Centrality statistics of symptom networks of schizophrenia: a systematic review

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Abstract

The network theory of psychological 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, we 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.

Background

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-Küstner, Martin, & Pastor, 2018), there is considerable impact on people diagnosed with schizophrenia (PDS), schizophreniform, schizoaffective disorder, 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, Hennekens, Hollar, & Casey, 2005; Laursen, Munk-Olsen, & Vestergaard, 2012; Saha, Chant, & McGrath, 2007). The heterogenous etiology, presentation, and prognosis of schizophrenia, schizophreniform, and schizoaffective disorders have led some authors to suggest these disorders may be better characterized as syndromes as opposed to distinct disease entities (Andreasen & Olsen, 1982; Carpenter, 2007; Kendell, 1987).

The network theory of mental disorders conceptualizes 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

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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, Boyette, Guloksuz, & Borsboom, 2021; 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 online Supplementary materials section 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 (R. J. 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, Wright, Markon, & Krueger, 2017). However, other authors later rejected this notion and found support for the replicability of networks (Borsboom et al., 2017; Fried, van Borkulo, & Epskamp, 2021; Funkhouser et al., 2020; Jones, Williams, & McNally, 2021). 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) synthesize 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 synthesize 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.

Methods

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 online Supplementary Materials: Methods section.

We systematically searched and selected studies based on predetermined inclusion and exclusion criteria. A research librarian specializing 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 online Supplementary Materials: Methods section.

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 online Supplementary materials.

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 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.

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.

Search methods for identification of studies

Information sources

Selection process

The search engines returned 2211 studies, 975 of which were duplicates. Conflicts were 5.3% ($\kappa = 0.58$) between KB and KA in the initial screen and were 10.0% ($\kappa = 0.58$) 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%, $\kappa = 0.48$) and the updated search MS and KB disagreed on three studies in the full text review (13%, $\kappa = 0.74$). A consensus was reached for each disagreement between KB and MS.

Results

Description of studies

Study selection

Database searches yielded 2211 studies to be screened, of these 975 were duplicates and removed. The remaining 1236 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 Fig. 1. 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 ($N = 8$).

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 online Supplementary Materials 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.

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, Drukker, Hasmi, & Van Jim, 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, Anthonis, Acsai, & Correll, 2022a; Hajdúk, Klein, Harvey, Penn, & Pinkham, 2019). Two studies presented a network based on ecological momentary assessment and therefore the outcome measures were not assessed as reliable or valid (Badal, Parrish, Holden, Depp, & Granholm, 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.

Fig. 2 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 Fig. 2 were colored in gray if this
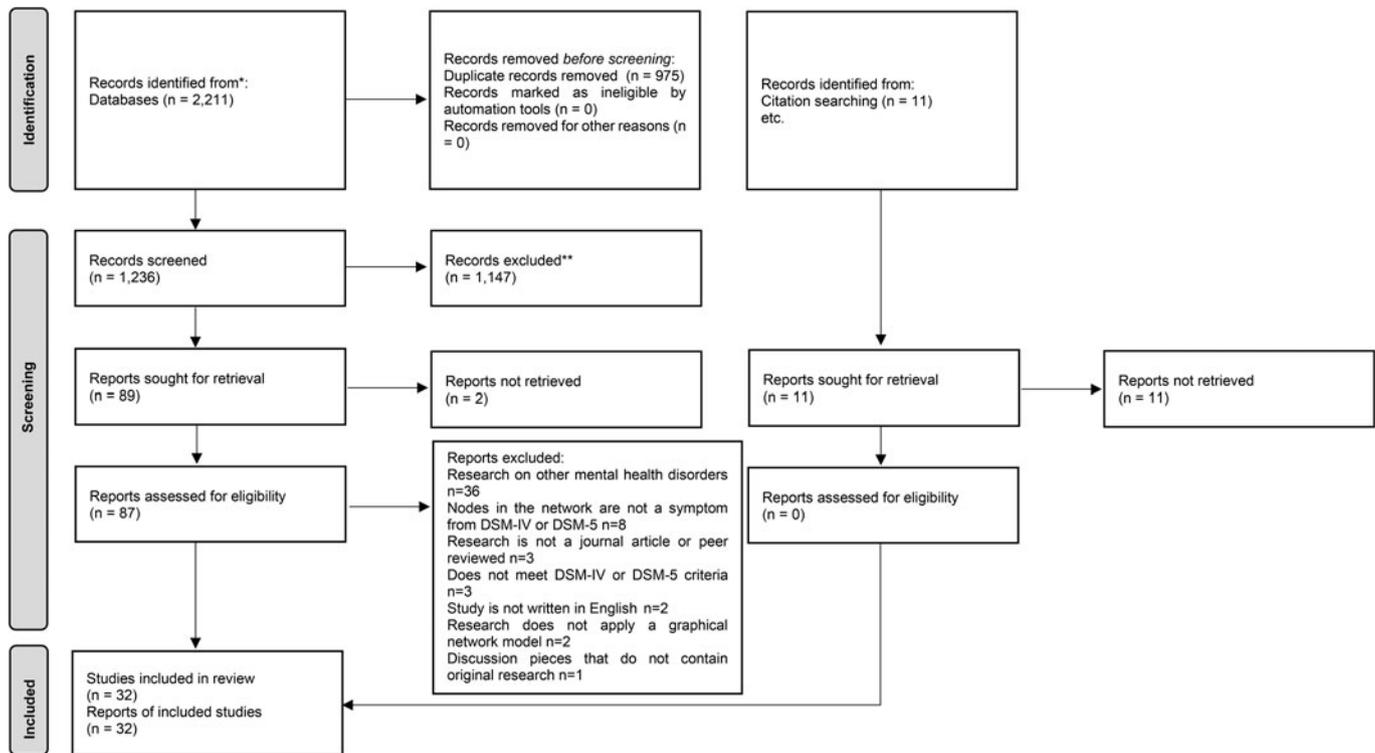
Figure 1. PRISMA flow chart.

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 sub-scales to the domain's depression, cognition, functioning, positive symptoms, and negative symptoms can be found in the online Supplementary Materials: Methods section. Additionally, the text version of this figure can be found in the online Supplementary Materials: Table 5A section. In Fig. 2, 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 Fig. 2. 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, Visser, Strauss, and Sayama (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 three 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 online Supplementary materials:

Table 1. Characteristics of included studies

Author	No. of patients	Mean age (s.d.); 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, Sayama, Visser, and Strauss (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, Goldzweig, Lavi-Rotenberg, Luther, and Lysaker (2018)	81	49.7 (10.8); 77 (PDS, SZA)	USA	None	PANSS, MAS-A, HT, BLERT, MATRICS, SAT, PST	Unnamed
Hopkins et al. (2022)	4863	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

Table 1. (*Continued.*)

Author	No. of patients	Mean age (s.d.); N males	Country	Comparisons	Assessments	Dataset
Li et al. (2022)	3681	39.9 (12.9); 2164	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, Gil-Berrozpe, Sánchez-Torres, and Cuesta (2020)	124	39.9 (14.9); 62	Spain	Schizoaffective, bipolar, and psychotic depression	CASH	Unnamed
Gregory Paul 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
Gregory Paul Strauss et al. (2019b)	201	41.6 (12.1); 146.	USA	PDS and schizoaffective, bipolar, and HC	BNSS	MPRC; SUNYB
Gregory P. 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)	2334	31.3 (7.9); 1207	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, Internalized 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, Optimization of Treatment and Management of Schizophrenia in Europe; REAP–AP, Research on Asian Psychotropic Prescription Patterns for Antipsychotics; RCT, Randomized 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.

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	151–200	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	151–200	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	151-200	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
	Yes	No	Cohort	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	Yes	No	No	Yes

Table 2. (*Continued.*)

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
Monteleone et al. (2022)																
Park et al. (2020)	Yes	Yes	Case–control	151-200	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
Gregory Paul Strauss et al. (2019a)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	No	Yes	No	Yes
Gregory Paul Strauss et al. (2019b)	Yes	Yes	Descriptive study	200+	Yes	Yes	Yes	Yes	NA	N/A	N/A	Yes	No	Yes	No	Yes
Gregory P. 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**	**101-150**	**Yes**	**Yes**	**NA**	**NA**	**NA**	**N/A**	**N/A**	**No**	**No**	**Yes**	**No**	**Yes**

Note. NA, Not addressed; N/A, Not applicable.
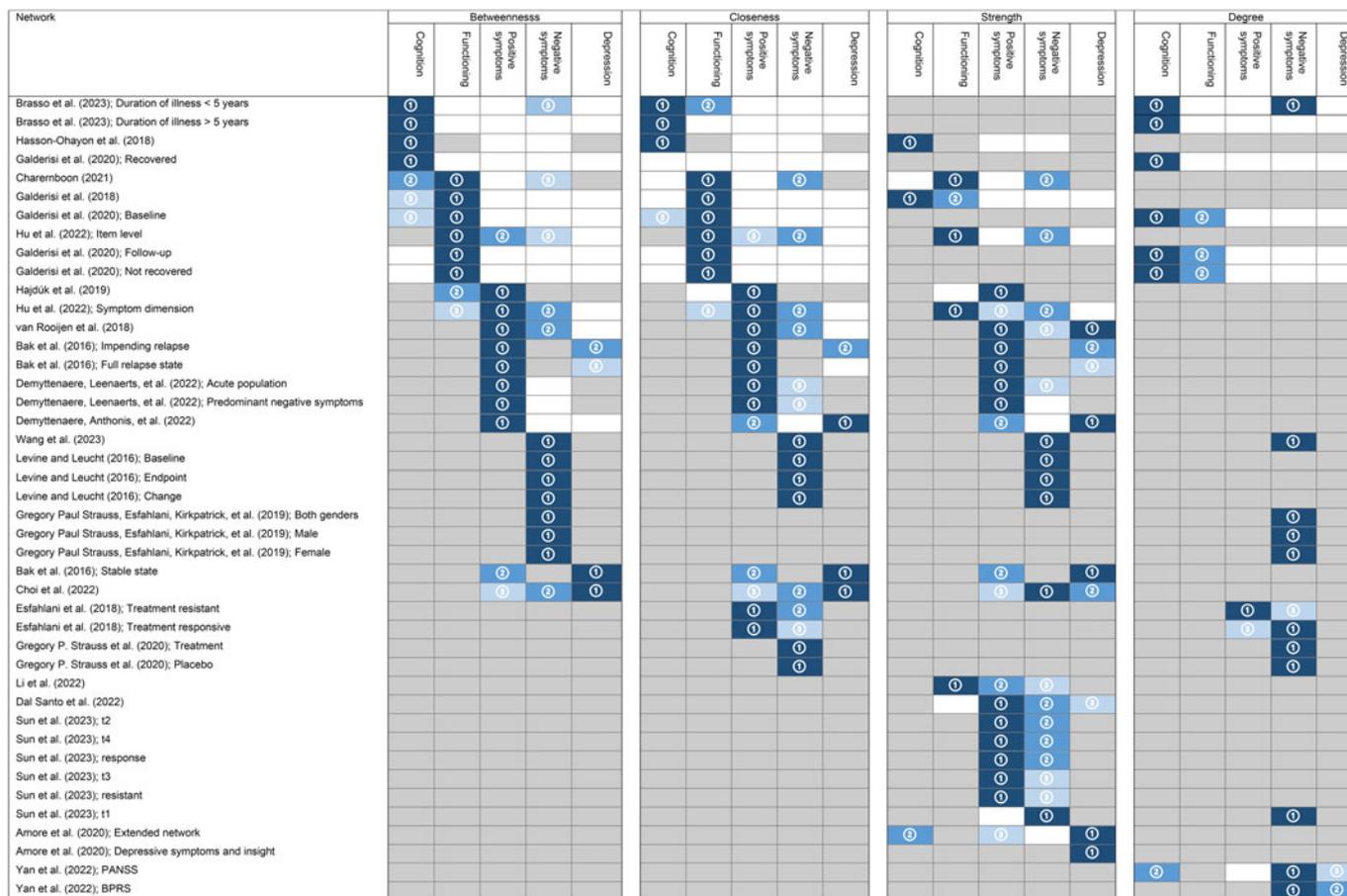
Figure 2. Ranks of domains across centrality indices.

Table 5B 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.

Discussion

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 inquiry 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 (R. McNally, Mair, Mugno, and Riemann, 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, Marwaha, & Birchwood, 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, Waldorp, Van Der Maas, & Borsboom, 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, Barrowclough, and Haddock (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, Addington, & Maticka-Tyndale, 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, Preti, Edwards, Dow, & Wykes, 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, Borsboom, & Fried, 2018). 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) penalization 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 the MCRF. 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, Ward, & Clack, 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.

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, Greene, & Spiller, 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 (Boyette et al., 2020; Isvoranu et al., 2016) 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 Fig. 2, or were focused on social, medical, or biological variables for Table 5B in the online Supplementary Materials section. 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.

Conclusions

Given the intertwined nature of symptoms, comorbidities, and mediating factors of symptoms, the network approach offers a new perspective on characterizing 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 (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).

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