approach. In H. Geffner, R. Dechter, & J. Y. Halpern (Eds.), *Probabilistic and Causal Inference: The Works of Judea Pearl*. University of California Los Angeles. https://doi.org/10.1145/3501714.350172
Pearl, J. (1985). Bayesian networks: A model of self-activated memory for evidential reasoning. *Proceedings of the 7th Conference of the Cognitive Science Society*, *USA*. 1-14. http://ftp.cs.ucla.edu/tech-report/198_-reports/850017.pdf
Pearl, J. (1988). *Probabilistic reasoning in intelligent systems: Networks of plausible inference*. Morgan Kaufmann Publishers Inc. https://dl.acm.org/doi/book/10.5555/534975
Pearl, J. (1995). From Bayesian networks to causal networks. In G. Coletti, D. Dubois, & R. Scozzafava (Eds.), *Mathematical models for handling partial knowledge in artificial intelligence* (pp. 157-182). Springer. https://doi.org/10.1007/978-1-4899-1424-8_9
Pearl, J. (2009). *Causality* (2nd ed.). Cambridge University Press. https://doi.org/10.1017/CBO9780511803161
Pearl, J. (2018). A personal journey into Bayesian networks. *University of California, Los Angeles*. https://ftp.cs.ucla.edu/pub/stat_ser/r476.pdf
Pearl, J. (2022). The causal foundations of structural equation modeling. In R. H. Hoyle (Ed.), *Handbook of structural equation modeling* (2nd ed., pp. 68-91). Guilford Press. https://guilford.com/books/Handbook-of-Structural-Equation-Modeling/Rick-Hoyle/9781462544646?srsltid=AfmBOoo1H29nHnZXqSe-4M6waZdtcNGgeZPP3fDsQgPJHe3ZxCzpeBH4
Pearl, J., & Russell, S. (2000). Bayesian networks. In M. A. Arbib (Ed.), *The handbook of brain theory and neural networks* (2nd ed.). The MIT Press. https://doi.org/10.7551/mitpress/3413.001.0001

Penttilä, M., Jääskeläinen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014). Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry*, *205*(2), 88-94. https://doi.org/10.1192/bjp.bp.113.127753

Peralta, V., & Cuesta, M. J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Research*, *53*(1), 31-40. https://doi.org/10.1016/0165-1781(94)90093-0

Peralta, V., Gil-Berrozpe, G. J., Sánchez-Torres, A., & Cuesta, M. J. (2020). The network and dimensionality structure of affective psychoses: An exploratory graph analysis approach. *Journal of Affective Disorders*, *277*, 182-191. https://doi.org/10.1016/j.jad.2020.08.008

Perestelo-Pérez, L. (2013). Standards on how to develop and report systematic reviews in psychology and health. *International Journal of Clinical and Health Psychology*, *13*(1), 49-57. https://doi.org/10.1016/S1697-2600(13)70007-3

Peritogiannis, V., Ninou, A., & Samakouri, M. (2022). Mortality in schizophrenia-spectrum disorders: Recent advances in understanding and management. *Healthcare*, *10*(12), 1-18. https://doi.org/10.3390/healthcare10122366

Petkari, E., Nikolaou, E., Oberleiter, S., Priebe, S., & Pietschnig, J. (2024). Which psychological interventions improve quality of life in patients with schizophrenia-spectrum disorders? A meta-analysis of randomized controlled trials. *Psychological Medicine*, *54*(2), 221-244. https://doi.org/10.1017/S0033291723003070

Peyrard, N., Cros, M. J., de Givry, S., Franc, A., Robin, S., Sabbadin, R., Schiex, T., & Vignes, M. (2019). Exact or approximate inference in graphical models: Why the choice is dictated by the treewidth, and how variable elimination can be exploited. *Australian & New Zealand Journal of Statistics*, *61*(2), 89-133. https://doi.org/10.1111/anzs.12257

Phillips, L. J., Leicester, S. B., O'Dwyer, L. E., Francey, S. M., Koutsogiannis, J., Abdel-Baki, A., Kelly, D., Jones, S., Vay, C., & Yung, A. R. (2002). The PACE Clinic: Identification and management of young people at "ultra" high risk of psychosis. *Journal of Psychiatric Practice*, *8*(5), 255-269. https://doi.org/10.1097/00131746-200209000-00002

Pieczynski, W., & Tebbache, A.-N. (2000). Pairwise Markov random fields and segmentation of textured images. *Machine Graphics and Vision*, *9*(4), 705-718. https://ieeexplore.ieee.org/document/839581

Plitman, E., Nakajima, S., de la Fuente-Sandoval, C., Gerretsen, P., Chakravarty, M. M., Kobylianskii, J., Chung, J. K., Caravaggio, F., Iwata, Y., & Remington, G. (2014). Glutamate-mediated excitotoxicity in schizophrenia: A review. *European Neuropsychopharmacology*, *24*(10), 1591-1605. https://doi.org/10.1016/j.euroneuro.2014.07.015

Pogue-Geile, M. F., & Harrow, M. (1985). Negative symptoms in schizophrenia: Their longitudinal course and prognostic importance. *Schizophrenia Bulletin*, *11*(3), 427-439. https://doi.org/10.1093/schbul/11.3.427

Popovic, D., Schmitt, A., Kaurani, L., Senner, F., Papiol, S., Malchow, B., Fischer, A., Schulze, T. G., Koutsouleris, N., & Falkai, P. (2019). Childhood trauma in schizophrenia: Current findings and research perspectives. *Frontiers in Neuroscience*, *13*, 1-14. https://doi.org/10.3389/fnins.2019.00274

Pourret, O., Na, P., & Marcot, B. (2008). *Bayesian networks: A practical guide to applications*. John Wiley & Sons. https://doi.org/10.1002/9780470994559

Preti, A., & Cella, M. (2010). Randomized-controlled trials in people at ultra high risk of psychosis: A review of treatment effectiveness. *Schizophrenia Research*, *123*(1), 30-36. https://doi.org/10.1016/j.schres.2010.07.026

Prochaska, J. O., & Norcross, J. C. (2024). *Systems of psychotherapy: A transtheoretical analysis* (10th ed.). Oxford University Press. https://global.oup.com/academic/product/systems-of-psychotherapy-9780197774908

Pruessner, M., Cullen, A. E., Aas, M., & Walker, E. F. (2017). The neural diathesis-stress model of schizophrenia revisited: An update on recent findings considering illness stage and neurobiological and methodological complexities. *Neuroscience & Biobehavioral Reviews*, *73*, 191-218. https://doi.org/10.1016/j.neubiorev.2016.12.013

Qiu, Y., Li, L., Gan, Z., Wang, J., Zheng, L., Zhao, J., Guan, N., & Wei, Q. (2019). Factors related to duration of untreated psychosis of first episode schizophrenia spectrum disorder. *Early Intervention in Psychiatry*, *13*(3), 555-561. https://doi.org/10.1111/eip.12519

R Core Team. (2024). *R: A language and environment for statistical computing* (Version 4.3.2) [Computer software]. R Foundation for Statistical Computing. https://r-project.org/

Radua, J., Ramella-Cravaro, V., Ioannidis, J. P., Reichenberg, A., Phiphopthatsanee, N., Amir, T., Yenn Thoo, H., Oliver, D., Davies, C., & Morgan, C. (2018). What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*, *17*(1), 49-66. https://doi.org/10.1002/wps.20490

Randhawa, A., Kühn, S., Schöttle, D., Moritz, S., Gallinat, J., & Ascone, L. (2023). The effects of assessing character strengths vs. psychopathology on mood, hope, perceived stigma and cognitive performance in individuals with psychosis. *PLOS ONE*, *18*(8), 1-12. https://doi.org/10.1371/journal.pone.0289872

Rapisarda, A., Kraus, M., Tan, Y. W., Lam, M., Eng, G. K., Lee, J., Subramaniam, M., Collinson, S. L., Chong, S. A., & Keefe, R. S. (2014). The Continuous Performance Test, Identical Pairs: Norms, reliability and performance in healthy controls and patients with schizophrenia in Singapore. *Schizophrenia Research*, *156*(2-3), 233-240. https://doi.org/10.1016/j.schres.2014.04.016

Read, J., Fosse, R., Moskowitz, A., & Perry, B. (2014). The traumagenic neurodevelopmental model of psychosis revisited. *Neuropsychiatry*, *4*(1), 65-79. https://doi.org/10.2217/npy.13.89

Read, J., van Os, J., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: A literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, *112*(5), 330-350. https://doi.org/10.1111/j.1600-0447.2005.00634.x

Reddy, L. F., Horan, W. P., & Green, M. F. (2014). Revisions and refinements of the diagnosis of schizophrenia in DSM-5. *Clinical Psychology: Science and Practice*, *21*(3), 236-244. https://doi.org/10.1111/cpsp.12071

Rek-Owodziń, K., Tyburski, E., Plichta, P., Waszczuk, K., Bielecki, M., Wietrzyński, K., Podwalski, P., Rudkowski, K., Michalczyk, A., & Grąźlewski, T. (2022). The relationship between cognitive functions and psychopathological symptoms in first episode psychosis and chronic schizophrenia. *Journal of Clinical Medicine*, *11*(9), 1-14. https://doi.org/10.3390/jcm11092619

Rekhi, G., Saw, Y. E., Lim, K., Keefe, R. S. E., & Lee, J. (2023). Impact of cognitive impairments on health-related quality of life in schizophrenia. *Brain Sciences*, *13*(2), 1-9. https://doi.org/10.3390/brainsci13020215

Revell, E. R., Neill, J. C., Harte, M., Khan, Z., & Drake, R. J. (2015). A systematic review and meta-analysis of cognitive remediation in early schizophrenia. *Schizophrenia Research*, *168*(1-2), 213-222. https://doi.org/10.1016/j.schres.2015.08.017

Ritunnano, R., Kleinman, J., Oshodi, D. W., Michail, M., Nelson, B., Humpston, C. S., & Broome, M. R. (2022). Subjective experience and meaning of delusions in psychosis: A systematic review and qualitative evidence synthesis. *The Lancet Psychiatry*, *9*(6), 458-476. https://doi.org/10.1016/S2215-0366(22)00104-3

Robinaugh, D. J., Hoekstra, R. H., Toner, E. R., & Borsboom, D. (2020). The network approach to psychopathology: A review of the literature 2008–2018 and an agenda for future research. *Psychological Medicine*, *50*(3), 353-366. https://doi.org/10.1017/S0033291719003404

Robinaugh, D. J., Millner, A. J., & McNally, R. J. (2016). Identifying highly influential nodes in the complicated grief network. *Journal of Abnormal Psychology*, *125*(6), 747-757. https://doi.org/10.1037/abn0000181

Rocca, E., & Anjum, R. L. (2020). *A CauseHealth resource for healthcare professionals and the clinical encounter: Rethinking causality, complexity and evidence for the unique patient*. Springer Cham. https://doi.org/10.1007/978-3-030-41239-5

Roche, E., Creed, L., MacMahon, D., Brennan, D., & Clarke, M. (2015). The epidemiology and associated phenomenology of formal thought disorder: A systematic review. *Schizophrenia Bulletin*, *41*(4), 951-962. https://doi.org/10.1093/schbul/sbu129

Rodebaugh, T. L., Tonge, N. A., Piccirillo, M. L., Fried, E., Horenstein, A., Morrison, A. S., Goldin, P., Gross, J. J., Lim, M. H., & Fernandez, K. C. (2018). Does centrality in a cross-sectional network suggest intervention targets for social anxiety disorder? *Journal of Consulting and Clinical Psychology*, *86*(10), 831-844. https://doi.org/10.1037/ccp0000336

Rose, D., Willis, R., Brohan, E., Sartorius, N., Villares, C., Wahlbeck, K., & Thornicroft, G. (2011). Reported stigma and discrimination by people with a diagnosis of schizophrenia. *Epidemiology and Psychiatric Sciences*, *20*(2), 193-204. https://doi.org/10.1017/S2045796011000254

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, *48*, 1-36. https://doi.org/10.18637/jss.v048.i02

Ruff, R., Light, R., Parker, S., & Levin, H. (1996). Benton Controlled Oral Word Association Test: Reliability and updated norms. *Archives of Clinical Neuropsychology*, *11*(4), 329-338. https://doi.org/10.1093/arclin/11.4.329

Rund, B. R. (2018). The research evidence for schizophrenia as a neurodevelopmental disorder. *Scandinavian Journal of Psychology*, *59*(1), 49-58. https://doi.org/10.1111/sjop.12414

Sachs, K., Perez, O., Pe'er, D., Lauffenburger, D. A., & Nolan, G. P. (2005). Causal protein-signaling networks derived from multiparameter single-cell data. *Science*, *308*(5721), 523-529. https://doi.org/10.1126/science.1105809

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry*, *64*(10), 1123-1131. https://doi.org/10.1001/archpsyc.64.10.1123

Salmerón, A., Rumí, R., Langseth, H., Nielsen, T. D., & Madsen, A. L. (2018). A review of inference algorithms for hybrid Bayesian networks. *Journal of Artificial Intelligence Research*, *62*(1), 799-828. https://doi.org/10.1613/jair.1.11228

Salomon, J. A., Haagsma, J. A., Davis, A., de Noordhout, C. M., Polinder, S., Havelaar, A. H., Cassini, A., Devleesschauwer, B., Kretzschmar, M., & Speybroeck, N. (2015). Disability weights for the Global Burden of Disease 2013 study. *The Lancet Global Health*, *3*(11), e712-e723. https://doi.org/10.1016/S2214-109X(15)00069-8

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403-428. https://doi.org/10.1037/0033-295x.103.3.403

Samanaite, R., Gillespie, A., Sendt, K.-V., McQueen, G., MacCabe, J. H., & Egerton, A. (2018). Biological predictors of clozapine response: A systematic review. *Frontiers in Psychiatry*, *9*, 1-25. https://doi.org/10.3389/fpsyt.2018.00327

Santos, B., González-Fraile, E., Zabala, A., Guillén, V., Rueda, J. R., & Ballesteros, J. (2018). Cognitive improvement of acetylcholinesterase inhibitors in schizophrenia. *Journal of Psychopharmacology*, *32*(11), 1155-1166. https://doi.org/10.1177/0269881118805496

Sarstedt, M., Hair, J. F., Nitzl, C., Ringle, C. M., & Howard, M. C. (2020). Beyond a tandem analysis of SEM and PROCESS: Use of PLS-SEM for mediation analyses! *International Journal of Market Research*, *62*(3), 288-299. https://doi.org/10.1177/1470785320915686

Sass, L. A., & Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophrenia Bulletin*, *29*(3), 427-444. https://doi.org/10.1093/oxfordjournals.schbul.a007017

Savill, M., Banks, C., Khanom, H., & Priebe, S. (2015). Do negative symptoms of schizophrenia change over time? A meta-analysis of longitudinal data. *Psychological Medicine*, *45*(8), 1613-1627. https://doi.org/10.1017/S0033291714002712

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42-50. https://doi.org/10.1016/j.schres.2013.07.009

Schmank, C. J., Goring, S. A., Kovacs, K., & Conway, A. R. A. (2019). Psychometric network analysis of the Hungarian WAIS. *Journal of Intelligence*, *7*(3), 1-13. https://doi.org/10.3390/jintelligence7030021

Schumacher, L., Burger, J., Echterhoff, J., & Kriston, L. (2022). *Methodological and statistical practices of using symptom networks to evaluate mental health interventions: A systematic review.* PsyarXiv. https://doi.org/10.31234/osf.io/ea7fu

Schumacher, L., Julian, B., Jette, E., & and Kriston, L. (2024). Methodological and statistical practices of using symptom networks to evaluate mental health interventions: A review and reflections. *Multivariate Behavioral Research*, *59*(4), 663-676. https://doi.org/10.1080/00273171.2024.2335401

Scutari, M. (2009). *Learning Bayesian networks with the bnlearn R package.* arXiv. https://doi.org/10.48550/arXiv.0908.3817

Scutari, M. (2017). Bayesian network constraint-based structure learning algorithms: Parallel and optimised implementations in the bnlearn R package. *Journal of Statistical Software*, *77*(2), 1-20. https://doi.org/10.18637/jss.v077.i02

Scutari, M., & Denis, J.-B. (2021). *Bayesian networks: With examples in R*. Chapman and Hall/CRC. https://doi.org/10.1201/9780429347436

Scutari, M., Graafland, C. E., & Gutiérrez, J. M. (2019). Who learns better Bayesian network structures: Accuracy and speed of structure learning algorithms. *International Journal of Approximate Reasoning*, *115*, 235-253. https://doi.org/10.1016/j.ijar.2019.10.003

Scutari, M., & Nagarajan, R. (2013). Identifying significant edges in graphical models of molecular networks. *Artificial Intelligence in Medicine*, *57*(3), 207-217. https://doi.org/10.1016/j.artmed.2012.12.006

Seeman, M. V. (2021). History of the dopamine hypothesis of antipsychotic action. *World Journal of Psychiatry*, *11*(7), 355-364. https://doi.org/10.5498/wjp.v11.i7.355

Shafer, A. (2005). Meta-analysis of the Brief Psychiatric Rating Scale factor structure. *Psychological Assessment*, *17*(3), 324-335. https://doi.org/10.1037/1040-3590.17.3.324

Shafer, A., & Dazzi, F. (2019). Meta-analysis of the Positive and Negative Syndrome Scale (PANSS) factor structure. *Journal of Psychiatric Research*, *115*, 113-120. https://doi.org/10.1016/j.jpsychires.2019.05.008

Sheppard, L. D., & Vernon, P. A. (2008). Intelligence and speed of information-processing: A review of 50 years of research. *Personality and Individual Differences*, *44*(3), 535-551. https://doi.org/10.1016/j.paid.2007.09.015

Shrivastava, A. K., & Johnston, M. E. (2010). Cognitive neurosciences: A new paradigm in management and outcome of schizophrenia. *Indian Journal of Psychiatry*, *52*(2), 100-105. https://doi.org/10.4103/0019-5545.64575

Shukla, R., Hirpara, D., Sagar, K., & Rajpura, A. (2024). Promising advances in schizophrenia treatment. *Journal of Pharma Insights and Research*, *2*(4), 59-66. https://doi.org/10.69613/v5mv2h28

Siegert, R. J. (2000). Culture, cognition, and schizophrenia. In J. F. Schumaker & T. Ward (Eds.), *Culture, cognition and psychopathology* (pp. 171-190). Praeger. https://doi.org/10.1176/appi.ajp.158.9.1545

Silverstein, S. M., & Lai, A. (2021). The phenomenology and neurobiology of visual distortions and hallucinations in schizophrenia: An update. *Frontiers in Psychiatry*, *12*, 1-18. https://doi.org/10.3389/fpsyt.2021.684720

Smeland, O. B., Frei, O., Dale, A. M., & Andreassen, O. A. (2020). The polygenic architecture of schizophrenia—rethinking pathogenesis and nosology. *Nature Reviews Neurology*, *16*, 366-379. https://doi.org/10.1038/s41582-020-0364-0

Smith, L. T. (2021). *Decolonizing methodologies: Research and indigenous peoples*. Bloomsbury Publishing. https://bloomsbury.com/us/decolonizing-methodologies-9781786998125/

Sommer, I. E., Tiihonen, J., van Mourik, A., Tanskanen, A., & Taipale, H. (2020). The clinical course of schizophrenia in women and men—a nation-wide cohort study. *NPJ Schizophrenia*, *6*, 1-7. https://doi.org/10.1038/s41537-020-0102-z

Spirtes, P., Glymour, C., & Scheines, R. (2001). *Causation, prediction, and search*. Springer New York. https://doi.org/10.1007/978-1-4612-2748-9

Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: Dopamine, serotonin, and glutamate. *CNS Spectrums*, *23*(3), 187-191. https://doi.org/10.1017/S1092852918001013

Stahl, S. M., & Buckley, P. F. (2007). Negative symptoms of schizophrenia: A problem that will not go away. *Acta Psychiatrica Scandinavica*, *115*(1), 4-11. https://doi.org/10.1111/j.1600-0447.2006.00947.x

Starzer, M., Hansen, H. G., Hjorthøj, C., Albert, N., Nordentoft, M., & Madsen, T. (2023). 20-year trajectories of positive and negative symptoms after the first psychotic episode in patients with schizophrenia spectrum disorder: Results from the OPUS study. *World Psychiatry*, *22*(3), 424-432. https://doi.org/10.1002/wps.21121

Stekhoven, D. J., & Bühlmann, P. (2012). MissForest—non-parametric missing value imputation for mixed-type data. *Bioinformatics*, *28*(1), 112-118. https://doi.org/10.1093/bioinformatics/btr597

Strassnig, M. T., Raykov, T., O'Gorman, C., Bowie, C. R., Sabbag, S., Durand, D., Patterson, T. L., Pinkham, A., Penn, D. L., & Harvey, P. D. (2015). Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity. *Schizophrenia Research*, *165*(1), 76-82. https://doi.org/10.1016/j.schres.2015.03.033

Strauss, G. P., Esfahlani, F. Z., Galderisi, S., Mucci, A., Rossi, A., Bucci, P., Rocca, P., Maj, M., Kirkpatrick, B., & Ruiz, I. (2019a). Network analysis reveals the latent structure of negative symptoms in schizophrenia. *Schizophrenia Bulletin*, *45*(5), 1033-1041. https://doi.org/10.1093/schbul/sby133

Strauss, G. P., Esfahlani, F. Z., Kirkpatrick, B., Allen, D. N., Gold, J. M., Visser, K. F., & Sayama, H. (2019b). Network analysis reveals which negative symptom domains are most central in schizophrenia vs bipolar disorder. *Schizophrenia Bulletin*, *45*(6), 1319-1330. https://doi.org/10.1093/schbul/sby168

Strauss, G. P., Zamani Esfahlani, F., Sayama, H., Kirkpatrick, B., Opler, M. G., Saoud, J. B., Davidson, M., & Luthringer, R. (2020). Network analysis indicates that avolition Is the most central domain for the successful treatment of negative symptoms: Evidence from the roluperidone randomized clinical trial. *Schizophrenia Bulletin*, *46*(4), 964-970. https://doi.org/10.1093/schbul/sbz141

Stroup, T. S., McEvoy, J. P., Swartz, M. S., Byerly, M. J., Glick, I. D., Canive, J. M., McGee, M. F., Simpson, G. M., Stevens, M. C., & Lieberman, J. A. (2003). The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: Schizophrenia trial design and protocol development. *Schizophrenia Bulletin*, *29*(1), 15-31. https://doi.org/10.1093/oxfordjournals.schbul.a006986

Sullivan, P. F., Kendler, K. S., & Neale, M. C. (2003). Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*, *60*(12), 1187-1192. https://doi.org/10.1001/archpsyc.60.12.1187

Sun, Y., Zhang, Y., Lu, Z., Yan, H., Guo, L., Liao, Y., Lu, T., Wang, L., Li, J., & Li, W. (2023). Longitudinal network analysis reveals interactive change of schizophrenia symptoms during acute antipsychotic treatment. *Schizophrenia Bulletin*, *49*(1), 208-217. https://doi.org/10.1093/schbul/sbac131

Swartz, M. S., Stroup, T. S., McEvoy, J. P., Davis, S. M., Rosenheck, R. A., Keefe, R. S., Hsiao, J. K., & Lieberman, J. A. (2008). Special section on implications of CATIE: What CATIE found: Results from the schizophrenia trial. *Psychiatric Services*, *59*(5), 500-506. https://doi.org/10.1176/ps.2008.59.5.500

Szasz, T. (2011). The myth of mental illness: 50 years later. *The Psychiatrist*, *35*(5), 179-182. https://doi.org/10.1192/pb.bp.110.031310

Taitimu, M., Read, J., & McIntosh, T. (2018). Ngā Whakāwhitinga (standing at the crossroads): How Māori understand what Western psychiatry calls “schizophrenia”. *Transcultural Psychiatry*, *55*(2), 153-177. https://doi.org/10.1177/1363461518757800

Takeuchi, H., Kantor, N., Sanches, M., Fervaha, G., Agid, O., & Remington, G. (2017). One-year symptom trajectories in patients with stable schizophrenia maintained on antipsychotics versus placebo: Meta-analysis. *The British Journal of Psychiatry*, *211*(3), 137-143. https://doi.org/10.1192/bjp.bp.116.186007

Tamminga, C. A., Pearlson, G. D., Stan, A. D., Gibbons, R. D., Padmanabhan, J., Keshavan, M., & Clementz, B. A. (2017). Strategies for advancing disease definition using biomarkers and genetics: The bipolar and schizophrenia network for intermediate phenotypes. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *2*(1), 20-27. https://doi.org/10.1016/j.bpsc.2016.07.005

Tanaka, J. S. (1993). Multifaceted conceptions of fit in structural equation models. In K. A. Bollen & J. S. Long (Eds.), *Testing structural equation models* (pp. 10-39). Sage. https://us.sagepub.com/en-us/nam/testing-structural-equation-models/book3893

Taylor, M., & Jauhar, S. (2019). Are we getting any better at staying better? The long view on relapse and recovery in first episode nonaffective psychosis and schizophrenia. *Therapeutic Advances in Psychopharmacology*, *9*, 1-11. https://doi.org/10.1177/2045125319870033

Telles-Correia, D., Moreira, A. L., & Gonçalves, J. S. (2015). Hallucinations and related concepts—their conceptual background. *Frontiers in Psychology*, *6*, 1-9. https://doi.org/10.3389/fpsyg.2015.00991

Thornicroft, G., Sunkel, C., Aliev, A. A., Baker, S., Brohan, E., El Chammay, R., Davies, K., Demissie, M., Duncan, J., & Fekadu, W. (2022). The Lancet Commission on ending stigma and discrimination in mental health. *The Lancet*, *400*(10361), 1438-1480. https://doi.org/10.1016/S0140-6736(22)01470-2

Thuaire, F., Rondepierre, F., Vallet, G. T., Jalenques, I., & Izaute, M. (2022). Executive deficits in schizophrenia: Mediation by processing speed and its relationships with aging. *Psychological Medicine*, *52*(6), 1126-1134. https://doi.org/10.1017/S0033291720002871

Thumiger, C., & Singer, P. N. (2018). Introduction. Disease classification and mental illness: Ancient and modern perspectives. In C. Thumiger & P. N. Singer (Eds.), *Mental Illness in Ancient Medicine* (pp. 1-32). Brill. https://doi.org/10.1163/9789004362260_002

Torjesen, I. (2024). Schizophrenia: US approves first new treatment in decades. *BMJ*, *386*, 1-2. https://doi.org/10.1136/bmj.q2133

Trotta, A., Murray, R., & MacCabe, J. (2015). Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. *Psychological Medicine*, *45*(2), 381-394. https://doi.org/10.1017/S0033291714001512

Tsamardinos, I., Aliferis, C. F., Statnikov, A. R., & Statnikov, E. (2003). Algorithms for large scale Markov blanket discovery. *Proceedings of the Sixteenth International Florida Artificial Intelligence Research Society Conference*, *USA*. *2*, 376-380. https://aaai.org/papers/flairs-2003-073/

Tsamardinos, I., Brown, L. E., & Aliferis, C. F. (2006). The max-min hill-climbing Bayesian network structure learning algorithm. *Machine Learning*, *65*, 31-78. https://doi.org/10.1007/s10994-006-6889-7

Tsuang, M. T., Van Os, J., Tandon, R., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R. E., Heckers, S., Malaspina, D., & Owen, M. J. (2013). Attenuated psychosis syndrome in DSM-5. *Schizophrenia Research*, *150*(1), 31-35. https://doi.org/10.1016/j.schres.2013.05.004

Turkheimer, F. E., Rosas, F. E., Dipasquale, O., Martins, D., Fagerholm, E. D., Expert, P., Váša, F., Lord, L.-D., & Leech, R. (2022). A complex systems perspective on neuroimaging studies of behavior and its disorders. *The Neuroscientist*, *28*(4), 382-399. https://doi.org/10.1177/1073858421994784

Turner, D. T., McGlanaghy, E., Cuijpers, P., Van Der Gaag, M., Karyotaki, E., & MacBeth, A. (2018). A meta-analysis of social skills training and related interventions for psychosis. *Schizophrenia Bulletin*, *44*(3), 475-491. https://doi.org/10.1093/schbul/sbx146

U.S. Food and Drug Administration. (2025, Janurary). *Drug trials snapshot: Cobenfy*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshot-cobenfy

Upthegrove, R., Marwaha, S., & Birchwood, M. (2017). Depression and schizophrenia: Cause, consequence, or trans-diagnostic issue? *Schizophrenia Bulletin*, *43*(2), 240-244. https://doi.org/10.1093/schbul/sbw097

Valton, V., Romaniuk, L., Steele, J. D., Lawrie, S., & Seriès, P. (2017). Comprehensive review: Computational modelling of schizophrenia. *Neuroscience & Biobehavioral Reviews*, *83*, 631-646. https://doi.org/10.1016/j.neubiorev.2017.08.022

van Bork, R., Rhemtulla, M., Waldorp, L. J., Kruis, J., Rezvanifar, S., & Borsboom, D. (2021). Latent variable models and networks: Statistical equivalence and testability. *Multivariate Behavioral Research*, *56*(2), 175-198. https://doi.org/10.1080/00273171.2019.1672515

van Borkulo, C., Boschloo, L., Borsboom, D., Penninx, B. W. J. H., Waldorp, L. J., & Schoevers, R. A. (2015). Association of symptom network structure with the course of depression. *JAMA Psychiatry*, *72*(12), 1219-1226. https://doi.org/10.1001/jamapsychiatry.2015.2079

Van Borkulo, C. D., van Bork, R., Boschloo, L., Kossakowski, J. J., Tio, P., Schoevers, R. A., Borsboom, D., & Waldorp, L. J. (2022). Comparing network structures on three aspects: A permutation test. *Psychological Methods*, *28*(6), 1273-1285. https://doi.org/10.1037/met0000476

Van Os, J. (2004). Does the urban environment cause psychosis? *The British Journal of Psychiatry*, *184*(4), 287-288. https://doi.org/10.1192/bjp.184.4.287

van Os, J., Guloksuz, S., Vijn, T. W., Hafkenscheid, A., & Delespaul, P. (2019). The evidence-based group-level symptom-reduction model as the organizing principle for mental health care: Time for change? *World Psychiatry*, *18*(1), 88-96. https://doi.org/10.1002/wps.20609

van Rooijen, G., Isvoranu, A.-M., Kruijt, O. H., van Borkulo, C. D., Meijer, C. J., Wigman, J. T., Ruhe, H. G., & de Haan, L. (2018). A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. *Schizophrenia Research*, *193*, 232-239. https://doi.org/10.1016/j.schres.2017.07.035

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., Van Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin*, *38*(4), 661-671. https://doi.org/10.1093/schbul/sbs050

Veerman, S. R., Schulte, P. F., & De Haan, L. (2017). Treatment for negative symptoms in schizophrenia: A comprehensive review. *Drugs*, *77*, 1423-1459. https://doi.org/10.1007/s40265-017-0789-y

Ventriglio, A., Ricci, F., Magnifico, G., Chumakov, E., Torales, J., Watson, C., Castaldelli-Maia, J. M., Petito, A., & Bellomo, A. (2020). Psychosocial interventions in schizophrenia: Focus on guidelines. *International Journal of Social Psychiatry*, *66*(8), 735-747. https://doi.org/10.1177/0020764020934827

Ventura, J., Thames, A. D., Wood, R. C., Guzik, L. H., & Hellemann, G. S. (2010). Disorganization and reality distortion in schizophrenia: A meta-analysis of the relationship between positive symptoms and neurocognitive deficits. *Schizophrenia Research*, *121*(1-3), 1-14. https://doi.org/10.1016/j.schres.2010.05.033

Verma, T., & Pearl, J. (1990). Equivalence and synthesis of causal models. *Proceedings of the Sixth Annual Conference on Uncertainty in Artificial Intelligence*, 255-270. https://ftp.cs.ucla.edu/tech-report/1991-reports/910020.pdf

Verma, T. S., & Pearl, J. (2022). *Probabilistic and causal inference: The works of Judea Pearl*. Association for Computing Machinery. https://doi.org/10.1145/3501714.3501732

Vita, A., & Barlati, S. (2018). Recovery from schizophrenia: Is it possible? *Current Opinion in Psychiatry*, *31*(3), 246-255. https://doi.org/10.1097/YCO.0000000000000407

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., & Wykes, T. (2021). Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: A systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*, *78*(8), 848-858. https://doi.org/10.1001/jamapsychiatry.2021.0620

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Durante, F., Facchi, M., Deste, G., & Wykes, T. (2024). Durability of effects of cognitive remediation on cognition and psychosocial functioning in schizophrenia: A systematic review and meta-analysis of randomized clinical trials. *American Journal of Psychiatry*, *181*(6), 520-531. https://doi.org/10.1176/appi.ajp.20230396

Vita, A., Gaebel, W., Mucci, A., Sachs, G., Erfurth, A., Barlati, S., Zanca, F., Giordano, G. M., Glenthøj, L. B., & Nordentoft, M. (2022). European Psychiatric Association guidance on assessment of cognitive impairment in schizophrenia. *European Psychiatry*, *65*(1), 1-24. https://doi.org/10.1192/j.eurpsy.2022.2316

Volkan, K. (2021). Schizophrenia, culture, and culture-bound syndromes. *Psychology Research and Applications*, *3*(1), 1-13. https://dx.doi.org/10.22606/pra.2021.31001

Walker, E. F., & Diforio, D. (1997). Schizophrenia: A neural diathesis-stress model. *Psychological Review*, *104*(4), 667-685. https://doi.org/10.1037/0033-295x.104.4.667

Walker, R., Hutchings, J., & Lee-Morgan, J. (2016). *Decolonisation in Aotearoa: Education, research, and practice*. New Zealand Council for Educational Research. https://nzcer.org.nz/nzcerpress/decolonisation

Walsh, J., Hochbrueckner, R., Corcoran, J., & Spence, R. (2016). The lived experience of schizophrenia: A systematic review and meta-synthesis. *Social Work in Mental Health*, *14*(6), 607-624. https://doi.org/10.1080/15332985.2015.1100153

Wang, L.-L., Tam, M. H., Ho, K. K., Hung, K. S., Wong, J. O., Lui, S. S., & Chan, R. C. (2023). Bridge centrality network structure of negative symptoms in people with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *273*(3), 589-600. https://doi.org/10.1007/s00406-022-01474-w

Weinberger, D. R., & Harrison, P. J. (2011). *Schizophrenia*. Blackwell Publishing. https://doi.org/10.1002/9781444327298

Wheeler, A. L., & Voineskos, A. N. (2014). A review of structural neuroimaging in schizophrenia: From connectivity to connectomics. *Frontiers in Human Neuroscience*, *8*, 1-18. https://doi.org/10.3389/fnhum.2014.00653

Widiger, T. A., & Samuel, D. B. (2005). Diagnostic categories or dimensions? A question for the Diagnostic and Statistical Manual of Mental Disorders--fifth edition. *Journal of Abnormal Psychology*, *114*(4), 494-504. https://doi.org/10.1037/0021-843X.114.4.494

Williams, D. R., Rhemtulla, M., Wysocki, A. C., & Rast, P. (2019). On nonregularized estimation of psychological networks. *Multivariate Behavioral Research*, *54*(5), 719-750. https://doi.org/10.1080/00273171.2019.1575716

Williams, M. N. (2021). Levels of measurement and statistical analyses. *Meta-Psychology*, *5*, 1-14. https://doi.org/10.15626/MP.2019.1916

Wilshire, C. E., Ward, T., & Clack, S. (2021). Symptom descriptions in psychopathology: How well are they working for us? *Clinical Psychological Science*, *9*(3), 323-339. https://doi.org/10.1177/2167702620969215

Wójciak, P., Remlinger-Molenda, A., & Rybakowski, J. (2016). Stages of the clinical course of schizophrenia-staging concept. *Psychiatria Polska*, *50*(4), 717-730. https://doi.org/10.12740/PP/5872

Wolf, E. J., Harrington, K. M., Clark, S. L., & Miller, M. W. (2013). Sample size requirements for structural equation models: An evaluation of power, bias, and solution propriety. *Educational and Psychological Measurement*, *73*(6), 913-934. https://doi.org/10.1177/0013164413495237

Woodberry, K. A., Shapiro, D. I., Bryant, C., & Seidman, L. J. (2016). Progress and future directions in research on the psychosis prodrome: A review for clinicians. *Harvard Review of Psychiatry*, *24*(2), 87-103. https://doi.org/10.1097/HRP.0000000000000109

Woods, B. T. (1998). Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *American Journal of Psychiatry*, *155*(12), 1661-1670. https://doi.org/10.1176/ajp.155.12.1661

Woods, S. W., Walsh, B. C., Powers, A. R., & McGlashan, T. H. (2019). Reliability, validity, epidemiology, and cultural variation of the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Scale of Psychosis-Risk Symptoms (SOPS). In H. Li, D. I. Shapiro, & L. J. Seidman (Eds.), *Handbook of attenuated psychosis syndrome across cultures: International perspectives on early identification and intervention* (pp. 85-113). Springer International Publishing. https://doi.org/10.1007/978-3-030-17336-4_5

World Health Organization. (2019). *ICD-11: International statistical classification of diseases and related health problems* (11 ed.). https://icd.who.int/

Worthington, M. A., & Cannon, T. D. (2021). Prediction and prevention in the clinical high-risk for psychosis paradigm: A review of the current status and recommendations for future directions of inquiry. *Frontiers in Psychiatry*, *12*, 1-10. https://doi.org/10.3389/fpsyt.2021.770774

Wyatt, R. J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, *17*(2), 325-351. https://doi.org/10.1093/schbul/17.2.325

Wykes, T., Huddy, V., Cellard, C., McGurk, S. R., & Czobor, P. (2011). A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *American Journal of Psychiatry*, *168*(5), 472-485. https://doi.org/10.1176/appi.ajp.2010.10060855

Yan, J., Chen, Y., Ju, P., Gao, J., Zhang, L., Li, J., Wang, K., Zhang, J., Li, C., Xia, Q., Zhu, C., & Zhang, X. (2022). Network association of biochemical and inflammatory abnormalities with psychiatric symptoms in first-episode schizophrenia patients. *Frontiers in Psychiatry*, *13*, 1-10. https://doi.org/10.3389/fpsyt.2022.834539

Yang, Z., Lee, S. H., Abdul Rashid, N. A., See, Y. M., Dauwels, J., Tan, B. L., & Lee, J. (2021). Predicting real-world functioning in schizophrenia: The relative contributions of neurocognition, functional capacity, and negative symptoms. *Frontiers in Psychiatry*, *12*, 1-8. https://doi.org/10.3389/fpsyt.2021.639536

Ypinazar, V. A., Margolis, S. A., Haswell-Elkins, M., & Tsey, K. (2007). Indigenous Australians' understandings regarding mental health and disorders. *Australian & New Zealand Journal of Psychiatry*, *41*(6), 467-478. https://doi.org/10.1080/00048670701332953

Yuan, K.-H., & Chan, W. (2016). Measurement invariance via multigroup SEM: Issues and solutions with chi-square-difference tests. *Psychological Methods*, *21*(3), 405-426. https://doi.org/10.1037/met0000080

Yung, A. R., & McGorry, P. D. (1996a). The initial prodrome in psychosis: Descriptive and qualitative aspects. *Australian and New Zealand Journal of Psychiatry*, *30*(5), 587-599. https://doi.org/10.3109/00048679609062654

Yung, A. R., & McGorry, P. D. (1996b). The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin*, *22*(2), 353-370. https://doi.org/10.1093/schbul/22.2.353

Yung, A. R., Nelson, B., Stanford, C., Simmons, M. B., Cosgrave, E. M., Killackey, E., Phillips, L. J., Bechdolf, A., Buckby, J., & McGorry, P. D. (2008). Validation of "prodromal" criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophrenia Research*, *105*(1-3), 10-17. https://doi.org/10.1016/j.schres.2008.07.012

Yung, A. R., Yung, A. R., Pan Yuen, H., Mcgorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E. M., & Killackey, E. (2005). Mapping the onset of psychosis: The comprehensive assessment of at-risk mental states. *Australian & New Zealand Journal of Psychiatry*, *39*(11-12), 964-971. https://doi.org/10.1080/j.1440-1614.2005.01714.x

Zheng, Z., & Pavlou, P. A. (2010). Research note—toward a causal interpretation from observational data: A new Bayesian networks method for structural models with latent variables. *Information Systems Research*, *21*(2), 365-391. https://doi.org/10.1287/isre.1080.0224

Zuk, O., Margel, S., & Domany, E. (2012). *On the number of samples needed to learn the correct structure of a Bayesian network.* arXiv. https://doi.org/10.48550/arXiv.1206.6862

Appendix A1 AUTEC Approval (Chapter 5 & Chapter 6)

TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

Auckland University of Technology Ethics Committee (AUTEC)

12 July 2023

Richard Siegert
Faculty of Health and Environmental Sciences

Dear Richard

Re Ethics Application: **22/387 Static Symptom Networks of Schizophrenia**

Thank you for your correspondence in relation to AUTEC's conditions.

Your ethics application has been approved for three years until 12 July 2026.

The amendment to the data repository has been noted. (No longer using Australia, using NIMH USA, therefore no need to obtain an additional data sharing agreement.

The change to the supervisor team has been noted.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC.
2. All public facing documents must have the AUTEC approval number and be of a high standard of spelling and grammar. Dates on the Information Sheet(s) and Consent Form(s) must be consistent.
3. Any amendments to the project must be approved by AUTEC prior to being implemented.
4. A progress report is due annually on the anniversary of the approval date.
5. A final report is due at the expiration of the approval period, or, upon completion of project.
6. Any serious or adverse events must be reported to AUTEC, this includes unforeseen issues that might affect continued ethical acceptability of the project.
7. AUTEC grants ethical approval only. You are responsible for obtaining management permission for access from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

The application number and title need to be referenced on all correspondence related to this project.

All forms are available online http://www.aut.ac.nz/research/researchethics

For any enquiries, please contact ethics@aut.ac.nz
(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: khanbm@live.com; Richard Siegert; Ajit Narayanan

Auckland University of Technology, D-88, Private Bag 92006, Auckland 1142, New Zealand.
T: +64 9 921 9999 ext. 8316: E: ethics@aut.ac.nz: www.aut.ac.nz/researchethics

Figure 18. Ethical Approval for the CATIE Study.

Appendix A2 AUTEC Approval (Chapter 6)

TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

Auckland University of Technology Ethics Committee (AUTEC)

20 April 2023

Richard Siegert
Faculty of Health and Environmental Sciences

Dear Richard

Re Ethics Application: **22/388 Dynamic Symptom Networks of Schizophrenia (American data set)**

Thank you for your response to AUTEC's conditions.

Your ethics application has been approved for three years until 19 April 2026.

The change to the supervision team has been noted.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC.
2. All public facing documents must have the AUTEC approval number and be of a high standard of spelling and grammar. Dates on the Information Sheet(s) and Consent Form(s) must be consistent.
3. Any amendments to the project must be approved by AUTEC prior to being implemented.
4. A progress report is due annually on the anniversary of the approval date.
5. A final report is due at the expiration of the approval period, or, upon completion of project.
6. Any serious or adverse events must be reported to AUTEC, this includes unforeseen issues that might affect continued ethical acceptability of the project.
7. AUTEC grants ethical approval only. You are responsible for obtaining management permission for access from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

The application number and title need to be referenced on all correspondence related to this project.

All forms are available online http://www.aut.ac.nz/research/researchethics

For any enquiries, please contact ethics@aut.ac.nz
(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: khanbm@live.com; Ajit Narayanan

Auckland University of Technology, D-88, Private Bag 92006, Auckland 1142, New Zealand.
T: +64 9 921 9999 ext. 8316: E: ethics@aut.ac.nz: www.aut.ac.nz/researchethics

Figure 19. Ethical Approval for the NAPLS3 Study.

Appendix B Pairwise Markov Random Fields

History and development

Markov random fields have had a long history, beginning with Ising's thesis in 1925, which focused on the study of ferromagnetism (Cross & Jain, 1983). Other advances included the covariance selection where elements of the precision matrix were set to zero to imply conditional independence between two variables (Dempster, 1972). Markov random field methods were then expanded by Besag (1974) and Pieczynski and Tebbache (2000), who coined PMRFs. Other prominent research in the late 1900s included the work by Lauritzen and Wermuth (1989), who modelled variables within a graph that may be discrete or continuous. The book, published by Lauritzen (1996), was perhaps the first textbook to integrate various independent pieces of research into a cohesive framework for statistical modelling within graphical networks. GGMs were used in other research fields, including gene regulatory networks and brain connectivity networks. Later in the 2000s came methods to handle high dimensional data and regularised methods. As with SN theory, GGMs were used to model systems of symptoms for the first time in Cramer et al. (2010). Since this development, statistical methods, software, and theory have rapidly increased in line with the growing popularity of using this as a theory of mental disorders.

Typology

The network can be dynamic or static. Static models only take into consideration one time period. Static networks are usually implemented on cross-sectional data on a snapshot in time. In terms of longitudinal or time series data, dynamic models introduce time into the model, where one person or multiple people are assessed two or more times throughout the study (Isvoranu et al., 2022). A dynamic network must be implemented on longitudinal data to avoid autocorrelation or row dependency (Jordan et al., 2020). The most common modelling technique for temporal data is lag one vector autoregression methods, where both within-time and between-time effects can be modelled (Isvoranu et al., 2022). However, when using vector autoregressive models, additional assumptions must be made. The first assumption is that the conditional distribution of variables at time t, given time t-1, is the same for all t (Epskamp et al., 2018b). This assumes that the network is homogeneous across further instances of t, even though the model may have a different structure at time t compared to time t-1. Additionally, time differences between measurements must be approximately equal, and the parameters do not change over time; hence, stationarity is assumed (Epskamp et al., 2018b). Dynamic models have the added advantage of being able to predict symptom experiences in time 2, given the structure of the symptom relationships in time 1 (Jordan et al., 2020). This inference cannot be made in a cross-sectional PMRF (Jordan et al., 2020).

Structure and parameter learning

There are many ways to estimate the structure and parameters of the network. Both structure and parameter learning occur simultaneously, as, in most cases, the structure is a direct outcome of the parameters. For example, if the partial correlation between two variables is zero, then no edge is found between these two variables. In most instances, partial correlations are used in place of a correlation; hence, in the remainder of Appendix B, edges are assumed to be partial correlations. When estimating the network from a sample, a key consideration is the population network. The final model may either have spurious edges, found edges in the sample network not present in the population model, or omitted edges, omitted edges present in the population model; hence, an optimal network or locally optimal network exists somewhere along the continuum of an empty network and a saturated network (Isvoranu et al., 2022). However, the method of estimation of the parameters can be grouped into four categories (Isvoranu et al., 2022). In the first category, the network is thresholded to obtain a saturated model where all edges are included in the model, but only edges above a threshold are visually displayed in the graph (Isvoranu et al., 2022). In pruning, the model is pruned where edges that are non-significant or do not satisfy a criterion; in this instance, the model is refitted to the data at each step (Isvoranu et al., 2022), similar to a combination of forward and backwards stepwise approaches. In model searching, the parameter space of the network is searched to find an optimal or locally optimal solution (Isvoranu et al., 2022). Although the model search leads to locally optimum solutions, these methods are generally slow compared to other network estimation methods (Isvoranu & Epskamp, 2023). Regularisation is implemented when machine learning is used to shrink small edge weights to zero (Isvoranu et al., 2022). Regularisation methods are more commonly used and are discussed below.

According to Isvoranu and Epskamp (2023), one widely used method includes EBIC graphical least absolute shrinkage and selection operator (GLASSO) for tuning parameter selection (Isvoranu & Epskamp, 2023). EBIC GLASSO estimates a network of partial correlations by penalising network complexity using EBIC as the criterion. Regularisation techniques shrink parameters to exactly zero when EBIC is improved via this simplification (Isvoranu & Epskamp, 2023). EBIC has an added term, gamma, that controls the amount of penalty EBIC places on model complexity (Isvoranu & Epskamp, 2023). Gamma usually has a value between zero and 0.5, and the value of gamma is arbitrary rather than estimated (Isvoranu et al., 2022). A value of zero represents no additional penalty on BIC (Isvoranu et al., 2022). The value of EBIC depends on BIC and the multiplicative relationships between gamma and the number of parameters. Although BIC also penalises overcomplex models, EBIC adds an additional penalty if gamma is greater than zero. The process attempts to avoid spurious associations, particularly in networks with low partial correlations. It is unlikely that any correlation in the natural world is exactly zero; hence, small correlations are removed from the model. EBIC GLASSO is very useful for sparse data, with high dimensionality and low sample size (Williams et al., 2019). EBIC GLASSO tends to have low false-positive and false-negative edges compared to others when the sample size is small, and regularised methods, in general, have good predictive validity across sample sizes (Isvoranu & Epskamp, 2023).

Many other statistical methods can fall under one of four possible categories of GGM selection by Isvoranu et al. (2022). Most of these methods are based on existing statistical tools and are implemented in various statistical packages for PMRF estimation. These methods include ggmModSelect, structural equation modelling (SEM), Bayesian sampling, GGM bootstrap, and GGM regression (Isvoranu & Epskamp, 2023). General methods such as Markov chain Monte Carlo using the Gibbs sampler can also be used to search the parameter space (Franco et al., 2024). Each method may be useful regarding its model fit index, specificity and sensitivity given the population network, or computational time.

Network testing

Network testing is a valuable method for comparing the structure of the PMRF networks to identify if there is any difference between groups. According to one review, 56.6% of the studies selected used a network comparison test to determine significant differences between two reconstructed networks (Schumacher et al., 2022). Most of these studies observed differences between treatment and control group networks, whereas a minority of research observed individual differences through time (Schumacher et al., 2022). People frequently use the network comparison test Van Borkulo et al. (2022) developed. These authors propose a method that does not assume the data is normally distributed and avoids specifying an incorrect null hypothesis (Van Borkulo et al., 2022). This method is conducted by estimating the network structure and identifying the test statistic for the observed networks (Van Borkulo et al., 2022). The data is then pooled and resampled based on permutations of the data, which creates a random reallocation of group labels in the data (Isvoranu et al., 2022; Van Borkulo et al., 2022). A test statistic is generated for each sample, and the collection of these test statistics is used to identify a null distribution of test statistics (Van Borkulo et al., 2022). The observed test statistic based on the original sample is then compared to the null distribution of test statistics generated in the permuted samples process, and a p-value is obtained (Van Borkulo et al., 2022). This technique is used for undirected networks only (Van Borkulo et al., 2022).

Other methods may be used to make probability inferences in undirected networks. An omnibus test tests whether all network edges are equal (Van Borkulo et al., 2022). Hence, this identifies if an edge strength differs between networks (Van Borkulo et al., 2022). Permutation tests are used here due to an increase in type one error with multiple tests, as the number of tests may get very large with increasing nodes in the network (Van Borkulo et al., 2022). If the omnibus test is significant, it may be unclear which edge is significantly different in the two groups (Van

Borkulo et al., 2022). Edge strength invariance tests can identify which edges are significant in a post hoc evaluation (Van Borkulo et al., 2022). Multiple testing can become problematic here, and adjusted p-value correction methods can be used in this instance; a particularly suitable method is the Bonferroni-Holm correction (Holm, 1979; Van Borkulo et al., 2022). Other testing methods can be used to compare networks, such as Bayesian tests, regularised moderated network analysis, and multivariate maximum likelihood in the psychometrics R package (Isvoranu et al., 2022). All of these methods use parametric methods to confirm or reject significance, as opposed to tests using permuted samples (Isvoranu et al., 2022).

Confidence intervals can also be constructed based on bootstrapped samples of the data. For each sample of the data, the centrality statistic is generated. For example, betweenness may be calculated on the node hallucinations. We could find a vector of numbers representing betweenness statistics for the node hallucinations from all bootstrapped networks. The bottom .025 and top .975 quantiles for the statistics in this vector are usually extracted to obtain 95% confidence intervals. These bootstrapped confidence intervals should not be used to assess significance (Isvoranu et al., 2022). Instead, they should be used to measure the stability of the underlying statistic (Isvoranu et al., 2022). Additionally, testing the significance of statistics generated from the model, such as centrality indices (when the null hypothesis is zero or greater than one) in LASSO regularized edges, is questionable (Epskamp et al., 2018a). Some authors argue that confidence intervals for centrality statistics are wide or have limited replicability (Bringmann et al., 2019; Forbes et al., 2017, 2021). However, the arguments by Forbes et al. (2017, 2021) are not supported by other theorists (Borsboom et al., 2017). Identifying the null hypothesis for edge weights within the bootstrapped samples is also difficult. Because the edge weights are simply a number, the number of times this edge was present from all networks, we cannot use them to test the significance of this edge being different from zero without multiple samples

Appendix C1 Supplementary Materials (Chapter 4)

Criteria for considering studies for this review

The present study aims to identify the current state of knowledge on networks in PDS. Hence, we set minimal constraints on the types of studies to be included. The selection criteria focus primarily on whether a symptom network was implemented in research on PDS, in the last 21 years. Therefore, the study must have been published between 01/06/2002 and the 30/04/2023. Because of the novelty of the network theory of psychological disorders we aimed to capture all symptom network studies that met the inclusion criteria to date. Furthermore, we included only people that had a confirmed primary diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder, and not other disorders unless these conditions were comorbid or were presented in separate networks. Therefore, participants whom the network was reconstructed on needed at least one of these three diagnoses. Hence, if the network was reconstructed on PDS and people with substance induced psychotic disorder (but diagnosed with schizophrenia, schizoaffective disorder, and/or schizophreniform) we excluded these studies. We also allowed studies that used the same dataset (several studies used a common dataset such as from the CATIE trial; Keefe et al., 2003) so long as the variable set or treatment and control groups differed.

Inclusion criteria

The inclusion criteria for study selection were as follows: (1) the network pertained to a treatment group with participants who had a Diagnostic and Statistical Manual (DSM) IV, DSM-5, International Classification of Diseases (ICD) 10, or ICD-11 diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder, (2) the nodes in the networks contained at least one symptom from criterion A in the DSM-5 for a diagnosis of schizophrenia (differences between criterion A in the DSM-IV and DSM-5 pertain only to the examples of negative symptoms), (3) the publication was a peer reviewed journal article, (4) the study was original research and not a review or discussion piece, (5) the study was written in English, (6) a graphical network model was applied, (7) the study had quantitatively derived networks, (8) the network was based on human participants, (9) the human participants were living at the time of the research or of the assessment, (10) the data was observed as opposed to simulated, and (11) the record was available in the search engine (11) given the dataset, variables included, and methodology of the study, this study was not a replication of previous research.

Exclusion criteria

The exclusion criteria for study selection were as follows: (1) research on a mental disorder other than schizophrenia, schizophreniform, or schizoaffective disorder, where this disorder was not used as a comparison group to schizophrenia, schizoaffective, or schizophreniform, (2) participants did not meet the DSM-IV, DSM-5, ICD-10, or ICD-11 diagnostic criteria for schizophrenia, schizophreniform, or schizoaffective disorder, (3) the nodes in the networks did not contain at least one symptom from criterion A in the DSM-5 for a diagnosis of schizophrenia, (4) the publication was not a peer reviewed journal article, (5) the study was not original research or was a discussion piece, (6) the study was not written in English, (7) a graphical network model was not applied, (8) the study did not have quantitatively derived networks, (9) the network was not based on human participants, (10) the human participants were not living at the time of the research or of the assessment, (11) the data was simulated as opposed to observed, and (12) the record was not available in the search engine (12) the dataset, variables included, and statistical methodology of the study was a replication of previous research.

Search methods for identification of studies

Information sources

We followed the systematic review guidelines documented by Perestelo-Pérez (2013). Two differences between the guidelines and our implementation of the systematic review were: (1) we did not used the PICOS question framing tool and (2) only one person collected the data (KB). The PICOS question framing tool was not applicable to our study as we did not compare treatment and control groups, we included a wide variety of outcome assessments, and we did not specify any treatment effects. Additionally, to avoid bias or errors in the data collection process, each result reported was quality checked against the original publications by KB. This strategy was preferred due to the large amount of unused data collected and the extensive time needed for a second person to collect the data. We also aligned with the PRISMA reporting guidelines (Page et al., 2021), found in the supplementary material section: PRISMA Checklist.

KB searched five search engines to collate a list of publications for screening. The five search engines were (1) Medline and (2) CINAHL through EBSCO Host, (3) Scopus, (4) Psychoinfo through Ovid, and (5) Google Scholar (https://scholar.google.com/). The last search was undertaken on the 27th of June 2022 for Medline, CINAHL, Scopus, and Psychinfo, and the 08th of July 2022 for Google Scholar. Hand searching the reference lists of the articles in the full text review occurred on the 5th of August 2022. We updated the list from Medline, CINAHL, Scopus, and Psychinfo on the 08/05/2023 to ensure this systematic review is up to date with current research for publications between 01/06/2022 until 30/04/2023.

Search strategy

The search strategy was designed by KB and validated by a librarian (AS) and author (MS). The peer review process involved optimising the search strategy through identifying the number of articles that would likely be included in full text review from the first 20 citations found by EBSCO host. If approximately 60% of the articles would likely be designated for full text review in the first 20 citations found by the search engine, this would then be a reasonable search. Search terms were sequentially added and deleted to identify if the search term resulted in articles not previously discovered without this search term. The use of 'Symptom' being required along with other search terms was discussed and implemented to minimise retrieving articles that were only biological or social in nature, as opposed to clinical, such as fMRI network analysis or social network analysis.

For the databases Medline, CINAL, Scopus, Psychoinfo the following search terms were used: (Schizophrenia OR Schizophreniform OR Schizoaffective) AND ("network analys*" OR "network Theor*" OR "network based analy*" OR "network model*" OR "network science" OR "network medicine" OR "network approach*" OR "network based approach*" OR "network-based approach*" OR "psycho* network*" OR "network perspective*" OR "transdiagnostic network*" OR "network* framework*" OR "network method*" OR "disorder network*" OR (network* N2 symptom*)), for publications between 01/06/2002 and the 31/05/2022. For searching Google Scholar, the first 200 journal articles listed were sent to the citations list for the screening stage using the following search terms: (Schizophrenia OR Schizophreniform OR Schizoaffective) AND (Symptom) AND (Network analysis OR Network Theory OR network based analysis OR network modelling OR network science OR network medicine OR network approach OR network based approach OR psychological network OR network perspective OR transdiagnostic network OR network framework OR network method OR disorder network) for publications of any time period. We updated the list from Medline, CINAHL, Scopus, and Psychinfo using the same search strategy for these search engines.

Selection process

The search engines returned 2,211 studies, 975 of which were duplicates. A disagreement over 52 studies (5.3%; $\kappa = .58$) between KB and KA occurred in the screening phase and 16 (10.0%; $\kappa =.58$) between MS and KB in the screening phase for the updated list. A consensus was reached on each publication. During the full text review, there was disagreement between 17 studies between the reviewers KB and KA (25.8%, $\kappa = 0.48$) and consensus could not be reached on three studies between KB and KA. MS reviewed the three publications and accepted one publication and rejected two publications, in consultation with KB and KA. Between MS and KB, there was a disagreement between three studies in the full text review (13%, $\kappa = .74$) in the updated list. A consensus was reached for each disagreement between KB and MS.

Information on the data collection process including data extraction, management and data items, a list of variables collected, risk of bias assessment, effect measures used in the study, and the synthesis method can be found in the supplementary materials: Data Collection Process.

Data collection process

Data extraction and management and data items

The data for each of the 32 publications selected for inclusion in this systematic literature review were entered into a data collection sheet in Covidence. Author KB entered the data and cleaned the data in R Studio version 4.2.0. The information on the methodology of the study was collected including: the model applied to the network, the edge statistics, the optimisation algorithm, whether the network was static or dynamic, whether the network was directed, whether resampling took place, and whether parametric or non-parametric tests or confidence intervals were included on the network or network properties. Information of publication details, analysis method, node and edge features were also obtained for the purposes of this research. The centrality statistics betweenness, closeness, strength, and degree were collected as these were most common across the publications. Other metrics for networks were available but were not included because: (1) They did not fit within the aims of the study (such as the clustering coefficient or the shortest path length), and (2) were not commonly used within the selected articles. Definitions of the centrality and edge statistics can be found in the Appendix C1: Effect Measures section.

Other variables collected

Additional data was collected to allow for extended research on this systematic review of symptom networks in schizophrenia. This additional data was only collected for the search between the dates 01/06/2002 and the 31/05/2023. This included information from: (a) the title page and journal such as DOI, publication date, title, lead author contact information, study funding sources, conflicts of interest declarations, notes made by the authors; (b) the methods section on diagnostic method, diagnostic manual, diagnostic tools, data collection start date and end date, descriptive statistics on participants, experimental group participants, assessment of severity results, the method of recruitment, location of the study, the datasets they acquired, list of assessments that were included in the networks, the study design, the experimental design; (c) the analysis section of the methods section including the data type included in the network, whether goodness of fit indexes were presented, optimisation criteria; (d) the results section of the article including whether the parameters of the network were included, whether the network was graphically presented, a list of nodes in the network, the diagnostic symptoms included in the network, whether the network was grouped or ungrouped, a list of groups, whether the metrics were presented, a list of metrics; and (e), qualitative components in the discussion section such as the text stating support of hypotheses, the evidence linking the results to schizophrenia symptomatology, interpretations of node, edge, and network properties, notes on congruences or differences with other studies, notes on theoretical implications, notes on applied implications, notes on future research, and notes on the importance of findings.

Study risk of bias assessment

All information used in the results of this study were quality checked against the original publications. Each article was appraised by adapting the McMaster's Critical Review Form – Quantitative Studies (Law et al., 1998) for network studies. The McMaster's Critical Review Form was selected as the included studies used a wide variety of designs, unlike other critical appraisal tools which have versions for randomised control trials, cohort studies, etc. No summation of the items was made to obtain a risk of bias total score. One person assessed each publication against the McMaster's Critical Review Form and quality checked the results in this manuscript against the original research. More information can be found on the McMaster's Critical Review Form from the McMaster's university website (Law et al., 1998).

Modifications to the McMaster's Critical Review Form were required to ensure that the form was relevant to network studies. Hence, the following changes were made to the McMaster's Critical Review Form: (1) the purpose needs to be stated as an aim at least once in the abstract or in the introduction section, (2) for relevant literature to be reviewed, symptom network of schizophrenia or other conditions needed to be mentioned in the introduction, (3) for whether the sample size was justified, the sample within the network could be derived from the methods section in the article or the methods section of previous studies referred to within the article, (4) any mention of reliability and validity of an assessment used in the study is sufficient for whether reliability or validity was addressed, (5) analysis methods were appropriate if an algorithm was used to derive the network, (6) clinical implications were reported if the author(s) ever reported a practical implication of the results, (7) conclusions were appropriate if they described direction or causation when the methods allowed for these inferences.

Effect measures

For the purposes of this study, betweenness is defined as how well a node acts as a connecting point by using the number of paths through that node to any other pair of nodes (Hevey, 2018). As in the publication by Boldi and Vigna (2014), betweenness is represented by the formula:

$$\sum_{y,z\neq x,\sigma_{y,z}\neq 0}\frac{\sigma_{yz}(x)}{\sigma_{yz}} \tag{1}$$

Where σ_{yz} is the number of shortest paths from y to z and $\sigma_{yz}(x)$ is the number of these paths that pass through x. Closeness is defined as how close a node is to all other nodes using the average partial correlation of the paths from or to that node (Hevey, 2018). It is given by the formula provided in Boldi and Vigna (2014):

$$\frac{1}{\sum_y d(y,x)} \tag{2}$$

Where distance $d(y, x)$ is the shortest path from y to x. Strength as the sum of all partial correlations (or other edge weight) from that node, and degree is the number of edges of a node (Hevey, 2018).

Synthesis methods

The results of the 32 studies were included in the results section with information on analysis methods, betweenness, closeness, strength, and degree as reported in the original articles. Within each study, there was a diversity of assessments included as far as the networks presented across the studies were concerned. For the results in Figure 13 and Table 3, we recoded every variable included in each network. To do this we retained the meaning of the subscale based on the validation sample of the assessment. We also excluded items of subscales, or the subscales themselves, that measured general psychopathology. Following this we only included domains that were frequently present across the networks included in this study. These five domains were: cognition, functioning, positive symptoms, negative symptoms, and depression. Hence, items that assess anxiety or stigma were not included in the results as these were only present in a minority of networks. To construct Figure 13, we looked at the centrality statistics of each article and selected the top three most central (Ranked) items or subscales that were represented by these domains. Variables in other domains were excluded in this ranking process. Ties between the ranks of the variables in the networks were allowed. In Figure 13, if a variable in a network was ranked more than once in the top three for a centrality statistic, only the highest rank was preserved. Hence, if two variables assessing cognition had the highest betweenness and second highest betweenness, we only report that cognition was most central in Figure 13. The conversion table to recode of items and subscales into domains can be found in the Appendix C1: Recoding of Variables section.

In the results in Table 14, we excluded centrality and edge statistics on assessments that were: (1) study design variables, (2) biological factors or medication related factors, (3) environmental factors, or (4) social factors acting on the person. Hence, in this review we included variables that can be considered internal to a person, were not impacted by an external influence, and were not biological variables.

Metrics within studies are usually reported graphically, where the results have been reported as standardised or unstandardized. We used the three top ranked nodes and edges across each metric: betweenness, closeness, strength, and degree. Ranks were used due to the heterogeneity in the values of the metrics reported across the 32 studies. In the case where there were ties in the results, both tied nodes and edges were included. We did not omit or segregate results based on different data types. We collected the data by visually inspecting the plots in figures for all studies to identify which node or edge had the larger metric. No corresponding authors were contacted to clarify their results. Although there were missing values reported in some studies, no data imputation strategy took place. The missing values were often associated with the study design and therefore are not likely to be missing at random. Some of the results collected were illegible, possibly due to the publication process, and this is reported in the results section.

In this study we do not report the metrics using a chart and all results are provided in a table format. Study descriptions, the analysis methods of the 32 studies, and the quality appraisal are presented. Items of the quality appraisal assessment were reported as present, absent, not addressed, or not available, in addition to the study's sample size and the design of the study.

Other supplementary materials: Gaps in the literature

Table 11 presents information about the analysis method for each retrieved document. Most studies implemented a static network ($N = 30$), and two studies implemented a dynamic network of symptoms. Dynamic networks on longitudinal data was used in Badal et al. (2021) who used ecological momentary assessment data, and Moffa et al. (2021) who applied a dynamic Bayesian network to schizophrenia symptoms and depressive symptoms. Only three studies were fully directed networks (Abplanalp et al., 2023; Bak et al., 2016; Moffa et al., 2021) and two studies were partially directed (Amore et al., 2020; Badal et al., 2021). Furthermore, many of the studies used Gaussian graphical models to examine the relationship between symptoms (some did not state the method although they used GLASSO, EBIC, and the package qgraph in R; (Epskamp et al., 2012)), partial correlations for the degree of associations between variables, and the GLASSO algorithm to optimise the network. Furthermore, most studies used resampling methods to identify network properties, such as edge weights, or for non-parametric hypothesis testing.

Table 11. Methods of Included Studies.

Author	Network model	Statistics	Optimization	Optimization criteria	Dynamic	Directed	Resampling	Parametric tests / confidence Intervals	Non-Parametric tests / confidence Intervals
Abplanalp et al.	Bayesian	Conditional dependency	Hill climbing	BIC	Static	Directed	Yes	No	No
Amore et al. (2020)	GGM; BN	Partial correlation	GLASSO; Hill	EBIC; BIC	Static	Undirected;	Yes	No	Yes
Badal et al. (2021)	Causal network analysis	Partial correlation	MCI	Conditional independence	Dynamic	Partially directed	No	No	No
Bak et al. (2016)	Not stated	Spearman's partial correlation	Not stated	None	Static	Directed	No	No	No
Brasso et al. (2023)	Not stated	Correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Charernboon (2021)	Not stated	Partial correlation	GLASSO	Not stated	Static	Undirected	Yes	No	Yes
Choi et al. (2022)	Not stated	Polychoric correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Dal Santo et al.	GGM	Patrial correlation	GLASSO	Not stated	Static	Undirected	Yes	No	Yes
Demyttenaere et al.	Not stated	Partial correlation coefficient	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Demyttenaere et al.	Not stated	Polychoric partial correlation	GLASSO	EBIC	Static	Undirected	Yes	Yes	Yes
Esfahlani et al.	None	Absolute value of Pearson's	None	None	Static	Undirected	No	No	Yes
Esfahlani et al.	None	Absolute value of partial	None	None	Static	Undirected	Yes	No	No
Galderisi et al.	Not stated	Nonparametric partial correlations	GLASSO	Not stated	Static	Undirected	Yes	No	Yes
Galderisi et al.	Not stated	Not stated	GLASSO	EBIC	Static	Undirected	Yes	Yes	Yes
Hajdúk et al. (2019)	GGM	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Hasson-Ohayon et	Not stated	Partial correlation	GLASSO	EBIC	Static	Undirected	No	No	No
Hopkins et al.	Not stated	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	No
Hu et al. (2022)	GGM	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Levine and Leucht	Not stated	Partial polychoric correlation	GLASSO	Not stated	Static	Undirected	Yes	No	Yes
Li et al. (2022)	Not stated	Correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Moffa et al. (2021)	DBN	Conditional independence	MCMC	Not stated	Dynamic	Directed	No	No	No
Monteleone et al.	Not stated	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Monteleone et al.	Not stated	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Park et al. (2020)	Not stated	Not stated	GLASSO	EBIC	Static	Undirected	No	No	No
Peralta et al. (2020)	Not stated	Partial correlation	GLASSO,	EBIC	Static	Undirected	Yes	Yes	Yes
Strauss et al.	None	Mutual information	None	None	Static	Undirected	No	Yes	No
Strauss et al.	None	Normalized mutual information	None	None	Static	Undirected	No	Yes	No
Strauss et al. (2020)	None	Cosine similarity	Not stated	None	Static	Undirected	No	Yes	No
Sun et al. (2023)	Not stated	Spearman's correlations	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
van Rooijen et al.	GGM	L1-regularized partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Wang et al. (2023)	GGM	Partial correlation	GLASSO	EBIC	Static	Undirected	Yes	No	Yes
Yan et al. (2022)	Not stated	Partial correlation	Not stated	Not stated	Static	Undirected	No	No	No

Note. GGM = Gaussian graphical model; BN = Bayesian networks; DBN = Dynamic Bayesian networks; GLASSO = Graphical least absolute shrinkage and selection operator; MCI = Momentary Conditional Independence; MCMC = Markov chain Monte Carlo; EBIC = Extended Bayesian information criterion; BIC = Bayesian information criterion.

Other supplementary materials: PRISMA checklist

Table 12. PRISMA Checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Other Supplementary Materials
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Other Supplementary Materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Other Supplementary Materials
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Other Supplementary Materials
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Other Supplementary Materials
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Other Supplementary Materials
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Other Supplementary Materials
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Other Supplementary Materials
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Other Supplementary Materials
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Other Supplementary Materials
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Other Supplementary Materials
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Other Supplementary Materials
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting	14	Describe any methods used to assess risk of bias due to missing results in a	NA

Section and Topic	Item #	Checklist item	Location where item is reported
bias assessment		synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Registration and Protocol
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Registration and Protocol
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Registration and Protocol
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Support and Conflicts of Interest
Competing interests	26	Declare any competing interests of review authors.	Support and Conflicts of Interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

Other supplementary materials: List of assessments

Table 13. List of Assessments by Exclusion Reason.

Abbreviation	Assessment name	N Studies	Internal variables	Domain
PANSS	Positive and negative symptom scale	18	Y	Psychopathology
BNSS	Brief negative symptom scale	10	Y	Psychopathology
CDSS	Calgary depression rating scale for schizophrenia	9	Y	Psychopathology
MATRICS	Measurement and treatment research to improve cognition in schizophrenia	5	Y	Cognition
FEIT	Facial emotion identification test	3	Y	Socio-emotional
ISMI	Internalised stigma of mental illness	3	N	Socio-emotional
SANS	Scale for the assessment of negative symptoms	3	Y	Psychopathology
BPRS	Brief psychiatric rating scale	2	Y	Psychopathology
EMA	Ecological momentary assessment	2	Y	Other
SLOF	Specific level of functioning scale	3	Y	Functioning
UPSA-B	UCSD performance-based skills assessment—brief	2	Y	Functioning
SOFAS	Social and occupational functioning assessment	2	Y	Functioning
TASIT	The awareness of social inference test	2	Y	Socio-emotional
SES	Service engagement scale	2	N	Other
RSA	Resilience scale for adults	2	N	Other
PSP	Personal social performance scale	2	Y	Functioning
MSCEIT	Mayer-Salovey-Caruso emotional intelligence Test	2	Y	Socio-emotional
SHRS	St Hans rating sale	2	N	Other
MAS	Metacognition assessment scale	2	Y	Other
SAPS	Scale for the assessment of positive symptoms	1	Y	Psychopathology
CAINS	Clinical assessment interview for negative symptoms	1	Y	Psychopathology
PS	Paranoia scale	1	Y	Psychopathology
CLANG	Clinical language disorder rating scale	1	Y	Other
CASH	Comprehensive assessment of symptoms and history	1	Y	Psychopathology
SFS	Social functioning scale	1	Y	Functioning
ACE III	Addenbrookes cognitive examination version III	1	Y	Cognition
FT	Faces test	1	Y	Other
REMT	Reading the mind in the eyes test	1	Y	Other
HT	Hinting task	1	Y	Other
BLERT	Bell–Lysaker emotional recognition task	1	Y	Socio-emotional
SAT	Social attributions test	1	Y	Other
PST	Picture sequencing task	1	Y	Other
HI	Hollingshead index	1	N	Other
PDD	Perceived devaluation and discrimination scale	1	N	Socio-emotional
SAS	Simpson-Angus extrapyramidal side effects scale	1	N	Other
BARS	Barnes akathisia rating scale	1	N	Other
IPH	Indiana psychiatric illness interview	1	Y	Psychopathology
SNS	Self-Evaluation of Negative Symptoms Scale	1	Y	Psychopathology
Clinical interview	Clinical interview	1	Y	Other
Medical record	Medical record	1	Y	Other
Duration	Illness duration	1	Y	Other

Other supplementary materials: Tables

Table 14. Node Metrics for all Included Assessments.

Author	Betweenness	Closeness	Strength	Degree
Amore et al. (2020) ; Depressive symptoms and insight			1. Depressed mood (CDSS; i) 2. Hopelessness (CDSS; I) 3. Observed depression (CDSS; I)	
Amore et al. (2020) ; Extended network			1. Depressed mood (CDSS; I) 2. Disorganization (PANSS; F) 2. Social cognition (Factor analysis; F)	
Bak et al. (2016); Stable state	1. Down (EMA; I) 2. Paranoia (EMA; I) 3. Relaxed (EMA; I)	1. Relaxed (EMA; I) 2. Down (EMA; I) 3. Paranoia (EMA; I)	1. Down (EMA; I) 2. Relaxed (EMA; I) 3. Paranoia (EMA; I)	
Bak et al. (2016); Impending relapse	1. Down (EMA; I) 2. Paranoia (EMA; I) 3. Loss of control (EMA; I) = Hearing voices (EMA; I) = Relaxed (EMA; I)	1. Paranoia (EMA; I) 2. Down (EMA; I) 3. Loss of control (EMA; I)	1. Paranoia (EMA; I)) 2. Relaxed (EMA; I) 3. Down (EMA; I)	
Bak et al. (2016); Full relapse state	1. Paranoia (EMA; I) 2. Loss of control (EMA; I) 3. Down (EMA; I)	1. Paranoia (EMA; I) 2. Hearing voices (EMA; I) 3. Relaxed (EMA; I)	1. Paranoia (EMA; I) 2. Hearing voices (EMA; I) 3. Down (EMA; I)	
Brasso et al. (2023); Duration of illness < 5 years	1. Disorganization (PANSS; F) 2. Visual learning (MATRICS; F) 3. Speed of processing (MATRICS; F)	1. Disorganization (PANSS; F) 2. Visual learning (MATRICS; F) 3. Total (SLOF; F)		1. Avolition (BNSS; F) = Speed of processing (MATRICS; F) 3. Expressive deficit (BNSS; F)
Brasso et al. (2023); Duration of illness > 5 years	1. Working memory (MATRICS; F) 2. Disorganization (PANSS; F) 3. Verbal learning (MATRICS; F)	1. Working memory (MATRICS; F) 2. Verbal learning (MATRICS; F) 3. Visual learning (MATRICS; F)		1. Working memory (MATRICS; F) 2. Disorganization (PANSS; F) 3. Verbal learning (MATRICS; F)
Charernboon (2021)	1. Total (PSP; F) 2. Total (ACE-III; F) 3. Asocial (SANS; F)	1. Total (PSP; F) 2. Asocial (SANS; F) 3. Avolition (SANS; F)	1. Total (PSP; F) 2. Alogia (SANS; F) 3. Avolition (SANS; F)	
Choi et al. (2022)	1. Depressive mood (BPRS; I) 2. Motor retardation (BPRS; I) 3. Unusual thought content (BPRS; I)	1. Excitement (BPRS; I) 2. Depressive mood (BPRS; I) 3. Grandiosity (BPRS; I)	1. Motor retardation (BPRS; I) 2. Depressive mood (BPRS; I) 3. Unusual thought content (BPRS; I)	
Dal Santo et al. (2022)			1. Depression (PANSS; I) 2. Delusions (PANSS; I) 3. Emotional withdrawal (PANSS; I)	
Demyttenaere et al. (2022a)	1. Anxiety (PANSS; I) 2. Tension (PANSS; I) 3. Lack of judgement and insight (PANSS; I)	1. Anxiety (PANSS; I) 2. Tension (PANSS; I) 3. Lack of judgement and insight (PANSS; I)	1. Depression (PANSS; I) 2. Depression (CDSS; I) 3. Anxiety (PANSS; I)	
Demyttenaere et al. (2022b); Acute population	1. Motor retardation (PANSS; I) 2. Delusions (PANSS; I) 3. Depression (PANSS; I)	1. Motor retardation (PANSS; I) 2. Delusions (PANSS; I) 3. Suspiciousness (PANSS; I)	1. Delusions (PANSS; I) 2. Uncooperativeness (PANSS; I) 3. Active social avoidance (PANSS; I)	

Demyttenaere et al. (2022b); Predominant negative symptoms	1. Hostility (PANSS; I) 2. Preoccupation (PANSS; I) 3. Delusions (PANSS; I)	1. Hostility (PANSS; I) 2. Guilt feelings (PANSS; I) 3. Grandiosity (PANSS; I)	1. Hostility (PANSS; I) 2. Delusions (PANSS; I) 3. Tension (PANSS; I)	
Esfahlani et al. (2018); Treatment resistant		1. Suspiciousness (PANSS; I) 2. Depression (PANSS; I) 3. Preoccupation (PANSS; I) = Anxiety (PANSS; I)		1. Preoccupation (PANSS; I) 2. Hostility (PANSS; I) 3. Delusions (PANSS; I)
Esfahlani et al. (2018); Treatment responsive		1. Excitement (PANSS; I) 2. Delusions (PANSS; I) 3. Blunted affect (PANSS; I)		1. Blunted affect (PANSS; I) 2. Lack of spontaneity and flow of conversation (PANSS; I) 3. Delusions (PANSS; I)
Galderisi et al. (2018)	1. Everyday life skills (SLOF; F) 2. Total (UPSA-B; F) 3. Total (TASIT-1; F)	1. Everyday life skills (SLOF; F) 2. Total (UPSA-B; F) 3. Work skills (SLOF; F)	1. Working memory (MATRICS; F) 2. Everyday Life skills (SLOF; F) 3. Total (TASIT-2; F)	
Galderisi et al. (2020); Baseline	1. Total (UPSA-B; F) 2. Everyday life skills (SLOF; F) 3. Working memory (MATRICS; F)	1. Total (UPSA-B; F) 2. Everyday life skills (SLOF; F) 3. Working memory (MATRICS; F)		1. Working memory (MATRICS; F) 2. Everyday life skills (SLOF; F) 3. Total (TASIT-2; F)
Galderisi et al. (2020); Follow-up	1. Work skills (SLOF; F) 2. Everyday life skills (SLOF; F) 3. Total (UPSA-B; F)	1. Work skills (SLOF; F) 2. Everyday life skills (SLOF; F) 3. Total (UPSA-B; F)		1. Working memory (MATRICS; F) 2. Everyday life skills (SLOF; F) 3. Total (TASIT-2; F)
Galderisi et al. (2020); Not recovered	1. Work skills (SLOF; F) 2. Interpersonal relationships (SLOF; F) 3. Everyday life skills (SLOF; F)	1. Work skills (SLOF; F) 2. Everyday life skills (SLOF; F) 3. Total (UPSA-B; F)		1. Working memory (MATRICS; F) 2. Everyday life skills (SLOF; F) 3. Total (TASIT-2; F)
Galderisi et al. (2020); Recovered	1. Working memory (MATRICS; F) 2. Attention (MATRICS; F) 3. Verbal learning (MATRICS; F)			1. Total (TASIT-2; F) 2. Working memory (MATRICS; F) 3. Total (TASIT-1; F)
Hajdúk et al. (2019)	1. P17 (PS; I) 2. IR07 (SLOF; I) 3. P14 (PS; I) = P3 (PS; I)	1. P17 (PS; I) 2. P14 (PS; I) 3. P18 (PS; I)	1. P14 (PS; I) 2. P18 (PS; I) 3. P19 (PS; I)	
Hasson-Ohayon et al. (2018)	1. Cognition (PANSS; F) 2. Working memory (MATRICS; F) 3. Mastery and decentration (MAS-A; F)	1. Cognition (PANSS; F) 2. Working memory (MATRICS; F) 3. Social cognition (BLERT; F)	1. Cognition (PANSS; F) 2. Visual learning (MATRICS; F) 3. Working memory (MATRICS; F)	
Hu et al. (2022); Symptom dimension	1. Positive (PANSS; F) 2. Illness duration (I) 3. Expressivity (CAINS; F)	1. Illness duration (I) 2. Positive (PANSS; F) 3. Expressivity (CAINS; F)	1. Total (SOFAS; F) 2. Motivation and pleasure (CAINS; F) 3. Positive (PANSS; F)	
Hu et al. (2022); Item level	1. Total (SOFAS; F) 2. Illness duration (I) 3. Delusions (PANSS; I)	1. Total (SOFAS; F) 2. Illness duration (I) 3. Vocational, motivation (CAINS; I)	1. Total (SOFAS; F) 2. Expression, speech (CAINS; I) 3. Expression, vocal prosody (CAINS; I)	
Levine and Leucht (2016); Baseline	1. Poverty of speech (SANS; I) 2. Paucity expressive gestures (SANS; I)	1. Poverty of speech (SANS; I) = Poverty of content of speech (SANS; I) =	1. Decreased spontaneous movements (SANS; I) 2. Paucity expressive gestures (SANS; I)	

	3. Decreased spontaneous movements (SANS; I)	Decreased spontaneous movements (SANS; I) = Paucity expressive gestures (SANS; I)	3. Relationships with friends & peers (SANS; I)	
Levine and Leucht (2016); Endpoint	1. Increased response latency (SANS; I) 2. Test inattentiveness (SANS; I) 3. Social inattentiveness (SANS; I)	1. Increased response latency (SANS; I) = Social inattentiveness (SANS; I) = Test inattentiveness (SANS; I)	1. Decreased spontaneous movements (SANS; I) 2. Ability feel intimacy & closeness (SANS; I) 3. Poverty of speech (SANS; I)	
Levine and Leucht (2016); Change	1. Inappropriate affect (SANS; I) 2. Physical anergia (SANS; I) 3. Increased response latency (SANS; I)	1. Inappropriate affect (SANS; I) 2. Lack vocal inflections (SANS; I) = Blocking (SANS; I) = Affective no responsivity (SANS; I)	1. Poverty of speech (SANS; I) = Poverty of content of speech (SANS; I) 3. Decreased spontaneous movements (SANS; I) = Paucity expressive gestures (SANS; I)	
Li et al. (2022)			1. Verbal aggression (Clinical interview; I) 2. Social and occupational dysfunction (Clinical interview; I) 3. Hallucinations (Clinical interview; I)	
Park et al. (2020)	1. Poverty of speech (CLANG; I) 2. Dysarthria (CLANG; I) 3. Disclosure failure (CLANG; I)	1. Disclosure failure (CLANG; I) 2. Aprosodic speech (CLANG; I) 3. Referential failure (CLANG; I)	1. Disclosure failure (CLANG; I) 2. Excess syntactic constrains (CLANG; I) 3. Abnormal prosody (CLANG; I)	
Strauss et al. (2019b); Both genders	1. Quantity of speech (BNSS, I) 2. Avolition inner experience (BNSS; I) 3. Spontaneous elaboration (BNSS; I)			1. Quantity of speech (BNSS; I) 2. Asociality inner experience (BNSS; I) = Avolition inner experience (BNSS; I)
Strauss et al. (2019b); Male	1. Quantity of speech (BNSS, I) 2. Spontaneous elaboration (BNSS, I) 3. Facial expression (BNSS, I)			1. Quantity of speech (BNSS, I) 2. Spontaneous elaboration (BNSS, I) 3. Asociality inner experience (BNSS, I)
Strauss et al. (2019b); Female	1. Vocal expression (BNSS, I) 2. Asociality inner experience (BNSS, I) 3. Avolition behavior (BNSS, I)			1. Vocal expression (BNSS, I) 2. Asociality inner experience (BNSS, I) 3. Facial expression (BNSS, I)
Strauss et al. (2020); Treatment		1. Frequency of pleasurable activities (BNSS; I) 2. Intensity of pleasure during activities (BNSS; I) 3. Avolition behavior (BNSS; I)		1. Frequency of pleasurable activities (BNSS; I) 2. Intensity of pleasure during activities (BNSS; I) 3. Avolition behavior (BNSS; I)
Strauss et al. (2020); Placebo		1. Intensity of pleasure during activities (BNSS; I) 2. Avolition behavior (BNSS; I) 3. Asociality behavior (BNSS; I)		1. Intensity of pleasure during activities (BNSS; I) 2. Asociality behavior (BNSS; I) = Avolition behavior (BNSS; I)
Sun et al. (2023); t1			1. Emotional withdrawal (PANSS; I) 2. Uncooperativeness (PANSS; I) 3. Lack of spontaneity and flow of conversation	

			(PANSS; I)	
Sun et al. (2023); t2			1. Delusions (PANSS; I) 2. Poor impulse control (PANSS; I) 3. Emotional withdrawal (PANSS; I)	
Sun et al. (2023); t3			1. Delusions (PANSS; I) 2. Excitement (PANSS; I) 3. Anxiety (PANSS; I)	
Sun et al. (2023); t4			1. Excitement (PANSS; I) 2. Emotional withdrawal (PANSS; I) 3. Delusions (PANSS; I)	
Sun et al. (2023); resistant			1. Excitement (PANSS; I) 2. Delusions (PANSS; I) 3. Emotional withdrawal (PANSS; I)	
Sun et al. (2023); response			1. Delusions (PANSS; I) 2. Emotional withdrawal (PANSS; I) 3. Difficulty in abstract thinking (PANSS; I)	
van Rooijen et al. (2018)	1. Delusions (PANSS; I) 2. Poor rapport (PANSS; I) 3. Stereotyped thinking (PANSS; I)	1. Delusions (PANSS; I) 2. Poor rapport (PANSS; I) 3. stereotyped thinking (PANSS; I)	1. Delusions (PANSS; I) = Depression (CDSS; I) 3. Emotional withdrawal (PANSS; I)	
Wang et al. (2023)	1. Avolition-apathy (SANS; F) 2. Avolition (BNSS; F) 3. Anhedonia-asociality (SANS; F)	1. Avolition-apathy (SANS; F) 2. Anhedonia-asociality (SANS; F) 3. Alogia (SANS; F)	1. Anhedonia-asociality (SANS; F) 2. Affective flattening (SANS; F) 3. Alogia (SANS; F)	1. Anhedonia-asociality (SANS; F) 2. Affective flattening (SANS; F) 3. Alogia (SANS; F)
Yan et al. (2022); BPRS				1. Total (BPRS; F) 2. Hostility Suspiciousness (BPRS; F) 3. Anergia (BPRS; F)
Yan et al. (2022); PANSS				1. Negative (PANSS, F) 2. Cognitive (PANSS, F) = Excited (PANSS, F) = Total (PANSS, F)

Note. Purple cells = items or subscales that measure cognition; Green cells = items or subscales that measure functioning; Red cells = items or subscales that measure positive symptoms; Yellow = represent items or subscales that measure negative symptoms; Blue cells = items or subscales that measure depression; I = item; F = Factor; ACE III = Addenbrookes cognitive examination version III; BLERT = Bell–Lysaker Emotional Recognition Task; BNSS = Brief negative symptom scale; BPRS = Brief psychiatric rating scale; CAINS = Clinical assessment interview for negative symptoms; CDSS = Calgary depression rating scale for schizophrenia; CLANG = Clinical language disorder rating scale; EMA = Ecological momentary assessment; MAS = Metacognition assessment scale; MATRICS = Measurement and treatment research to improve cognition in schizophrenia; PANSS = Positive and negative syndrome scale; PS = Paranoia scale; PSP = Personal social performance scale; SANS = Scale for the assessment of negative symptoms; SLOF = Specific level of functioning scale; SOFAS = Social and occupational functioning assessment scale; TASIT = The awareness of social inference test; UPSA-B = UCSD Performance-Based Skills Assessment—Brief.

Recoding of variables to domains

Table 15. Recoding of Variables to Domains.

Assessment	Factor / Item	Variables	Domain	Reference	Assessment	Factor / Item	Variables	Domain	Reference
ACE-III	Factor	Total	Cognition		MATRICS	Factor	Reasoning and problem solving	Cognition	
BARS	Factor	Side effects	Side effects		MATRICS	Factor	Speed of processing	Cognition	
BLERT	Factor	Social cognition	Cognition		MATRICS	Factor	Verbal learning	Cognition	
BNSS	Factor	Alogia	Negative symptoms		MATRICS	Factor	Verbal and Spatial learning	Cognition	
BNSS	Factor	Anhedonia	Negative symptoms		MATRICS	Factor	Visual learning	Cognition	
BNSS	Factor	Asociality	Negative symptoms		MATRICS	Factor	Working memory	Cognition	
BNSS	Factor	Avolition	Negative symptoms		MSCEIT	Factor	Managing emotion section	Cognition	
BNSS	Factor	blunted affect	Negative symptoms		MSCEIT	Factor	Social Cognition	Cognition	
BNSS	Factor	Expressive deficits	Negative symptoms		MSCEIT	Factor	Social cognition 1	Cognition	
BNSS	Item	Asociality Behavior	Negative symptoms		MSCEIT	Factor	Social cognition 2	Cognition	
BNSS	Item	Asociality internal experience	Negative symptoms		PANSS	Factor	Cognitive	Cognition	Mohr et al. (2004)
BNSS	Item	Avolition Behavior	Negative symptoms		PANSS	Factor	Depressive	Depression	
BNSS	Item	Avolition internal experience	Negative symptoms		PANSS	Factor	Disorganisation	Disorganisation	Dollfus et al. (1991)
BNSS	Item	Body gestures	Negative symptoms		PANSS	Factor	Emotional discomfort	Emotional discomfort	Bell et al. (1994)
BNSS	Item	Facial expression	Negative symptoms		PANSS	Factor	Excited	Excited	Park et al. (2020)
BNSS	Item	Frequency of pleasurable activities	Negative symptoms		PANSS	Factor	Hostility	Hostility suspiciousness	Mohr et al. (2004)
BNSS	Item	Intensity of future pleasure	Negative symptoms		PANSS	Factor	Negative	Negative symptoms	Kay et al. (1987)
BNSS	Item	Intensity of pleasurable activities	Negative symptoms		PANSS	Factor	Positive	Positive symptoms	Kay et al. (1987)
BNSS	Item	Lack of normal distress	Negative symptoms		PANSS	Factor	General	General psychopathology	Kay et al. (1987)
BNSS	Item	Quantity of speech	Negative symptoms		PANSS	Factor	Total	Other	Kay et al. (1987)
BNSS	Item	Spontaneous elaboration	Negative symptoms		PANSS	Item	Active social avoidance	General psychopathology	
BNSS	Item	Vocal expression	Negative symptoms		PANSS	Item	Anxiety	General psychopathology	
BNSS	Item	Avolition	Negative symptoms		PANSS	Item	Blunted affect	Negative symptoms	
BNSS	Item	Poor emotional expression	Negative symptoms		PANSS	Item	Conceptual disorganisation	Positive symptoms	
BPRS	Factor	Activation	Activation	Yan et al. (2022)	PANSS	Item	Delusions	Positive symptoms	

BPRS	Factor	Anergia	Negative symptoms	Yan et al. (2022)	PANSS	Item	Depression	General psychopathology
BPRS	Factor	Anxious depression	Depressive	Yan et al. (2022)	PANSS	Item	Difficulty in abstract thinking	Negative symptoms
BPRS	Factor	Hostility suspiciousness	Hostility suspiciousness	Yan et al. (2022)	PANSS	Item	Disorientation	General psychopathology
BPRS	Factor	Total	General Psychopathology		PANSS	Item	Disturbance in volition	General psychopathology
BPRS	Item	Anxiety	Anxiety	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Emotional withdrawal	Negative symptoms
BPRS	Item	Blunted affect	Negative symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Excitement	Positive symptoms
BPRS	Item	Conceptual disorganisation	Positive symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Grandiosity	Positive symptoms
BPRS	Item	Depressive mood	Depression	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Guilt feelings	General psychopathology
BPRS	Item	Disorientation	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Hallucinatory behaviour	Positive symptoms
BPRS	Item	Emotional withdrawal	Negative symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Hostility	Positive symptoms
BPRS	Item	Excitement	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Lack of judgement and insight	General Psychopathology
BPRS	Item	Grandiosity	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Lack of spontaneity and flow of conversation	Negative symptoms
BPRS	Item	Guilt feelings	Depression	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Mannerisms and posturing	General Psychopathology
BPRS	Item	Hallucinatory behaviour	Positive symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Motor retardation	General Psychopathology
BPRS	Item	Hostility	Hostility suspiciousness	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Passive/apathetic social withdrawal	Negative symptoms
BPRS	Item	Mannerisms and posturing	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Poor attention	General Psychopathology
BPRS	Item	Motor retardation	Negative symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Poor impulse control	General Psychopathology
BPRS	Item	Somatic concern	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Poor rapport	Negative symptoms
BPRS	Item	Suspiciousness	Hostility suspiciousness	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Preoccupation	General Psychopathology
BPRS	Item	Tension	Other	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Somatic concern	General Psychopathology
BPRS	Item	Uncooperativeness	Hostility suspiciousness	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Stereotyped thinking	Negative symptoms
BPRS	Item	Unusual thought content	Positive symptoms	Overall, 1967, as cited in Shafer (2005)	PANSS	Item	Suspiciousness/persecution	Positive symptoms
CAINS	Factor	Expressivity	Negative symptoms		PANSS	Item	Tension	General Psychopathology

CAINS	Factor	Motivation and Pleasure	Negative symptoms		PANSS	Item	Uncooperativeness	General Psychopathology
CAINS	Item	Social, family relationships	Negative symptoms		PANSS	Item	Unusual thought content	General Psychopathology
CAINS	Item	Social, friendships	Negative symptoms		PDD	Factor	Perceived Discrimination	Social
CAINS	Item	Social, past-week pleasure	Negative symptoms		PS	Item	P1	Positive symptoms
CAINS	Item	Social, expected pleasure	Negative symptoms		PS	Item	P10	Positive symptoms
CAINS	Item	Vocational, motivation	Negative symptoms		PS	Item	P11	Positive symptoms
CAINS	Item	Vocational, expected pleasure	Negative symptoms		PS	Item	P12	Positive symptoms
CAINS	Item	Recreation, motivation	Negative symptoms		PS	Item	P13	Positive symptoms
CAINS	Item	Recreation, past-week pleasure	Negative symptoms		PS	Item	P14	Positive symptoms
CAINS	Item	Recreation, expected pleasure	Negative symptoms		PS	Item	P15	Positive symptoms
CAINS	Item	Expression, facial	Negative symptoms		PS	Item	P16	Positive symptoms
CAINS	Item	Expression, vocal prosody	Negative symptoms		PS	Item	P17	Positive symptoms
CAINS	Item	Expression, gestures	Negative symptoms		PS	Item	P18	Positive symptoms
CAINS	Item	Expression, speech	Negative symptoms		PS	Item	P19	Positive symptoms
CASH	Item	Affective flattening	Negative symptoms	Peralta et al. (2020)	PS	Item	P2	Positive symptoms
CASH	Item	Alogia	Negative symptoms	Peralta et al. (2020)	PS	Item	P20	Positive symptoms
CASH	Item	Anhedonia/Asociality	Negative symptoms	Peralta et al. (2020)	PS	Item	P3	Positive symptoms
CASH	Item	Attentional disturbances	Positive symptoms	Peralta et al. (2020)	PS	Item	P4	Positive symptoms
CASH	Item	Avolition/Apathy	Negative symptoms	Peralta et al. (2020)	PS	Item	P5	Positive symptoms
CASH	Item	Bizarre Behavior	Positive symptoms	Peralta et al. (2020)	PS	Item	P6	Positive symptoms
CASH	Item	Catatonia	Positive symptoms	Peralta et al. (2020)	PS	Item	P7	Positive symptoms
CASH	Item	Change in appetite or weight	Depression	Peralta et al. (2020)	PS	Item	P8	Positive symptoms
CASH	Item	Decreased need for sleep	Mania	Peralta et al. (2020)	PS	Item	P9	Positive symptoms
CASH	Item	Delusions	Positive symptoms	Peralta et al. (2020)	PSP	Factor	Total	Functioning
CASH	Item	Depressive mood	Depression	Peralta et al. (2020)	PSP	Item	Disturbing and aggressive behaviour	Functioning
CASH	Item	Distractibility	Mania	Peralta et al. (2020)	PSP	Item	Personal and social relationships	Functioning
CASH	Item	Euphoric mood	Mania	Peralta et al. (2020)	PSP	Item	self care	Functioning
CASH	Item	Feelings of worthlessness	Depression	Peralta et al. (2020)	PSP	Item	Socially useful activities	Functioning
CASH	Item	Formal thought disorders	Positive symptoms	Peralta et al. (2020)	PST	Factor	Total	Functioning
CASH	Item	Hallucinations	Positive symptoms	Peralta et al. (2020)	RMET	Factor	Total	Cognition
CASH	Item	Inability to think or concentrate	Depression	Peralta et al. (2020)	RSA	Factor	Family cohesion	Social
CASH	Item	Increase in activity	Mania	Peralta et al. (2020)	RSA	Factor	Perception of future	Social
CASH	Item	Inflated self-esteem	Mania	Peralta et al. (2020)	RSA	Factor	Perception of self	Social
CASH	Item	Insomnia or hypersomnia	Depression	Peralta et al. (2020)	RSA	Factor	Social competence	Social
CASH	Item	Loss of energy	Depression	Peralta et al. (2020)	SANS	Factor	Alogia	Negative symptoms

CASH	Item	Loss of interest or pleasure	Depression	Peralta et al. (2020)	SANS	Factor	Anhedonia	Negative symptoms
CASH	Item	Poor judgment	Mania	Peralta et al. (2020)	SANS	Factor	Anhedonia-asociality	Negative symptoms
CASH	Item	Psychomotor agitation	Depression	Peralta et al. (2020)	SANS	Factor	Asociality	Negative symptoms
CASH	Item	Psychomotor retardation	Negative symptoms	Peralta et al. (2020)	SANS	Factor	Attention	Negative symptoms
CASH	Item	Racing thoughts	Mania	Peralta et al. (2020)	SANS	Factor	Avolition	Negative symptoms
CASH	Item	Suicide thoughts/Behavior	Depression	Peralta et al. (2020)	SANS	Factor	Avolition-apathy	Negative symptoms
CASH	Item	Talkativeness/pressure of speech	Mania	Peralta et al. (2020)	SANS	Factor	Blunted affect	Negative symptoms
CDSS	Factor	Depression	Depression		SANS	Item	Unchanged facial expression	Negative symptoms
CDSS	Factor	Total	Depression		SANS	Item	Decreased spontaneous movements	Negative symptoms
CDSS	Item	Depression	Depression		SANS	Item	Paucity expressive gestt	Negative symptoms
CDSS	Item	Early awakening	Depression		SANS	Item	Lack vocal inflections	Negative symptoms
CDSS	Item	Guilt ideas of reference	Depression		SANS	Item	Blocking	Negative symptoms
CDSS	Item	Hopelessness	Depression		SANS	Item	Increased response latency	Negative symptoms
CDSS	Item	Morning depression	Depression		SANS	Item	Poor eye contact	Negative symptoms
CDSS	Item	Observed depression	Depression		SANS	Item	Affective nonresponsivity	Negative symptoms
CDSS	Item	Pathological guilt	Depression		SANS	Item	Inappropriate affect	Negative symptoms
CDSS	Item	Self-depreciation	Depression		SANS	Item	Recreational interests and activities	Negative symptoms
CDSS	Item	Suicide	Depression		SANS	Item	Sexual interest and activity	Negative symptoms
CLANG	Item	Excess phonetic association	Thought disorder		SANS	Item	Ability feel intimacy and closeness	Negative symptoms
CLANG	Item	Abnormal syntax	Thought disorder		SANS	Item	Relationship with friends and peers	Negative symptoms
CLANG	Item	Excess syntactic constrains	Thought disorder		SANS	Item	Grooming & hygiene	Negative symptoms
CLANG	Item	Lack of semantic association	Thought disorder		SANS	Item	Impersistence at work or school	Negative symptoms
CLANG	Item	Referential failures	Thought disorder		SANS	Item	Physical anergia	Negative symptoms
CLANG	Item	Disclosure failure	Thought disorder		SANS	Item	Poverty of speech	Negative symptoms
CLANG	Item	Excess details	Thought disorder		SANS	Item	poverty content of speech	Negative symptoms
CLANG	Item	Lack of details	Thought disorder		SANS	Item	social inattentiveness	Negative symptoms
CLANG	Item	Aprosodic speech	Thought disorder		SANS	Item	Test inattentiveness	Negative symptoms
CLANG	Item	Abnormal prosody	Thought disorder		SAPS	Factor	Total	Positive symptoms
CLANG	Item	Pragmatics disorder	Thought disorder		SAS	Factor	Side effects	Side effects
CLANG	Item	Dysfluency	Thought disorder		SAT	Factor	Social cognition attribution	Cognition
CLANG	Item	Dysarthria	Thought disorder		SES	Factor	Total	Social
CLANG	Item	Poverty of speech	Thought disorder		SFS	Factor	Communication	Functioning
CLANG	Item	Pressure of speech	Thought disorder		SFS	Factor	Prosocial activities	Functioning
CLANG	Item	Neologisms	Thought disorder		SFS	Factor	Social engagement/withdrawal	Functioning
CLANG	Item	Paraphasic error	Thought disorder		SHRS	Item	extrapyramidal side effect	Side effects

Clinical Interview	Item	Affective symptoms	General psychopathology
Clinical Interview	Item	Delusions	Positive symptoms
Clinical Interview	Item	Disorganised speech	Thought disorder
Clinical Interview	Item	Grossly disorganised or catatonic behaviour	Other
Clinical Interview	Item	Hallucinations	Positive symptoms
Clinical Interview	Item	Negative symptoms	Negative symptoms
Clinical Interview	Item	Physical aggression	Hostility suspiciousness
Clinical Interview	Item	Social and occupational dysfunction	Functioning
Clinical Interview	Item	Verbal aggression	Hostility suspiciousness
Illness duration	Item	Illness duration	Other
EMA	Item	Down	Depression
EMA	Item	Loss of control	Positive symptoms
EMA	Item	Relaxed	Anxiety
EMA	Item	Paranoia	Positive symptoms
EMA	Item	Hearing voices	Positive symptoms
FEIT	Factor	Total	Cognition
FT	Factor	Total	Cognition
HT	Factor	Total	Cognition
ISMI	Factor	Stigma	Social
ISMI	Factor	Total	Social
MAS	Factor	Awareness of the other	Cognition
MAS	Factor	Decentration	Cognition
MAS	Factor	Mastery	Cognition
MAS	Factor	Self-reflectivity	Cognition
MAS	Factor	Meta cognition	Cognition
MATRICS	Factor	Attention	Cognition
MATRICS	Factor	Managing emotions	Cognition
MATRICS	Factor	Neurocognitive factor	Cognition

SLOF	Factor	Functioning	Functioning
SLOF	Factor	Total	Functioning
SLOF	Factor	Everyday life skills	Functioning
SLOF	Factor	Interpersonal relationships	Functioning
SLOF	Factor	Work skills	Functioning
SLOF	Item	IR01	Functioning
SLOF	Item	IR02	Functioning
SLOF	Item	IR03	Functioning
SLOF	Item	IR04	Functioning
SLOF	Item	IR05	Functioning
SLOF	Item	IR06	Functioning
SLOF	Item	IR07	Functioning
SLOF	Item	SA01	Functioning
SLOF	Item	SA02	Functioning
SLOF	Item	SA03	Functioning
SLOF	Item	SA04	Functioning
SLOF	Item	SA05	Functioning
SLOF	Item	SA06	Functioning
SNS	Factor	Anhedonia	Negative symptoms
SNS	Factor	Avolition	Negative symptoms
SNS	Factor	Diminished emotional range	Negative symptoms
SNS	Factor	social withdrawal	Negative symptoms
SOFAS	Factor	Total	Functioning
TASIT-1	Factor	Total	Cognition
TASIT-2	Factor	Total	Cognition
TASIT-3	Factor	Total	Cognition
UPSA-B	Factor	Total	Functioning

Note. Reference provided if the factor structure applied differed over the studies included; ACE III = Addenbrookes cognitive examination version III; BARS = Barnes Akathisia Rating Scale; BLERT = Bell–Lysaker Emotional Recognition Task; BNSS = Brief negative symptom scale; BPRS = Brief psychiatric rating scale; CAINS = Clinical assessment interview for negative symptoms; CASH = Comprehensive assessment of symptoms and history; CDSS = Calgary depression rating scale for schizophrenia; CLANG = Clinical language disorder rating scale; EMA = Ecological momentary assessment; FEIT = Facial emotion identification test; FT = Faces test; HT = Hinting task; ISMI = Internalised stigma of mental illness; MAS = Metacognition assessment scale; MATRICS = Measurement and treatment research to improve cognition in schizophrenia; MSCEIT = Mayer-Salovey-caruso emotional intelligence Test; PANSS = Positive and negative syndrome scale; PDD = Perceived devaluation and discrimination scale; PS = Paranoia scale; PSP = Personal social performance scale; PST = Picture Sequencing Task; REMT = Reading the mind in the eyes test; RSA = Resilience scale for adults; SANS = Scale for the assessment of negative symptoms; SAPS = Scale for the assessment of positive symptoms; SAS = Simpson-Angus Extrapyramidal Side Effects Scale; SAT = Social Attributions Test; SES = Service engagement scale; SFS = Social functioning scale; SHRS = St Hans rating sale; SLOF = Specific level of functioning scale; SNS = Self-Evaluation of Negative Symptoms Scale; SOFAS = Social and occupational functioning assessment scale; TASIT = The awareness of social inference test; UPSA-B = UCSD Performance-Based Skills Assessment—Brief.

Appendix C2 Supplementary Materials (Chapter 5)

Table 16. Adjusted p-Values for Model 1.

Parent	Child	p (orginal)	p (adjusted)
Chi Square model fit		<.001	<.001
Age	Marital.Status	<.001	<.001
Age	Education	<.001	.002
Age	DAI	<.001	<.001
Age	CGI.Drug.Use	<.001	<.001
Race	CGI.Drug.Use	.001	.017
Marital.Status	Sex	<.001	<.001
Age	MATRICS.Processing.Speed	<.001	<.001
Education	MATRICS.Processing.Speed	<.001	<.001
Sex	CDSS	.004	.040
DAI	CDSS	<.001	<.001
CGI.Drug.Use	CDSS	<.001	<.001
Age	MATRICS.Reasoning	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Reasoning	<.001	<.001
Sex	CGI.Alcohol.Use	<.001	<.001
CGI.Drug.Use	CGI.Alcohol.Use	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Memory	<.001	<.001
MATRICS.Reasoning	MATRICS.Memory	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Vigil	<.001	<.001
MATRICS.Memory	MATRICS.Vigil	<.001	<.001
CDSS	PANSS.General	<.001	<.001
DAI	PANSS.General	<.001	<.001
MATRICS.Memory	PANSS.General	<.001	<.001
CDSS	PANSS.Negative	<.001	<.001
MATRICS.Processing.Speed	PANSS.Negative	<.001	<.001
PANSS.General	PANSS.Negative	<.001	<.001
CGI.Alcohol.Use	PANSS.Negative	.231	1
DAI	PANSS.Positive	<.001	.001
PANSS.General	PANSS.Positive	<.001	<.001
PANSS.Negative	PANSS.Positive	.002	.022
CGI.Drug.Use	PANSS.Positive	<.001	.001
MATRICS.Memory	CGI.Severity	.005	.048
PANSS.General	CGI.Severity	.001	.010
PANSS.Negative	CGI.Severity	<.001	<.001
PANSS.Positive	CGI.Severity	<.001	<.001
Employment	QOL	<.001	<.001
CDSS	QOL	<.001	.003
DAI	QOL	<.001	<.001
MATRICS.Processing.Speed	QOL	<.001	<.001
PANSS.Negative	QOL	<.001	<.001
CGI.Severity	QOL	<.001	<.001
CDSS	ITAQ	<.001	<.001
DAI	ITAQ	<.001	<.001
PANSS.General	ITAQ	<.001	<.001
QOL	ITAQ	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Verbal	<.001	<.001
MATRICS.Memory	MATRICS.Verbal	<.001	<.001
QOL	MATRICS.Verbal	<.001	<.001

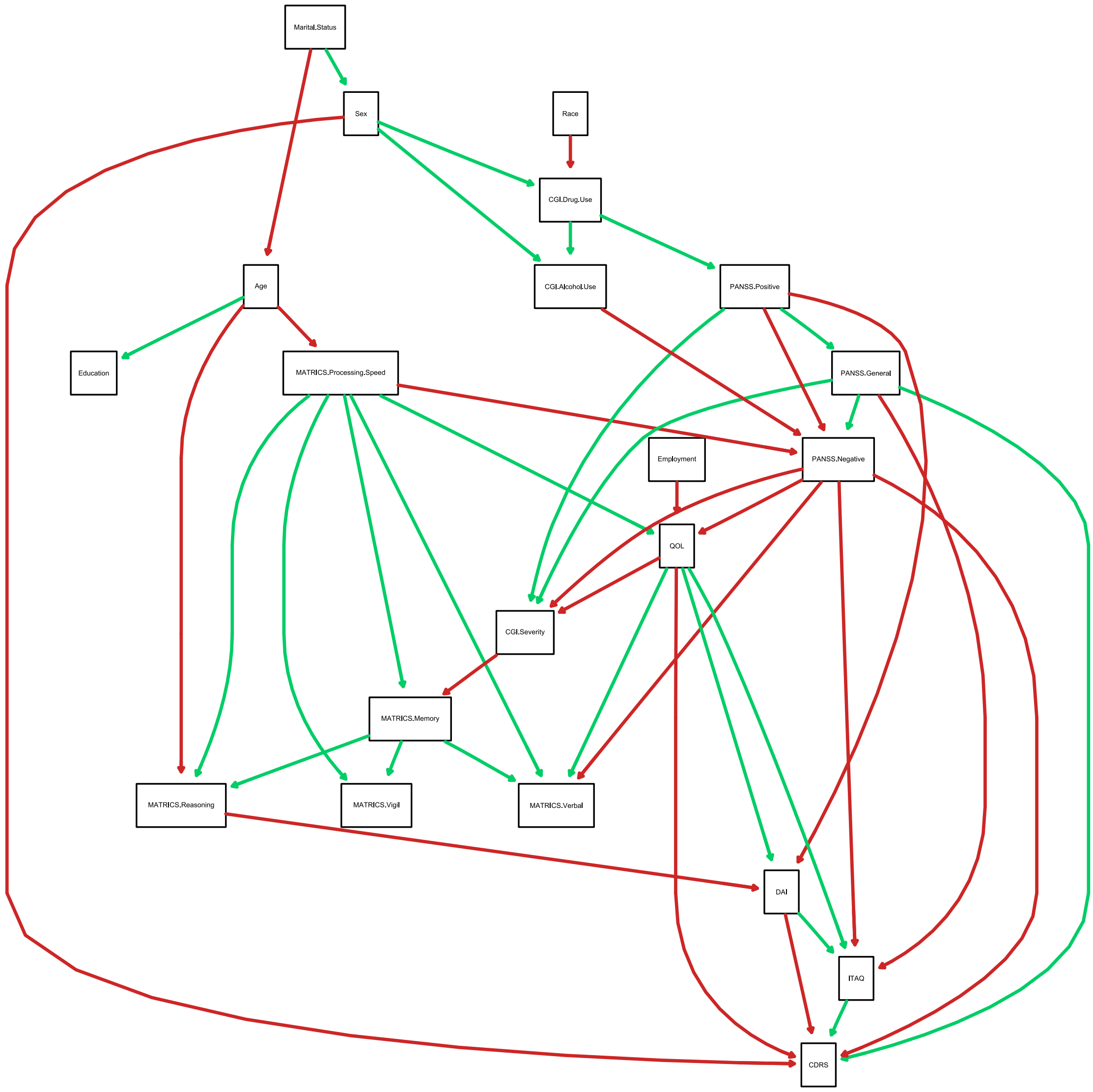

Figure 20. Averaged Bayesian Network.

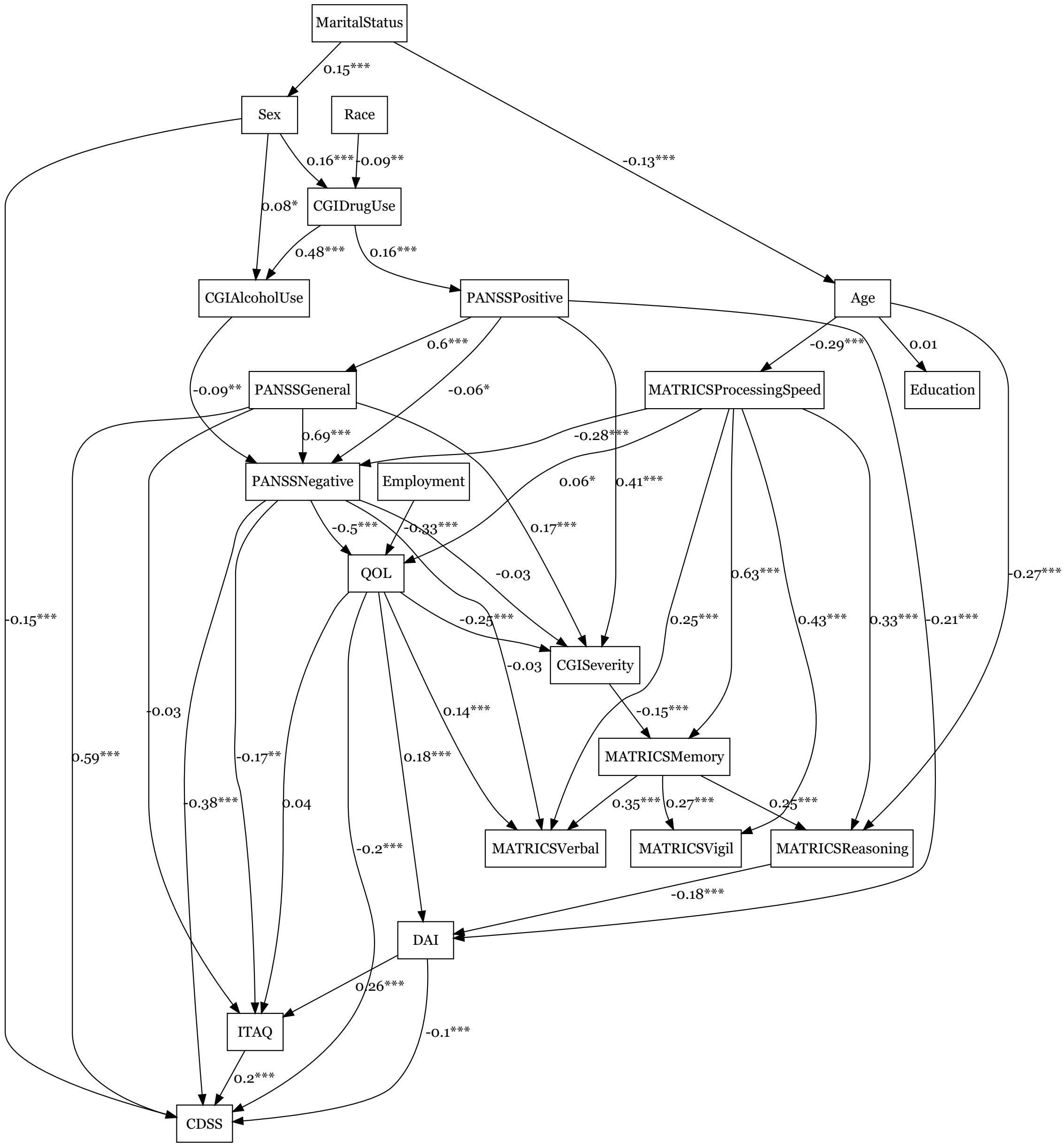

Figure 21. Structural Equation Model of Averaged Bayesian Network.

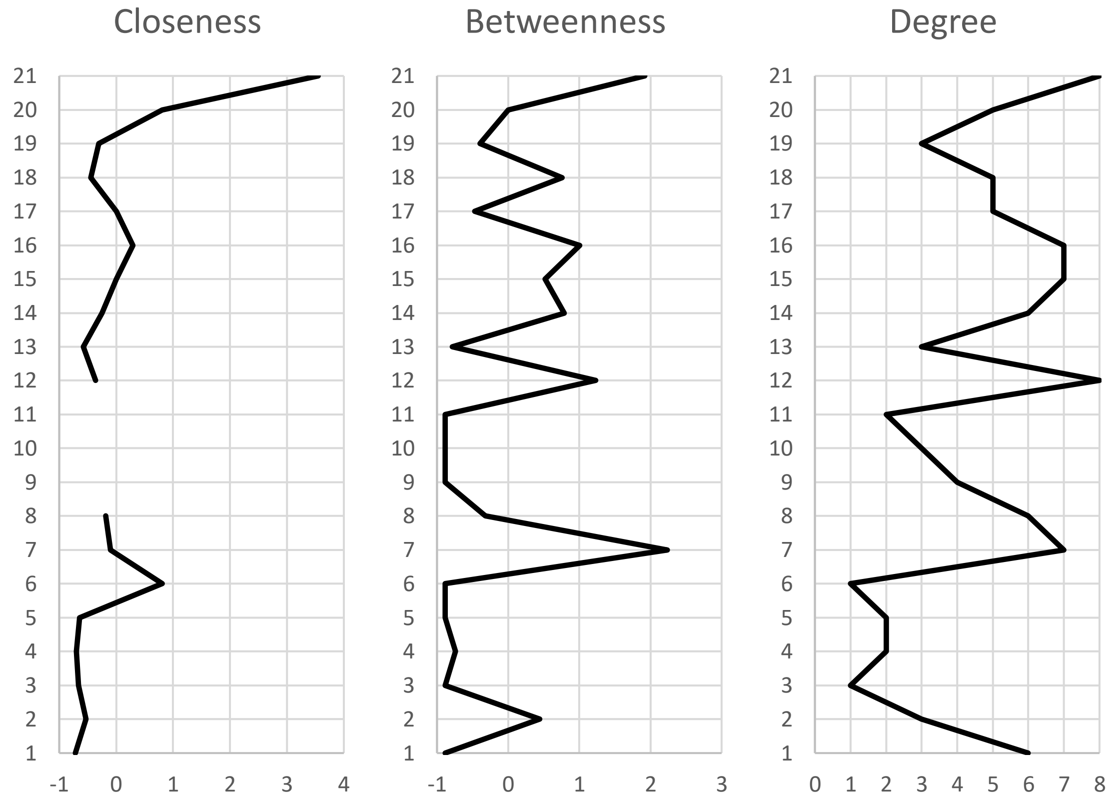

Figure 22. Centrality Statistics of the Averaged Bayesian Network.

Note. Standardised values given for closeness and betweenness; 1 = Age; 2 = Sex; 3 = Race; 4 = Marital Status; 5 = Education ;6 = Employment; 7 = CDSS total; 8 = DAI total; 9 = ITAQ total; 10 = MATRICS verbal; 11 = MATRICS Vigilance; 12 = MATRICS processing speed; 13 = MATRICS reasoning; 14 = MATRICS working memory; 15 = PANSS general; 16 = PANSS negative; 17 = PANSS positive; 18 =CGI Drug Use; 19 =CGI Alcohol use; 20 = CGI Severity; 21 = QOL

Table 17. Adjusted p-Values for Model 2.

Parent	Child	p (orginal)	p (adjusted)
Chi Square model fit		<.001	<.001
Marital.Status	Age	<.001	.008
Marital.Status	Sex	<.001	.001
Age	Education	.908	1
Age	MATRICS.Processing.Speed	<.001	<.001
Sex	CGI.Drug.Use	<.001	<.001
Race	CGI.Drug.Use	.001	.017
CGI.Drug.Use	PANSS.Positive	<.001	<.001
Sex	CGI.Alcohol.Use	.022	.174
CGI.Drug.Use	CGI.Alcohol.Use	<.001	<.001
PANSS.Positive	PANSS.General	<.001	<.001
MATRICS.Processing.Speed	PANSS.Negative	<.001	<.001
PANSS.General	PANSS.Negative	<.001	<.001
PANSS.Positive	PANSS.Negative	.036	.255
CGI.Alcohol.Use	PANSS.Negative	.001	.017
Employment	QOL	<.001	<.001
MATRICS.Processing.Speed	QOL	.017	.153
PANSS.Negative	QOL	<.001	<.001
PANSS.General	CGI.Severity	<.001	.006
PANSS.Negative	CGI.Severity	.555	1
PANSS.Positive	CGI.Severity	<.001	<.001
QOL	CGI.Severity	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Memory	<.001	<.001
CGI.Severity	MATRICS.Memory	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Verbal	<.001	<.001
MATRICS.Memory	MATRICS.Verbal	<.001	<.001
PANSS.Negative	MATRICS.Verbal	.431	1
QOL	MATRICS.Verbal	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Vigil	<.001	<.001
MATRICS.Memory	MATRICS.Vigil	<.001	<.001
Age	MATRICS.Reasoning	<.001	<.001
MATRICS.Processing.Speed	MATRICS.Reasoning	<.001	<.001
MATRICS.Memory	MATRICS.Reasoning	<.001	<.001
MATRICS.Reasoning	DAI	<.001	<.001
PANSS.Positive	DAI	<.001	<.001
QOL	DAI	<.001	<.001
DAI	ITAQ	<.001	<.001
PANSS.General	ITAQ	.549	1
PANSS.Negative	ITAQ	.002	.025
QOL	ITAQ	.173	1
Sex	CDSS	<.001	<.001
DAI	CDSS	<.001	.003
ITAQ	CDSS	<.001	<.001
PANSS.General	CDSS	<.001	<.001
PANSS.Negative	CDSS	<.001	<.001
QOL	CDSS	<.001	<.001

Appendix C3 Supplementary Materials (Chapter 6)

Descriptive statistics for the CATIE study

Table 18 presents the descriptive statistics of people who participated in the CATIE study and completed the PANSS assessment (N = 1,446). Multiple assessments of the PANSS were collected during the trial, and we used the pretreatment assessment for this study. In terms of the participants from the CATIE study, the large majority of the participants from the CATIE study sample were Males (1070; 74.1%), and the sample had an average age of 40.5 years, and the sample mostly identified as White or European American (869; 60.3%). Fewer participants identified as Black or African American (503; 34.9%) or Asian (33; 2.3%). Some individuals reported multiple ethnicities, or other minority ethnic groups were reported, and these were categorized, along with other minority ethnic groups, as other. Most (1,413; 97.7%) participants had received a diagnosis of schizophrenia in the past five years.

Table 18. Demographics for the CATIE Study.

Demographic	*N* (*M*)	% (*SD*)	Missing
Age	(40.5)	(11.1)	2
Gender			2
Male	1070	74.1	
Female	374	25.9	
Ethnicity			4
White or European American	869	60.3	
Black or African American	503	34.9	
Asian	33	2.3	
American Indian/Alaska Native	8	0.6	
Other	29	2.0	
Diagnosis (SCID-5, Past five years)			
Schizophrenia	1,413	97.7	0

Note. N = Sample size; M = Mean; SD = Standard deviation; Proportions do not include missing values; SCID-5 = Structed clinical interview for the DSM-5

Summary scores for the NAPLS3 and CATIE study

The summary scores of the SOPS for the participants in the NAPLS3 study can be found in Table 19. On average, participants presented with 'questionably present' to mild symptoms. The average score per item for the SOPS positive, negative, and disorganized subscales was 1.7, 1.5, and 1.0, respectively, where a score of zero refers to 'absent symptoms' and a score of six refers to 'severe or extreme symptoms' (McGlashan et al., 2001). Based on the item levels, the results in this table indicate that the participants had 'mild' symptoms (score of two) on the positive and negative subscales and 'questionably present' disorganization symptoms (score of one) on average. There was also considerable variation in the scores obtained. Most of the sample scored three or more on at least one item on each subscale. However, a minority of people scored six on at least one item of the positive symptoms (61; 7.7%), negative (94; 11.8%), and disorganization subscale (12; 1.5%).

Table 19. Scale of Prodromal Symptoms Summary Scores From the NAPLS3 Study.

Subscale	M	Mdn	SD	Min	Max	Three or more on an item	Six on an item
Positive	8.9	9	6.0	0	29	579	61
Negative	9.1	8	7.2	0	33	511	94
Disorganized	4.0	3	3.7	0	20	374	12

Note. *M* = Mean; Mdn = Median; *SD* = Standard deviation; *Min* = Minimum value; *Max* = Maximum value.

Similarly, for the CATIE study, Table 20 presents the descriptive statistics for the PANSS. On average, people presented between the 50th and 55th percentiles for the positive subscale, between the 40th and 45th percentiles for the negative subscale, and between the 45th and 50th percentiles for the general subscale on the PANSS assessment (Kay et al., 1987). Hence, the cohort of participants in the CATIE trial presented with average symptom severity across the sample.

Table 20. Positive and Negative Syndrome Scale Summary Scores From the CATIE Study.

Subscale	M	Mdn	SD	Min	Max
Positive	18.5	18	5.6	7	38
Negative	20.2	20	6.4	7	41
General	37.0	37	9.3	16	70

Note. *M* = Mean; Mdn = Median; *SD* = Standard deviation; *Min* = Minimum value; *Max* = Maximum value.

Model structures

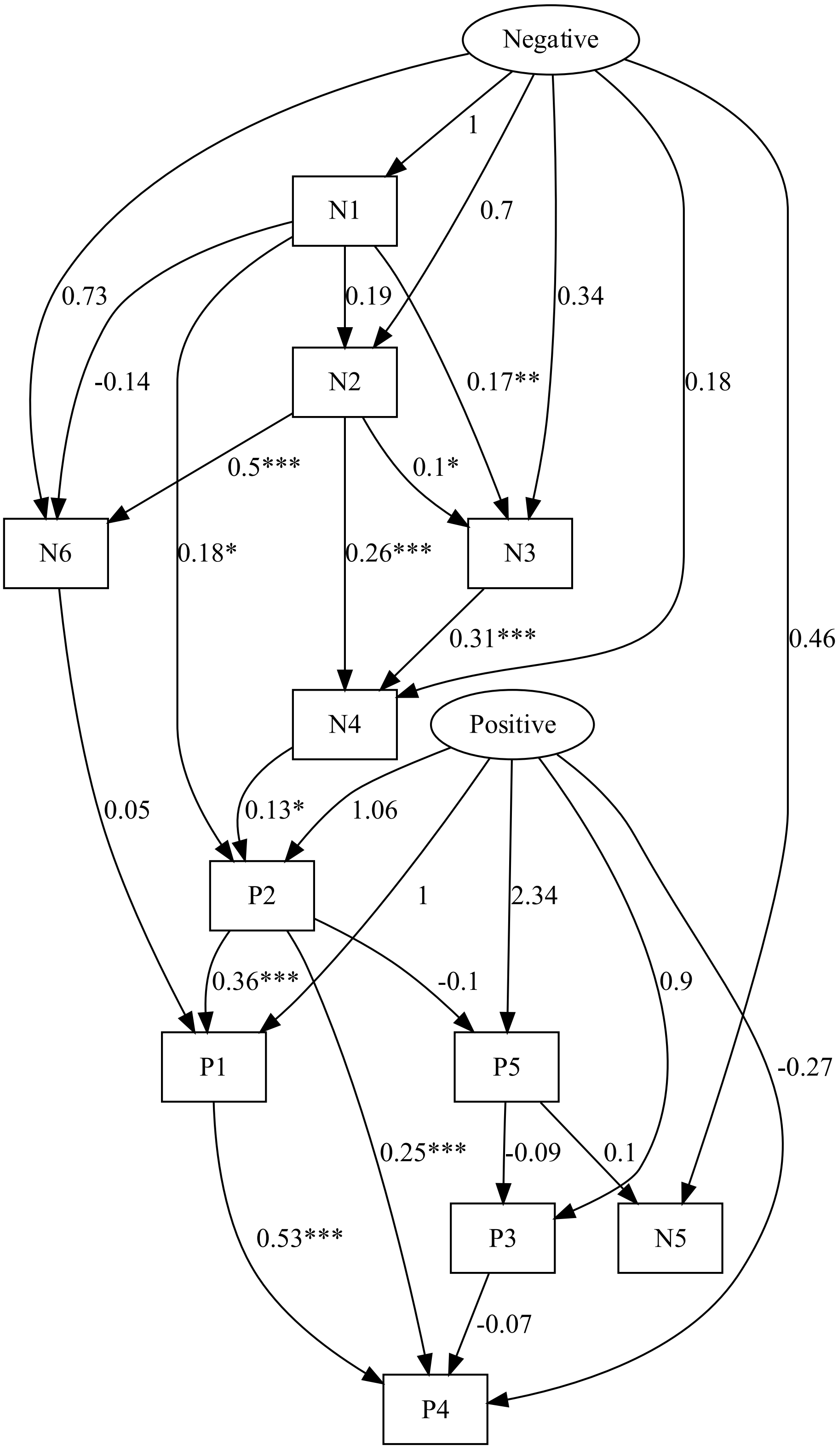

Figure 23. Structural Equation Model of the Integrated Model of the SOPS, Test Dataset Two.

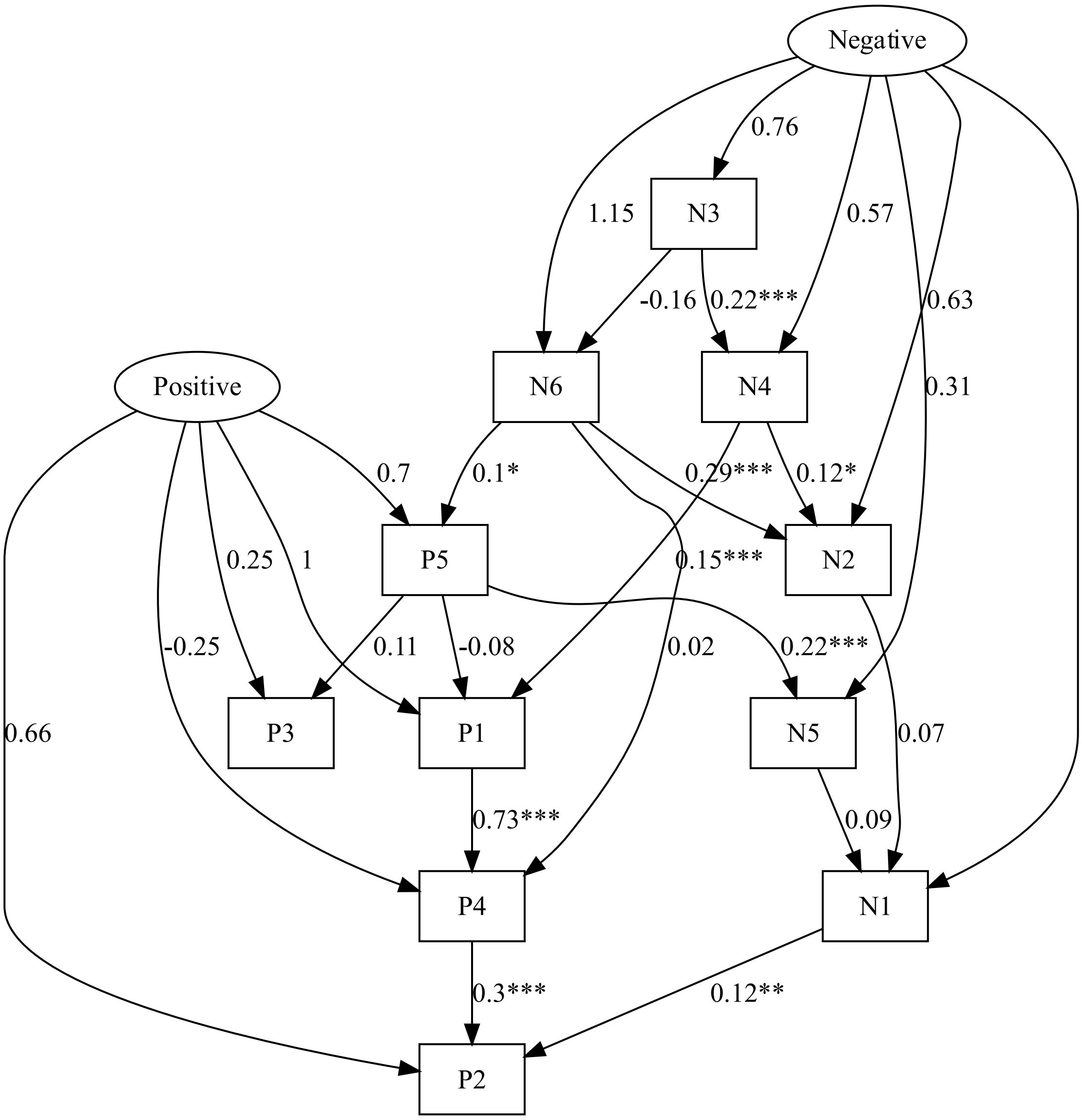

Figure 24. Structural Equation Model of the Integrated Model of the SOPS, Test Dataset Three.

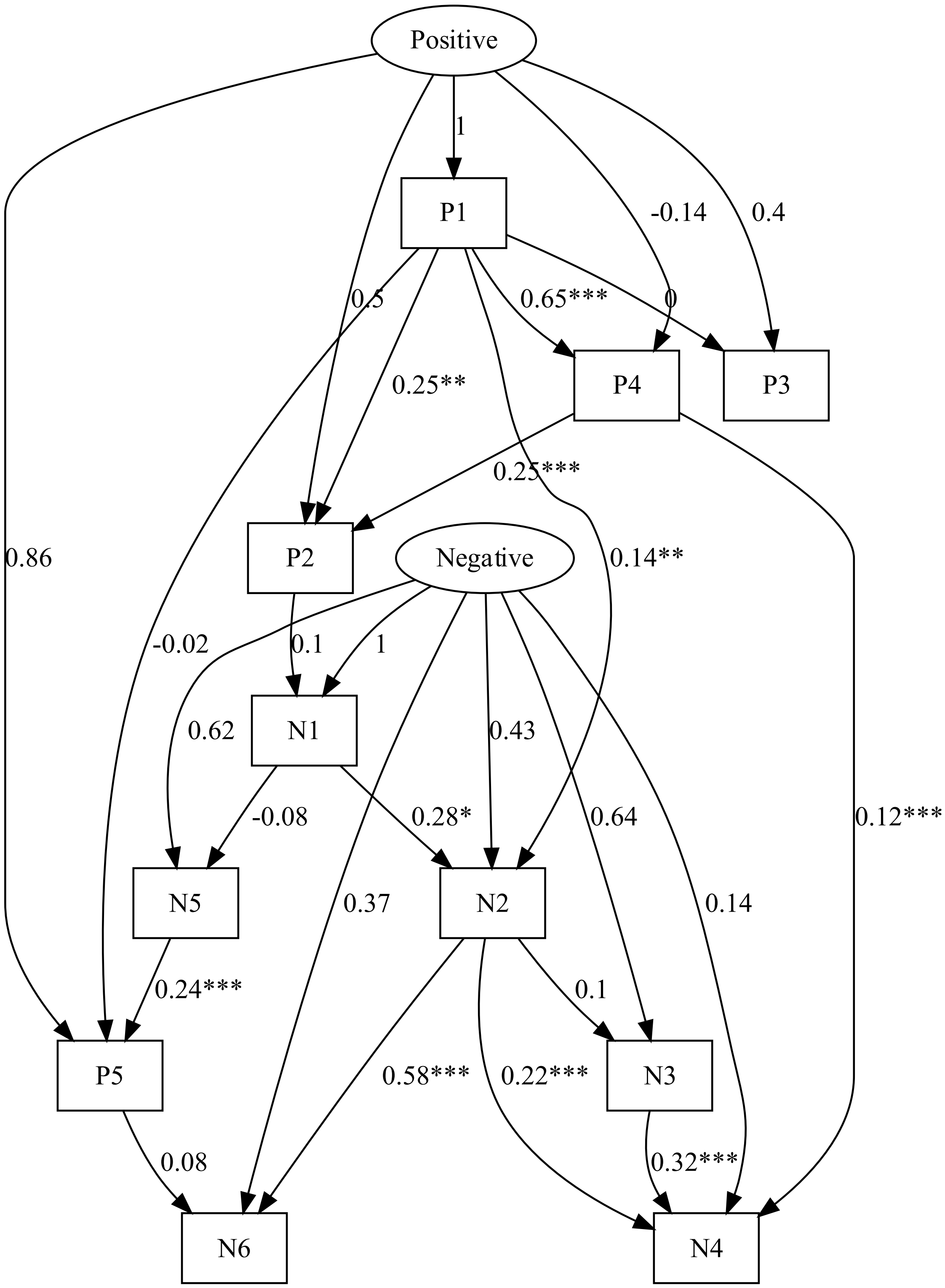

Figure 25. Structural Equation Model of the Integrated Model of the SOPS, Test Dataset Four.

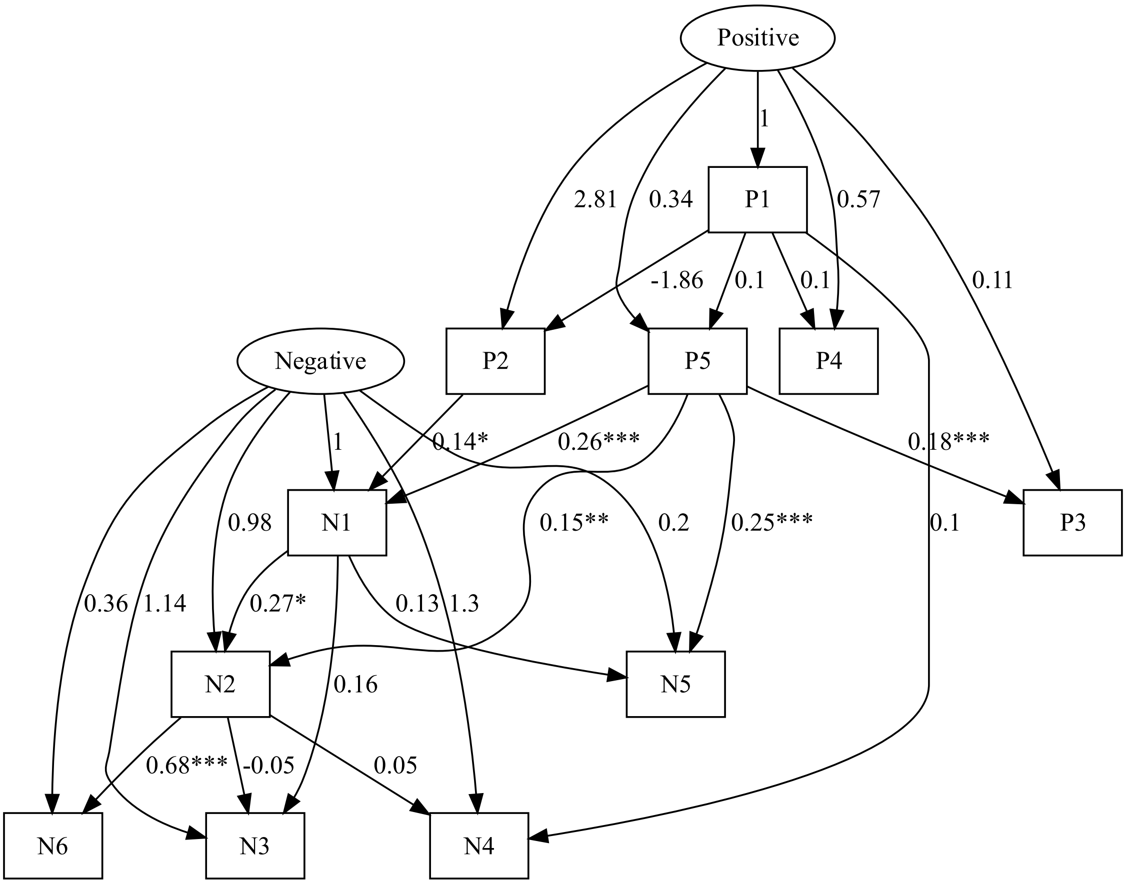

Figure 26. Structural Equation Model of the Integrated Model of the SOPS, Test Dataset Five.

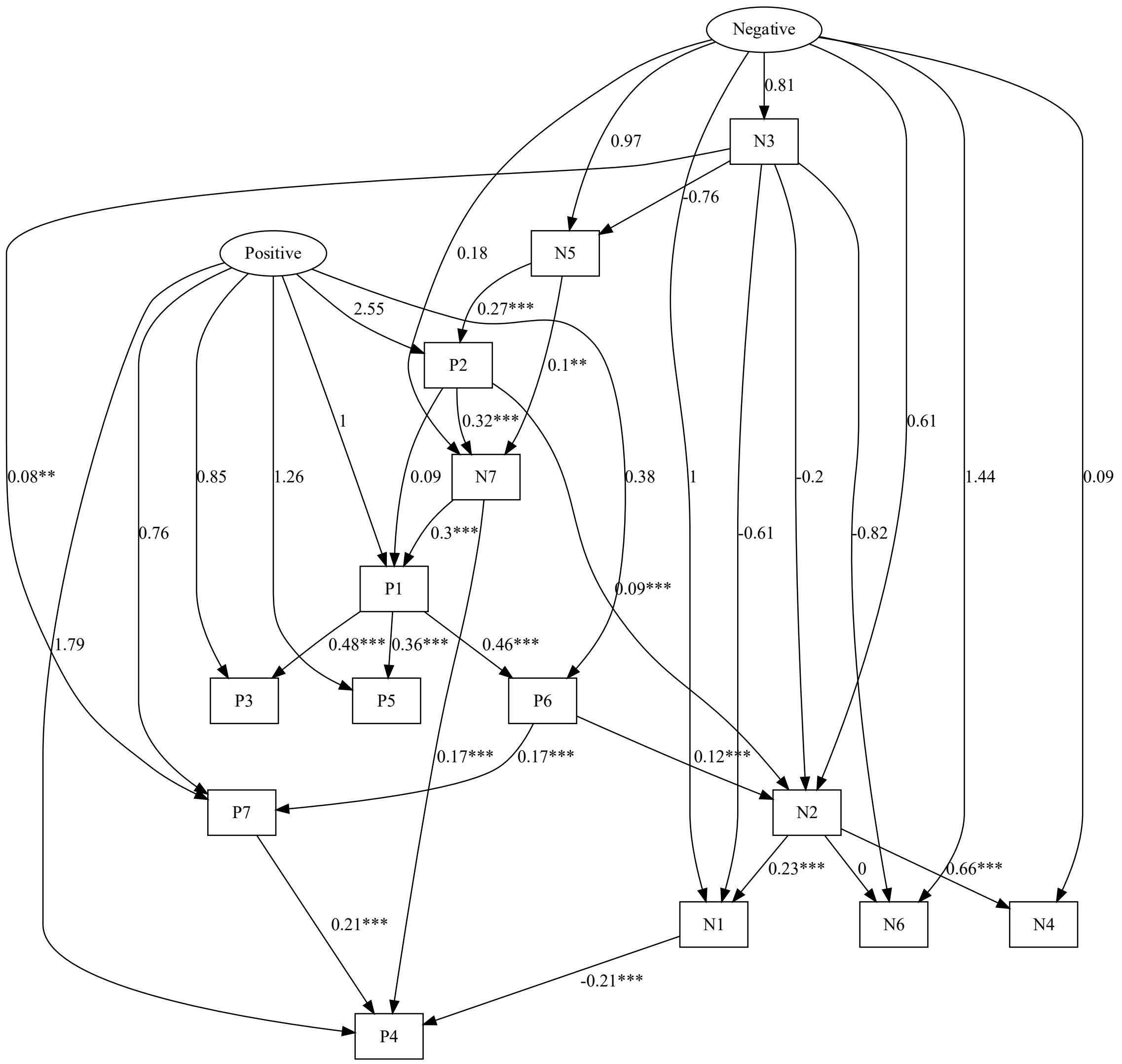

Figure 27. Structural Equation Model of the Integrated Model of the PANSS, Test Dataset One.

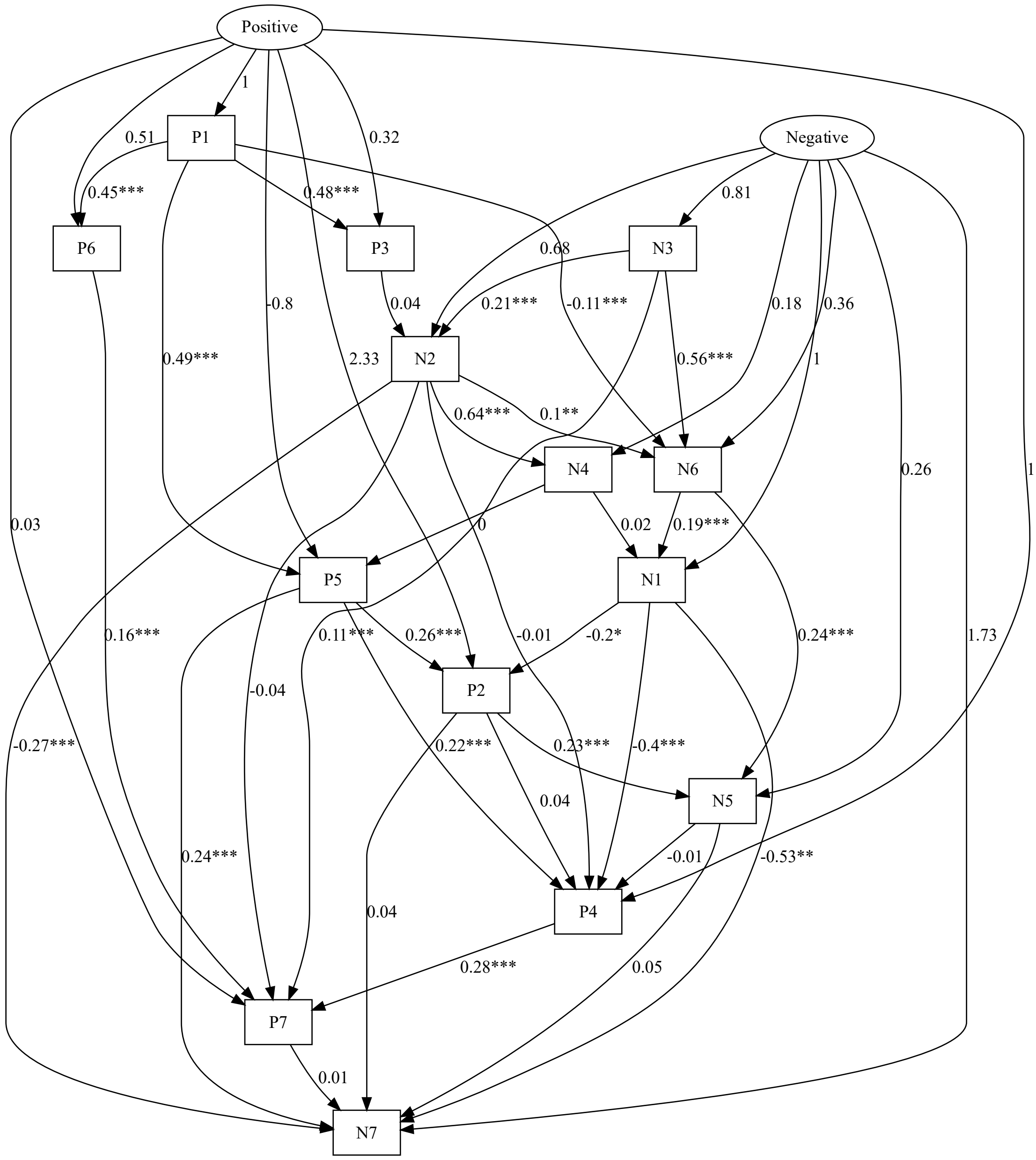

Figure 28. Structural Equation Model of the Integrated Model of the PANSS, Test Dataset Two.

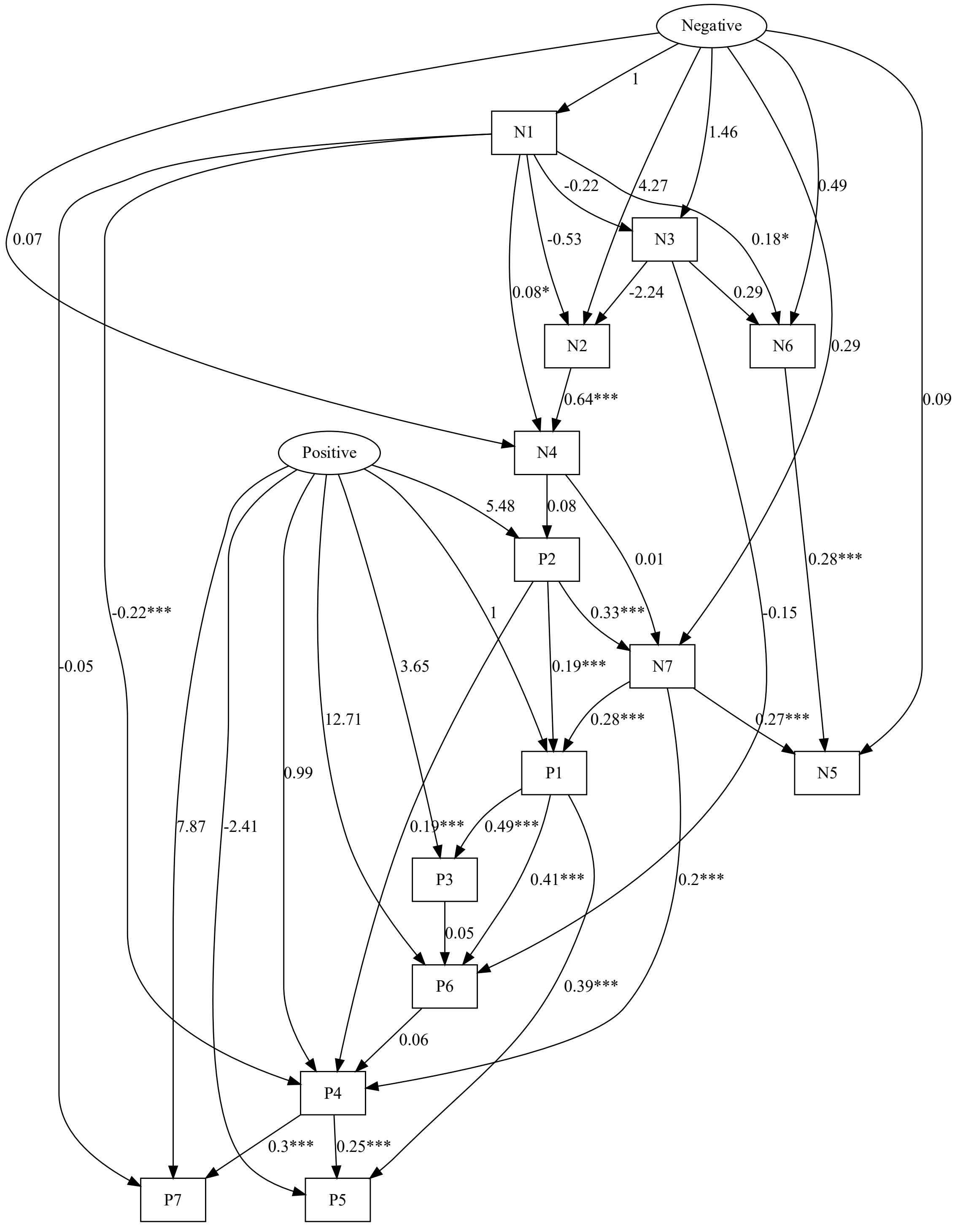

Figure 29. Structural Equation Model of the Integrated Model of the PANSS, Test Dataset Three.

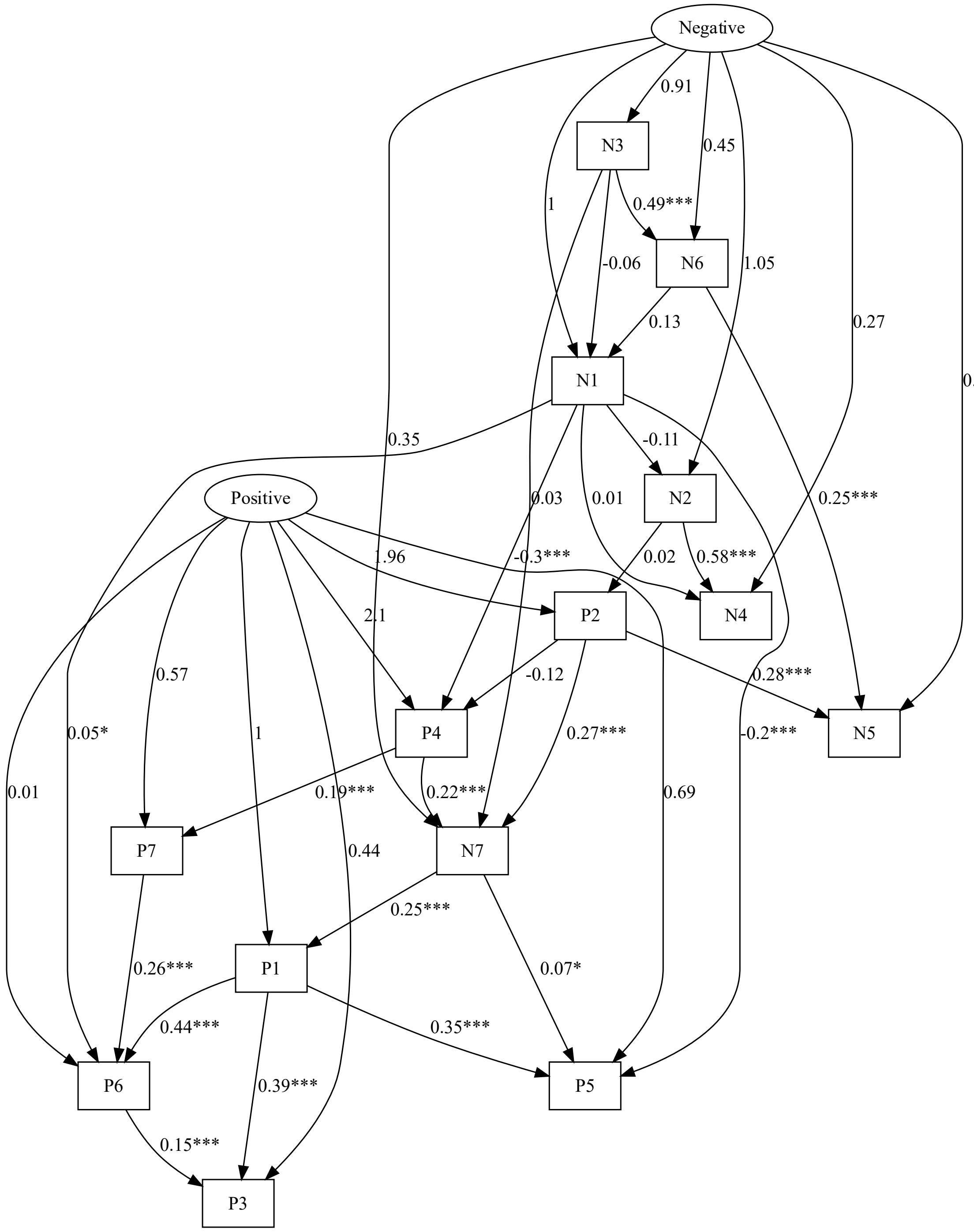

Figure 30. Structural Equation Model of the Integrated Model of the PANSS, Test Dataset Four.

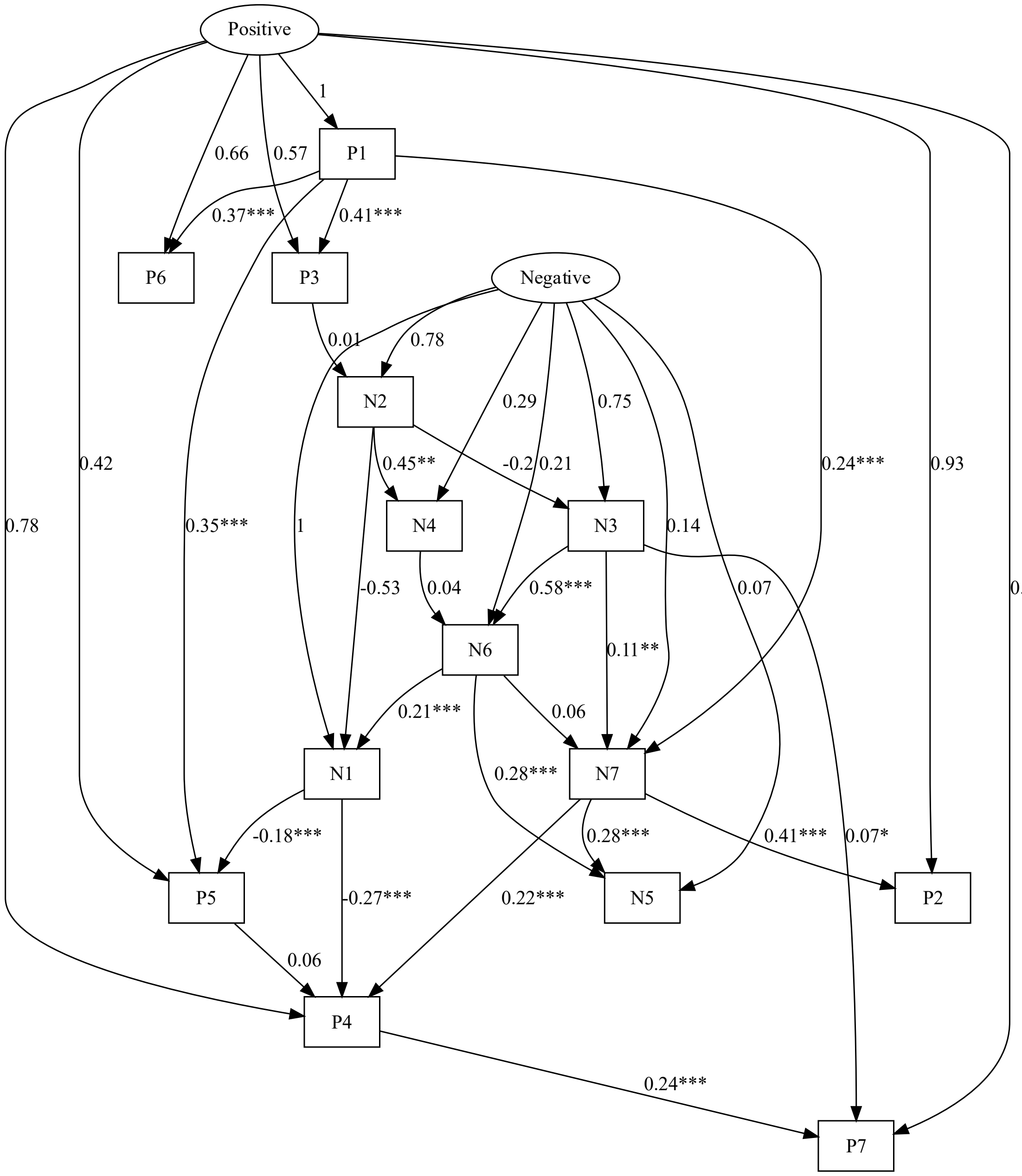

Figure 31. Structural Equation Model of the Integrated Model of the PANSS, Test Dataset Five.