Implications of data-driven analyses for personalized therapy in psychosis: a systematic review of cluster- and trajectory-based modelling studies

Running title: Implications of cluster- and trajectory-based modelling studies

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Abstract

Introduction: To tackle the phenotypic heterogeneity of schizophrenia, data-driven methods are often applied to identify subtypes of its (sub)clinical symptoms though there is no systematic review.

Aims: To summarize the evidence from cluster- and trajectory-based studies of positive, negative and cognitive symptoms in patients with schizophrenia spectrum disorders, their siblings and healthy people. Additionally, we aimed to highlight knowledge gaps and point out future directions to optimize the translatability of cluster- and trajectory-based studies.

Methods: A systematic review was performed through searching PsycINFO, PubMed, PsycTESTS, PsycARTICLES, SCOPUS, EMBASE, and Web of Science electronic databases. Both cross-sectional and longitudinal studies published from 2008 to 2019, which reported at least two statistically derived clusters or trajectories were included. Two reviewers independently screened and extracted the data.

Results: Of 2,285 studies retrieved, 50 studies (17 longitudinal and 33 cross-sectional) conducted in 30 countries were selected for review. Longitudinal studies discovered two to five trajectories of positive and negative symptoms in patient, and four to five trajectories of cognitive deficits in patient and sibling. In cross-sectional studies, three clusters of positive and negative symptoms in patient, four clusters of positive and negative schizotypy in sibling, and three to five clusters of cognitive deficits in patient and sibling were identified. These studies also reported multidimensional predictors of clusters and trajectories.

Conclusions: Our findings indicate that (sub)clinical symptoms of schizophrenia are more heterogeneous than currently recognized. Identified clusters and trajectories can be used as a basis for personalized psychiatry.

Keywords: psychosis, schizophrenia, cluster analysis, growth mixture modelling, trajectory analysis, systematic review

Introduction

In psychiatry, one of the major challenges for tailoring individualized therapies are phenotypic heterogeneity of disorders and its overlapping symptoms that may presumably share some fundamental biologic underpinnings.[1] In schizophrenia, a complex psychotic disorder that affects individuals and families, the phenotypic expression and course of disease are variable.[2] The prevalence of schizophrenia is 4.6 per 1.000 individuals with a lifetime morbidity risk of 0.7%.[3] The twin- and SNP-based heritability estimate of schizophrenia was 80%[4] and 30%[5], respectively. The clinical symptoms of schizophrenia are positive symptoms (hallucinations and delusions), negative symptoms (emotional expressive deficit, social amotivation, social withdrawal and difficulty in experiencing pleasure) and cognitive deficits (selective or global).[6] These symptoms are assessed by standard psychometric tools, which rate symptoms in quantitative scales.[7-12] The prevalence of negative symptoms is 50-90% in first-episode psychosis and persists in 20-40% of patients with schizophrenia.[13-15] Cognitive deficits affects 75-80% of patients with schizophrenia.[16] The most common deficits occur in executive function, processing speed, memory (e.g. episodic, verbal and working), attention, verbal fluency, problem-solving and social cognition.[17-25] Thus far, patients harbor a wide range of subjectively defined symptoms and phenotypes, which together yields instinctively to heterogeneous groups of people who are collectively diagnosed as schizophrenia. Subclinical symptoms are also evident in siblings of patients with schizophrenia spectrum disorders and healthy general population. [26-28]

Heterogeneity in schizophrenia

Despite a century of efforts, understanding the heterogeneity in presentation and course of schizophrenia has been unsuccessful due to the subjective measurement of its clinical symptoms, variation in response to treatment, lack of valid, stable, and meaningful subphenotyping methods, and limited understanding of the disease mechanism.[29-31] Heterogeneity in clinical outcomes can be manifested within patients and between groups of patients, within subjects over time, and within and between diseases subphenotypes, and caused by several intrinsic and extrinsic factors.[30,32] Identification of meaningful homogeneous subgroups of the population based on clinical features or endophenotypes (e.g.

neuropsychological markers, neural substrates, and neurological soft signs) requires the use of both supervised and unsupervised analyses. Distinguishing heterogeneous patients to more homogeneous subgroups is expedient not only to unveil common etiologies, but also at practical level to examine the patterns of clinical symptoms, understand the inherent course of the disease, predict treatment response and develop new treatment strategies specific to that subgroup to improve recovery and functional outcomes (Figure 1).[29,30,33,34]

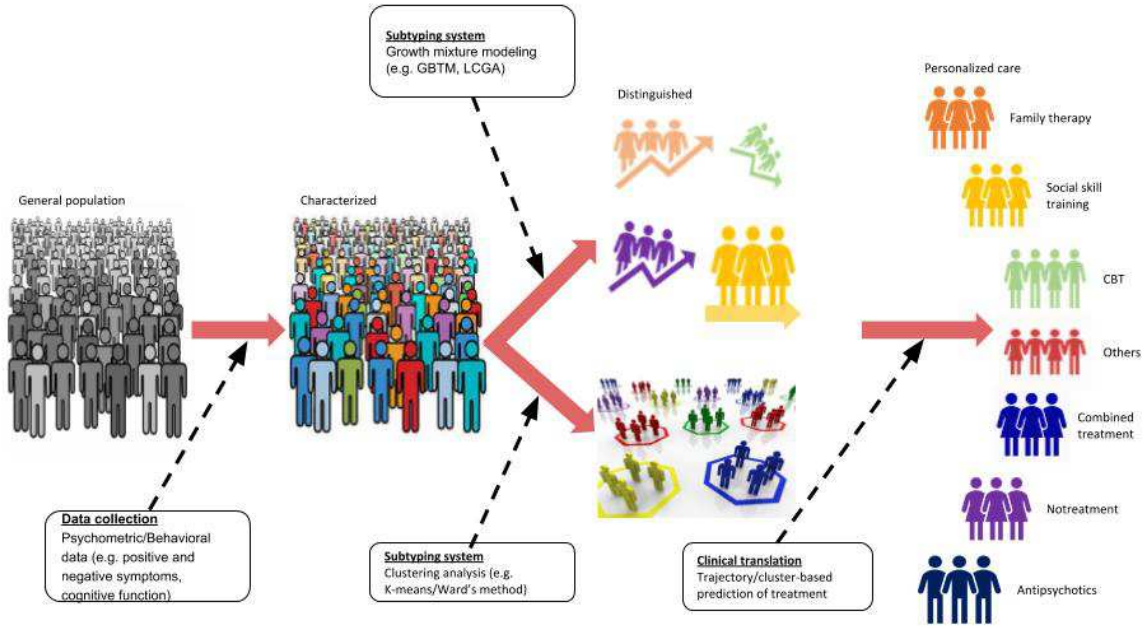

Figure 1: Precision in psychiatric care through measurement, characterization and subtyping.

Tackling heterogeneity in schizophrenia

For tackling heterogeneity, in the past decade, numerous efforts have been undertaken by carefully designing studies and developing statistical models implemented in various programming language and software.[30] As a result, clusters or trajectories of clinical symptoms have been estimated using latent class cluster analysis and growth mixture models respectively.[29,35,36] A trajectory or cluster is a group of individuals that has a homogenous

symptom profile within that group and a significantly dissimilar profile from other groups.[33] Statistical methods can identify subgroups and describe within and between-variation that help clinicians and statisticians to explore the relationship of schizophrenia with various clinical and functional outcomes, treatment response, and neuropathological change. Dichotomization of clinical outcomes, such as recovered or not, and symptom remission or not is also a common practice within schizophrenia research.[33] However, dichotomization may lead to the loss of information, inefficient analysis of continuous data and difficulties in the translation of results to clinically meaningful evidence.[33] Moreover, subtyping using imaging, biological and symptom data is a recognizable method.[35]

Cluster- and trajectory-based studies of clinical symptoms of schizophrenia show inconsistent findings and have several limitations. Possible reasons of inconsistencies are the heterogeneity of study population, high symptomatic variability between patients and within patients over time, use of various assessment tools, use of different clustering algorithms, and use of different scoring and standardization techniques.[13,18,37] The major limitations are small sample size, short duration of follow-up, and limited used of data from healthy siblings and/or controls.[37] All these factors blur our understanding of the heterogeneity of the course of schizophrenia. Several reviews have been conducted on cognitive dysfunction[16,38-47], negative symptoms[15,48,49] and positive symptoms.[50] However, these proceedings have largely focused on the traditional approach in determining average change in the course of symptoms over time, and variation between subjects (patient vs sibling, sibling vs control, patient vs control) and diagnosis. They are also based on correlation analysis, which is believed not to be a strong measure of association between predictors and outcomes. In addition, none of these reviews fully addressed symptomatic clusters and trajectories in patients with schizophrenia spectrum disorders, their siblings and healthy controls. Therefore, there is a pressing need to synthesize the contemporary evidence, evaluate the extent and origin of heterogeneity, and to inform personalized and preventive strategies for clinical practice.In this systematic review, we summarized the contemporary evidence from cluster- and trajectory-based studies of positive and negative symptoms/schizotypy, and cognitive deficits in patients with schizophrenia spectrum disorders, their siblings and healthy people. Additionally, we explored the

methodological approaches applied to distinguish homogeneous subgroups. We further highlighted current knowledge gaps and point out future directions to optimize the translatability of cluster- and trajectory-based studies within outlooks of personalized approach.

Methods

Registration and reporting

This systematic review was conducted and reported based on a registered protocol[51] and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guideline (Supplementary file 1) respectively.[52,53] The screening and selection process of the reviewed articles are further illustrated using a PRISMA flow diagram.

Databases and search terms

A systematic search of PubMed, PsycINFO, PsycTESTS, PsycARTICLES, SCOPUS, EMBASE and Web of Science electronic databases was performed. A comprehensive search strategy was developed for PubMed and adapted for each database in consultation with a medical information specialist (Supplementary file 1). The following search terms were used in their singular or plural form in their title, abstract, keywords and text: “schizophrenia”, “psychosis”, “non-affective psychosis”, “cognitive deficit”, “cognitive dysfunction”, “cognitive alteration”, “negative symptoms”, “deficit syndrome”, “positive symptoms”, “psychopathology”, “cognit*”, “neuropsycholog*”, “neurocognition”, “longitudinal”, “follow-up”, “course”, “heterogeneity”, “endophenotype”, “profile”, “cluster analysis”, “siblings”, “healthy controls”, “latent class analyses”, “Symptom trajectories”, “traject*”, “group modelling” and “trajectory”. Cross-references of included articles and grey literature were also hand-searched. Furthermore, we searched the table of contents of the journals of Schizophrenia Research, Schizophrenia Bulletin, Acta Psychiatrica Scandinavica and British Journal of Psychiatry to explore relevant studies. The freezing date for final search was August 2019. In this review, we use ‘trajectory’ for groups identified by longitudinal studies and ‘cluster’ for groups identified by cross-sectional studies.

Inclusion and exclusion criteria

Studies meeting the following criteria were included: (1) cross-sectional and longitudinal studies; (2) studies that reported at least two clusters or trajectory groups of individuals using a statistical method based on distinct positive symptom, negative symptom, and neurocognitive or social cognitive impairment dimensions or a combination of these symptom dimensions; (3) studies conducted in patients with schizophrenia-spectrum disorders, and/or their unaffected

siblings, and/or healthy individuals irrespective of any clinical (e.g. medication status, severity of illness) and sociodemographic characteristics; and (4) studies published in English from 2008 to 2019. The publication year was limited to the last decade to capture the latest available evidence, which are likely to provide statistically powerful precise estimates and successful subtyping of schizophrenia symptoms due to the increased number of large cohorts. In order to maximize the number of searched articles, the follow-up period in longitudinal studies was not restricted. Trajectory studies based on analyses of the mean level of change for the entire sample were excluded because they did capture individuals' patterns of change over time and treat between-subject variation as error, so that the actual heterogeneity of groups cannot be revealed.[54] In addition, studies based on the non-statistical methods of clustering (e.g. family-based clustering) were excluded. Review papers, commentaries, duplicate studies, editorials, and qualitative studies were excluded as well. Furthermore, we excluded studies in which the trajectory groups or clusters were generated based on scores constructed using a combination of schizophrenia symptoms and other unspecified psychotic symptoms.

Data retrieval and synthesis

Studies retrieved from all databases were exported to RefWorks version 2.0 for Windows web-based citation manager. Close and exact duplicates were deleted. All independent studies were exported to a Microsoft Excel spreadsheet to screen for further inclusion criteria. Authors TD and LR independently screened the titles and abstracts. The two reviewers had substantial agreement, as shown by a Kappa coefficient of 0.62. Inconsistent decisions on title and abstract inclusion were discussed with corresponding author BZA. Finally, full-text was reviewed, and the following data were independently extracted by TD and LR: first author name, publication year, country, cohort/research center, study population, sample size, symptom dimension(s), assessment tool, study design, duration of follow-up for longitudinal studies, frequency of assessment, method of calculating composite score, method of clustering/trajectory analysis, number of identified clusters or trajectory groups and significant predictors of clusters and trajectories.[55] The corresponding author was contacted by email if full-text of included article was not accessible. If the cohort or research center was not clearly reported, we extracted the institutional affiliation of the first or corresponding author.

Results

Search results

In total, 2,262 studies were identified through database searching and an additional 23 studies through manual searching of cross-references and tables of content of relevant journals. After removing duplicate articles and applying the inclusion and exclusion criteria, titles and abstracts of 1,294 articles were screened, resulting in the exclusion of 1,236 articles. In total, 58 articles were selected for full-text review, and eight articles[56-63] were excluded due to unclear outcome, mixed diagnosis of the study population, use of non-statistical method of clustering or clustering based on different phenotypes of schizophrenia. Finally, data were extracted from 50 cluster- and trajectory-based studies. The PRISMA flow diagram of screening and the selection process is shown in Figure 2.

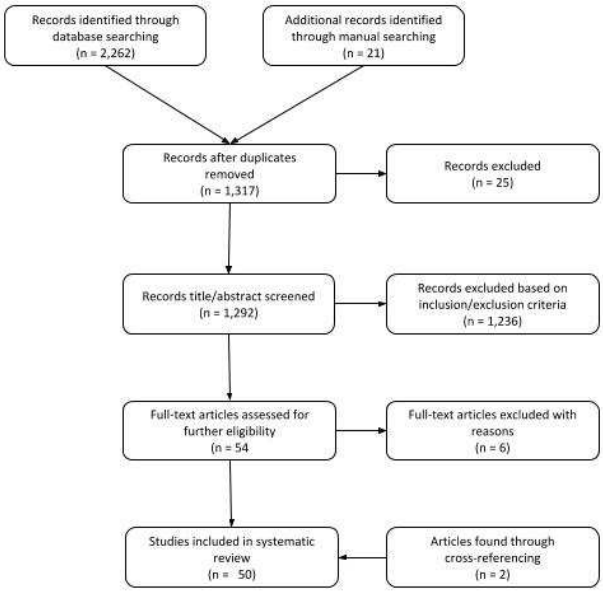

Figure 2: PRISMA flow diagram illustrating the screening and selection of literatures.

Overview of included studies

The included 50 studies were conducted globally in 30 countries (16 studies in the USA) and published over a decade from 2009 to 2019. Of these, 17 studies were longitudinal that involved 11,475 patients, 1,059 siblings and 2,194 controls/general population, whereas 33 studies were cross-sectional that involved 5,598 patients, 7,423 siblings, and 2,482 controls. Only one longitudinal study[64] and three cross-sectional studies[65-67] examined symptomatic subtypes among siblings. Most of the longitudinal studies examined trajectories of positive and negative symptoms, whereas most cross-sectional studies explored clusters based on cognitive function. A minimum of two and maximum of five schizophrenia symptoms subtypes were discovered.

Symptomatic trajectories

Of the total of 17 longitudinal studies (Table 1), conducted in more than eight countries, 11 studies[31,33,34,36,68-74] investigated the trajectory of both positive and negative positive symptoms in patients, three studies[75-77] the trajectory of only negative symptoms in patients, one study[78] the trajectory of schizotypy, and two studies[30,64] examined the trajectory of neurocognitive impairment in patients and siblings. The duration of follow-up ranged from six weeks to 10 years and included all population age groups. The sample size ranged from 138 to 1,990 subjects, though variation observed between symptom dimension. One study[64] investigated the association between patients' and siblings' cognitive trajectories, whereas another study[74] examined the association between positive and negative symptom trajectories in patients. Additionally, five studies reported the influence of trajectories on long-term social, occupational and global functioning, and health-related or general quality of life.[34,73,75-77]

Even though all studies had similar aims, they used slightly different methods of trajectory analysis, such as growth mixture modelling (GMM)[31,69,74], latent class growth analysis (LCGA)[30,33,34,70,73,76,77], mixed mode latent class regression modelling[36,68,72] and group-based trajectory modelling (GBTM).[64,71,75] Akaike's Information Criterion (AIC), Bayesian information criterion (BIC), logged Bayes factor, sample-size-adjusted BIC (aBIC), bootstrap likelihood ratio test [BLRT], Lo–Mendell–Rubin Likelihood Ratio Test (LMR-LRT) and entropy were reported model selection indices. Of these indices, Bayesian information criterion (BIC) was reported by all studies except for one study[30] that reported deviance information criterion (DIC).

As shown in Table 1, five studies[33,36,69,71,72] discovered five trajectories, three studies[31,68,74] identified three trajectories, and two studies[34,73] found two trajectories of positive symptoms. Similarly for the negative symptom dimension, four studies[36,69,71,72] discovered five trajectories, five studies[31,33,34,74,77] reported four trajectories, one study[76] depicted three trajectories and one study[73] found two trajectories. In addition, a study[75] from our research group identified four trajectories of negative symptom subdomains of social amotivation and expressive deficits. Combining both positive and negative symptom dimensions, three studies[36,70,72] discovered five trajectories, one study[31] found four trajectories and one study[74] identified three trajectories. One study[78] identified four trajectories of positive and negative schizotypy in college students without psychosis. With regard to cognitive deficits, a six year longitudinal study[64] from our research group discovered five trajectories of cognitive impairment in patients and four trajectories in healthy siblings. Another study[30] reported three trajectories of global cognitive function combining patients and controls together. Overall, these studies characterized trajectories as progressive deterioration, relapsing, progressive amelioration and stable.

Table 1: Detailed characteristics of longitudinal studies (n = 17).

Authors' and publication year	Country	Research centre/Cohort	Participants	Assessment tool	Frequency of assessment	Duration of follow-up	Method of calculating test score	Method of trajectory analysis	Number of trajectories identified	Predictors of trajectories
a. Positive and/or negative symptoms										
Chen 2013[74]	USA	Mulitcenter trial study, mental health outpatient clinics	400 patients with Schizophrenia spectrum disorder and treated with first- and second-generation antipsychotics	PANSS	Seven times	1 year	Sum score	Growth mixture modelling	Three for positive symptom: Class 1, Class 2, Class 3 Four for negative symptom: Class 1, Class 2, Class 3, Class 4 Positive and negative symptom combined: dramatic and sustained early improvement, mild and sustained improvement, no improvement	Positive and negative symptoms
Case et al 2011[31]	3 countries	64 research centres	628 patients with psychosis and treated with antipsychotics	PANSS	Eight times	3 months	Sum score	Growth-mixture modelling	Four: moderate-gradual, rapid, high-gradual, unsustained improvement	Extrapyramidal and depression symptoms, quality of life, age at onset of illness, ethnicity, positive and negative symptoms, general psychopathology
Stauffer et al 2011[69]	USA and other countries	Multicentre study	1,990 patients with chronic schizophrenia and receiving treatment	PANSS	11 times	≤6 months	Sum score	Growth mixture modelling	Five: dramatic responders, partial responders, partial responders-unsustained (late), partial responders-unsustained (early), Delayed Responders	Age, gender, ethnicity, weight, age of onset, depression symptoms, extrapyramidal symptoms
Levine 2010a[36]	12 countries	International cohort/ Johnson & Johnson Pharmaceutical Research	491 patients with early episode psychosis and	PANSS	Six times	6 months	Sum score	Mixed-mode latent class regression	Five: stable (3 groups), improved and stable, marked improvement)	Diagnosis of schizophrenia, age of onset, cognitive functioning, premorbid

		and Development	receiving treatment for more than three months					modelling		functioning
Levine et al 2012[68]	USA	57 clinical sites	1,124 patients with chronic schizophrenia and receiving treatment	PANSS	Eight times	1.5 years	Sum score adjusted for the baseline score	Mixed-mode latent regression modelling	Three: low deteriorators, responders, high deteriorators	Type of antipsychotics, exacerbation, positive and negative symptoms
Levine 2010b[72]	12 countries	International cohort/ Johnson & Johnson Pharmaceutical Research and Development	263 patients with early episode psychosis and receiving treatment for more than three months	PANSS	More than six times	2 years	Sum score	Mixed-mode latent class regression modelling	Five: Trajectory 1, Trajectory 2, Trajectory 3, Trajectory 4 and Trajectory 5	Diagnosis, premorbid functioning, cognitive performance, positive and negative symptoms
Pelayo-Terán et al 2014[71]	Spain	University Hospital Marqués de Valdecilla/Clinical Programme on First-Episode Psychosis of Cantabria (PAFIP)	161 patients with a first episode of non-affective psychosis and no prior treatment	SANS and SAPS	Six times	6 weeks	Sum score	Group-based trajectory modelling	Five for positive symptom: responders, dramatic responders, partial responders, slow partial responders, non-responders Five for negative symptom: responders, mild non-responders, moderate non-responders, partial responders, poor responders	Positive symptom: Duration of untreated psychosis and cannabis use Negative symptom: SCZ diagnosis
Stiekema et al 2017[75]	Netherlands	Four medical centres (UMCG, UMCM, UMCU, UMCA)/ GROUP cohort study	1,067 patients with nonaffective psychosis	PANSS	Three times	6 years	Sum score	Group-based trajectory modelling	Four for social amotivation domain: low, decreased low, increased, decreased high Four for expressive deficit domain: low, decreased, increased and high	Age, gender, educational status, ethnicity, marital status, functioning, quality of life, diagnosis, neurocognitive performance, negative and psosive symptoms

Schennach et al 2012[70]	German	Multi-centre study/ German Research Network on Schizophrenia (GRNS)	399 patients with schizophrenia spectrum disorder	PANSS	More than 10 times	> 5 months	Sum score	Latent class growth analysis	Five: early and considerable response, rapid and dramatic response, early and satisfying response, gradual response	Depressive symptoms at admission, functioning, duration of illness, previous hospitalizations, positive and negative symptoms
Abdin 2017[34]	Singapore	Institute of Mental Health/Early Psychosis Intervention Programme (EPIP) clinical database.	1,724 patients with first-episode psychotic disorder and with no prior or minimal treatment (<12wks)	PANSS	Five times	2 years	Not clearly reported	Latent class growth analysis	Two for positive symptom: early response and stable trajectory, and delayed response trajectory. Four for negative symptom: early response and stable trajectory, early response and relapse trajectory, slower response and no response trajectory and delayed response trajectory	Positive symptom: Gender, educational status, duration of untreated psychosis, diagnosis Negative symptom: Occupational status, educational status, diagnosis
Austin 2015[33]	Denmark	Centre for psychiatric research/OPUS trial trail	496 patients with first-episode schizophrenia spectrum disorder and had received less than 12 weeks of antipsychotic medication	SAPS and SANS	Five times	10 years	Composite score using global scores	Latent class analysis	Five for positive symptom: response, delayed response, relapse, non-response and episodic response. Four for negative symptom: response, delayed response, relapse and non-response	Positive symptom: duration of untreated psychosis, global functioning, diagnosis and substance abuse Negative symptom: gender, social and global functioning, disorganized symptoms and diagnosis
Jager 2014[73]	Germany	ELAN study, psychiatric hospitals	268 patients with schizophrenia or schizoaffective disorder and receiving treatment	PANSS	Five times	2 years	Sum score	Latent class growth analysis	Two: amelioration/decrease in all symptoms, stable positive and negative symptoms and deteriorating general psychopathology symptoms	Global functioning, gender, age, living situation and involuntary admission

			for more than one year							
Chang et al 2018[76]	China	Public psychiatric units	138 patients with first-episode nonaffective psychosis and not received any antipsychotics more than one week	HEN	Four times	3 years	Sum score	Latent class growth analysis	Three: minimal-stable, mild-stable, and high-increasing trajectories	Gender, educational status, premorbid adjustment, cognitive performance, depressive symptoms, positive and negative symptoms
Gee 2016[77]	UK	National EDEN study	1,006 patients with first episode psychosis and receiving treatment for 12 months	PANSS	Three times	1 year	Mean score	Latent class growth analysis	Four trajectories: minimal decreasing, mild stable, high decreasing, high stable.	Gender, family history of non-affective psychosis, poor premorbid adjustment and depression
b. Positive and negative schizotypy										
Wang et al 2018[78]	China	University of Chinese Academy of Sciences/Key Laboratory of Mental Health	1,541 college students	CPPS (4 subscales)	Four times	1.5 years	Sum score	Latent class growth analysis	Four trajectories: non-schizotypy, stable-high schizotypy, high-reactive schizotypy, low-reactive schizotypy	Gender, severe schizotypy
c. Neurocognitive impairment										
Islam et al 2018[64]	Netherlands	Four medical centres (UMCG, UMCM, UMCU, UMCA)/ GROUP cohort study	1119 patients with nonaffective psychosis, 1,059 siblings, and 586 controls	NTB	Three times	6 years	Gender and age adjusted z-score and then averaging	Group-based trajectory modelling	Five trajectories in patients: severely altered, moderately altered, mildly altered, normal, and high performer Four trajectories in siblings: moderately altered, mildly altered, normal, and high performer	Patients: education, IQ, premorbid functioning, and positive and negative symptoms Siblings: age, gender, education, ethnicity, IQ, premorbid functioning, positive symptoms, frequency of psychotic

										experiences, and neurocognitive performances
Thomspson et al 2013[30]	USA	University of California, San Diego Advanced Centre in Innovation in Services and Interventions Research (ACISIR)	201 old community-dwelling patients with schizophrenia and 67 controls	MDRS	Four time)	3.5 years	Sum score	Latent growth curve model	Three: high and stable, low and modestly declining, low and rapidly declining	Negative symptoms, living situation, years of education, global cognition

Abbreviations: HEN = High Royds Evaluation of Negativity Scale; MDRS = Mattis Dementia Rating Scale; NTB = Neuropsychological Test Battery (seven tests were used); PANSS = Positive and Negative Syndrome Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS=Scale for the Assessment of Negative Symptoms; CPPS = Chapman Psychosis Proneness Scales

Symptomatic clusters

Of the 49 included studies, 33 studies were cross-sectional conducted in 14 countries (Table 2). The total sample size per study ranged from 62 to 6,600 individuals irrespective of participants' diagnostic status. Among 32 studies, 21 studies[32,37,65,66,79-96] reported clusters in patients and one study[66] in unaffected siblings based on neurocognitive and/or social cognitive function. In addition, two studies were conducted on negative symptoms[29,97], one study on positive symptom[98], three studies on positive and negative symptoms[35,99,100], and three studies on positive and negative schizotypy.[67,101,102]

The reported clustering methods were K-means or non-hierarchical clustering analysis[35,65,67,88,90,93,95,100-103], Ward's method or hierarchical analysis[82,83,87,89,92,98,99], K-means clustering and Ward's method[32,37,66,80,85,91,94,97,104], latent class or profile analysis[29,79,86] and two-step cluster analysis.[84,96] One study[81] identified clusters using a combination of clinical/empirical and clustering methods. The model selection criteria or similarity metrics were visual inspection of dendrogram, Pearson correlation, squared Euclidean distance, agglomeration coefficients, Dunn index, Silhouette width, Duda and Hart index, elbow test, variance explained, inverse scree plot, average proportion of non-overlap, Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size adjusted Bayesian (ABIC), Schwarz's Bayesian information criterion (BIC), Lo–Mendell–Rubin (LMR) test, adjusted LMR and the bootstrap likelihood ratio test (BLRT). Squared Euclidean distance was the most common index used to determine the number of clusters.

Of these 21 studies on neurocognitive deficits, 16 studies[37,65,79-84,87-90,92,95,96] found three clusters, five studies[32,85,86,91,93] reported four clusters and one study[94] discovered five clusters of patients. One study found three clusters in unaffected siblings based on neurocognitive function.[66] Two studies[29,97] reported three clusters of patients based on the negative symptom dimension. Regarding positive symptoms, only one study[98] identified three clusters of patients and two clusters in the general population. One study[104] found three clusters of patients by combining social cognition and negative symptom whereas another study[103] found four clusters of patients based on neurocognition and negative symptom. In addition, two studies[35,99] reported three clusters while another study[100] found out four clusters by combining both

positive and negative symptoms. Moreover, three studies[67,101,102] consistently reported four clusters of unaffected siblings or general population based on positive and negative schizotypy dimensions. Generally, the identified clusters had low, mixed (intermediate) and high symptom profiles. Details has been presented in Table 2.

Table 2: Detailed characteristics of cross-sectional studies (n = 33).

Authors' and publication year	Country	Research centre/Cohort	Participants	Assessment tool	Method of calculating score	Method of clustering	Number of clusters identified	Predictors
a. Positive and/or negative symptoms								
Ahmed 2018[29]	USA	Maryland Psychiatric Research Center (MPRC)	706 patients with chronic schizophrenia	SDS	Sum score	Latent class analysis with prior hypothesis	Three: deficit, persistent, transient	Sex, season of birth, ethnicity, years of education, illness onset, positive symptoms, neurocognitive performance, premorbid adjustment, psychosocial functioning
Strauss et al 2013[97]	USA	Veterans Affairs Greater Los Angeles Healthcare System	199 patients with schizophrenia	SANS	Mean factor scores (PCA)	Ward's and K-means cluster analysis	Three: diminished expression, avolition–apathy, low negative symptoms	General psychopathology, severity of positive and negative symptoms, social anhedonia, attitude, global functioning, social cognition, hospitalization
Chang 2015[98]	Korea	Seoul National University Hospital and Boramae Medical Center	111 patients with schizophrenia and 223 nonclinical population	LSHS-R	Sum score	Ward's cluster analysis	Three for clinical sample: Cluster 1, Clusters 2, Cluster 3 Two for nonclinical sample: Cluster 1, Cluster 2	Not reported. It explores only clusters
Talpalaru et al 2019[99]	Multination	Northwestern University Schizophrenia Data and Software Tool (NUSDAST) dataset	104 patients with schizophrenia and 63 healthy controls	SAPS, SANS	Z-scores	Ward's cluster analysis	Three: high positive and negative symptom, predominantly positive symptom, low symptom	Gender
Trauelsen et al 2016[100]	Denmark	OPUS	97 patients with first-episode non-affective psychosis and 101 controls	PANSS	Z-scores	K-means cluster analysis	Four: low positive/low negative, high positive/low negative, low positive/high negative, high positive/high negative	Metacognition

Craddock 2018[35]	USA	National Institute of Mental Health (NIMH)/Childhood-onset schizophrenia (COS) cohort	125 patients with childhood-onset schizophrenia (COS)	SAPS, SANS	Factor score (CFA)	K-means cluster analysis	Three: low positive and negative, high negative low positive, high positive and negative	IQ, global functioning, positive and negative symptoms
b. Positive and negative schizotypy								
Lui et al 2018[67]	China	Castle Peak Hospital	194 unaffected first-degree relatives of patients with schizophrenia	CPPS (4 subscales)	Sum score	K-means cluster analysis	Four: high positive schizotypy, high negative schizotypy, mixed schizotypy, low schizotypy	Positive and negative schizotypy, everyday life pleasure experiences, emotional expressivity
Barrantes-Vidal et al 2010[102]	USA	University of North Carolina at Greensboro (UNCG)	6,137 healthy college students	CPPS	Normalized component score (PCA)	K-means cluster analysis	Four: low (nonschizotypic), high positive, high negative, and mixed (high positive and negative) schizotypy	Severity of positive and negative schizotypy, gender, social functioning, psychotic-like experiences, depression, substance use and abuse, schizoid and negative symptoms, personality, social adjustment
Wang et al 2012[101]	China	Neuropsychology and Applied Cognitive Neuroscience Laboratory	418 healthy college students	CPPS	Normalized component score (PCA)	K-means cluster analysis	Four: low (nonschizotypic), high positive, high negative, and mixed (high positive and negative) schizotypy	Psychotic-like symptoms, depression, and social function, emotional expression, pleasure experiences, somatic symptoms, neurocognitive functioning, proneness to positive and negative symptoms
c. Cognition								
Bechi 2018[96]	Italy	IRCCS San Raffael Scientific Institute	452 patients with stable schizophrenia	BACS, WAIS-R	Global cognition: mean score adjusted to age and education	Two-step cluster analysis (both scores together)	Three for whole sample: high, medium, low Two for subsamples with high pre-morbid IQ: high, medium	Age, years of education, age of onset, negative and positive symptoms, IQ, cognition

					IQ: sum score			
Rocca et al 2016[84]	Italy	Multicentre study/Italian Network for Research on Psychoses (NIRP)	809 patients with schizophrenia and 780 controls	MCCB (3 tests)	Z-scores of scales	Two-step cluster analysis	Three: unimpaired, impaired, very impaired	Age, educational status, cognitive performance, functioning, positive and negative symptoms, disorganization
Bell 2010[95]	USA	Community mental health center (CMHC)	151 patients with schizophrenia or schizoaffective disorder - clinically stable	HVLT-R	Sum score	K-means cluster analysis (with prior hypothesis)	Three: nearly normal, subcortical, cortical	Educational status, neurocognitive performance, social cognition
Wells et al 20115[81]	Australia	Australian Schizophrenia Research Bank (ASRB)	534 patients with schizophrenia or schizoaffective disorder and 635 healthy controls	Neuropsychological tests (5 tests)	Z-scores standardized by healthy controls	Ward's and K-means cluster analysis, and clinical method	Three: preserved, deteriorated, compromised	Age, years of education, age onset of illness, gender, neurocognitive performance, positive and negative symptoms, functioning
Dawes 2011[94]	USA	University of California/San Diego (UCSD) Advanced Center for Innovation in Services and Interventions Research (ACISIR)	144 patients with schizophrenia or schizoaffective disorder	Comprehensive neuropsychological test battery (7 tests)	Sum of deviation scores adjusted to age, gender, education and ethnicity	Ward's and K-means cluster analysis	Five: Cluster 1, Cluster 2, Cluster 3, Cluster 4, Cluster 5	Educational status, ethnicity
Lewandowski 2014[32]	USA	McLean Hospital/Schizophrenia and Bipolar Disorder Program (SBDP)	167 patients with psychosis	Neuropsychological battery test (5 tests)	Z-scores adjusted to age or age and education	Ward's and K-means cluster analysis	Four: globally normal, normal processing speed/executive function, normal visuospatial function, globally impaired	Cognition, age, educational attainment, antipsychotics dosage, positive and negative symptoms, community functioning
Lewandowski 2018[91]	USA	McLean Hospital/Schizophrenia and Bipolar Disorder Program (SBDP)	120 patients with psychosis and 31 healthy controls	MCCB (10 subtests)	Age and gender adjusted T-scores	Ward's and K-means cluster analysis	Four: normal, mildly impaired, moderately impaired, significantly impaired	Educational status, premorbid IQ, state mania, positive and negative symptoms, antipsychotic dosage, cognition, community functioning
Sauve et al 2018[37]	Canada	Douglas Mental Health	201 patients with	CogState	Composite	Ward's and K-	Three: no impairment,	IQ, severity of positive symptoms,

		University Institute (DMHUI)/ PEPP-Montreal program	psychosis (first- and multiple-episode) receive treatment and 125 healthy controls	Schizophrenia Battery (13 tests)	scores standardized to controls	means cluster analyses	generally impaired, intermediately impaired	age, years of education, stage of illness, antipsychotics dosage
Quee et al 2014[66]	Netherlands	UMCG, UMCU, UMCM, UMCA/GROUP cohort	654 health siblings of patients with schizophrenia	Neuropsychological battery test (8 tests)	Mean score of gender and age-adjusted z-scores	Ward's and K-means cluster analysis	Three: normal, mixed, impaired	Age, educational status, IQ, premorbid adjustment, positive schizotypy
Reser et al 2015[85]	Australia	Early Psychosis Prevention and Intervention Centre (EPPIC)	128 patients with a first-episode psychosis	Comprehensive cognitive battery test (15 tests)	Range standardized test scores	Ward's and K-means cluster analysis	Four: cluster 1, cluster 2, cluster 3, cluster 4	Age, IQ (premorbid and current), years of education, negative symptoms, neurocognitive performance
Uren et al 2017[80]	Australia	Early Psychosis Prevention and Intervention Centre (EPPIC)	133 patients with first episode psychosis and 46 controls	Comprehensive battery test (14 tests)	Z-scores	Ward's and K-means cluster analysis	Three: severe global impairment, moderate impairment, intact	Age, premorbid IQ, positive and negative symptoms, cognitive performance, years of education, functioning
Geisler 2015[93]	USA	Four research centers (MGH, UI, UMN, UNM)/Mind Clinical Imaging Consortium (MCIC) study of schizophrenia	129 patients with schizophrenia and 165 healthy controls	Comprehensive neuropsychological test battery (18 tests)	PC score (PCA)	K-means cluster analysis	Four: diminished verbal fluency, diminished verbal memory and poor motor control, diminished face memory and slowed processing, diminished intellectual function	Duration of illness, positive symptoms, years of education, premorbid adjustment, cortical thickness, neural activity
Ochoa et al 2013[90]	Spain	Hospital and community psychiatric services	62 patients with a first-episode psychosis	Neuropsychological battery tests (5 tests)	Demographically adjusted score	K-means cluster analysis	Three: higher neurodevelopment contribution, higher genetic contribution, lower neurodevelopment contribution	Neurocognition performance, premorbid IQ, neurological soft signs, premorbid adjustment, family history of mental disorders, obstetric complications

Ohi et al 2017[65]	Japan	Kanazawa Medical University Hospital/ Kanazawa Medical University	81 patients with schizophrenia, 20 relatives and 25 healthy controls	BACS (6 subscales)	Age- and gender-corrected raw scores	K-means cluster analysis	Three: neuropsychologically normal, intermediate impaired, widespread impaired	Clinical diagnosis, neurocognitive performance, years of education, premorbid IQ, antipsychotics dosage
Potter et al 2010[88]	USA	University of Massachusetts	73 patients with schizophrenia and 74 controls	Neuropsychological tests (6 tests)	Scaled scores	K-means cluster analysis	Three: intellectually compromised, intellectually deteriorated, intellectually preserved	Negative symptoms, neurocognitive performance, educational status, general psychopathology
Prouteau et al 2017[87]	France	Public psychiatric hospitals	69 patients with schizophrenia-spectrum disorders	Objective: Neuropsychological tests (6 tests) Subjective: SSTICS	Standardized Z-scores	Ward's cluster analysis	Three: high cognitive impairment/moderate cognitive complaints, good cognitive functioning/moderate cognitive complaints, moderate cognitive impairment/high cognitive complaints	Age, educational status, negative symptoms, quality of life, anxiety, depression, stigma, neurocognitive performance
Gilbert 2014[92]	Canada	Institut en santé mentale de Québec	112 patients with schizophrenia	Cognitive battery test (> 8 tests)	Average Z-scores	Ward's cluster analysis	Three: generally impaired, selectively impaired, near normal	IQ, gender, socioeconomic status, cognition, global functioning, positive and negative symptoms
Crouse et al 2018[89]	Australia	Brain and Mind Research Institute	135 patients with a psychosis-spectrum illness and 50 healthy controls	CANTAB (9 tests)	Age-adjusted Z-scores	Ward's cluster analysis	Three: normal-range, mixed, grossly impaired performance	Socio-occupational functioning, neurocognitive performance, gender, diagnosis, risky drinking, employment status, educational status, premorbid IQ, negative symptoms
Rodrigez et al 2017[83]	Czech	National Institute of Mental Health	28 patients with first-episode schizophrenia spectrum disorders and 91	Neuropsychological battery tests (15 tests)	Z-scores standardized using controls	Ward`s cluster analysis	Three: generalized severe, partial mild, near normal	Neurocognitive performance

			healthy controls					
Wu et al 2010[82]	Taiwan	Psychiatric rehabilitation hospital	76 patients with schizophrenia	BNCE (10 subscales)	Mean scores	Ward's cluster analysis	Three: near normal, deteriorated conceptual thinking, anomia and impaired executive function	Severity of negative symptoms
Rangel et al 2015[86]	Colombia	Universities of Antioquia, Pontificia Bolivariana, Nacional of Colombia	253 patients with schizophrenia	Neuropsychological tests (5 tests)	Not reported	Latent classes analysis	Four: global cognitive deficit, memory and executive function deficit, memory and facial emotion recognition deficit, without cognitive deficit	Gender, age, negative symptoms, global functioning, employment status, adherence to treatment, neurocognitive performance, depression
Smucny et al 2019[79]	USA	CNTRACS consortium	223 psychosis patients and 73 healthy controls	Neuropsychological tests (3 tests)	Z-score and Factor score	Latent profile analysis (LPA)	Three: low, moderate, high	Negative, positive, disorganization, mania, and depressed mood symptoms, functioning, educational status, neurocognitive perfomance
d. Cognition and negative symptom								
Bell 2013[104]	USA	Community mental health center (CMHC)	77 patients with stable schizophrenia or schizoaffective disorder	SANS, PANSS, MSCEIT	Sum score	Ward's and K-means cluster analysis	Three: high negative symptom, low negative symptom with higher social cognition, low negative symptom with poorer social cognition	Quality of life, hospitalization, marital status, negative symptoms, social cognition
Lysaker et al 2009[103]	USA	Roudebush VA Medical Center and Community Mental Health Center (CMHC)	99 patients with stable schizophrenia or schizoaffective disorder and on treatment	PANSS, CPT	Normalized z-scores	K-means cluster analysis	Four groups: low negative/relatively better attention, low negative/relatively poor attention, high negative/ relatively poor attention, and high negative/relatively better attention	Self-esteem, attention performance, acceptance of stigma, severity of positive and negative symptoms, social functioning

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia; BNCE = Brief Neuropsychological Cognitive Examination; CANTAB = Cambridge Neuropsychological Test Automated Battery; CPPS = Chapman Psychosis Proneness Scales; CPT = Continuous Performance Tests; HVLT-R = Hopkins Verbal Learning Test—Revised; LSHS-R = Launay–Slade Hallucination Scale-Revised; MCCB = MATRICS Consensus Cognitive Battery; MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SDS = Schedule for the Deficit Syndrome; SSTICS = Subjective Scale to Investigate Cognition in Schizophrenia; WAIS-R = Wechsler Adult Intelligence Scale–Revised

Predictors of schizophrenia symptoms subgroups

Predictors of symptomatic trajectories

Based on evidence from longitudinal studies (Figure 3)[31,33,34,36,68-77], the most common identified predictors of severe positive and/or negative symptoms trajectories were older age, male gender, ethnic minority, late age of illness onset, diagnosis of schizophrenia, long duration of untreated psychosis, long duration of illness, poor premorbid, global functioning, and quality of life, low cognitive performance, and severe baseline positive and negative symptoms. Furthermore, gender was identified as a predictor of positive and negative schizotypy in one study.[78] Regarding neurocognitive impairment, patients with poor trajectories had younger age, low educational status, non-Caucasian ethnicity, lived in a sheltered facility, low IQ, poor premorbid adjustment, severe positive and negative symptoms, and low baseline neurocognitive performance.[30,64] Likewise, siblings with poor neurocognitive trajectories had younger age, female gender, low educational status, non-Caucasian ethnicity, low IQ, poor premorbid adjustment, severe schizotypy, frequent positive psychotic experience, and low baseline neurocognitive performance.[64]

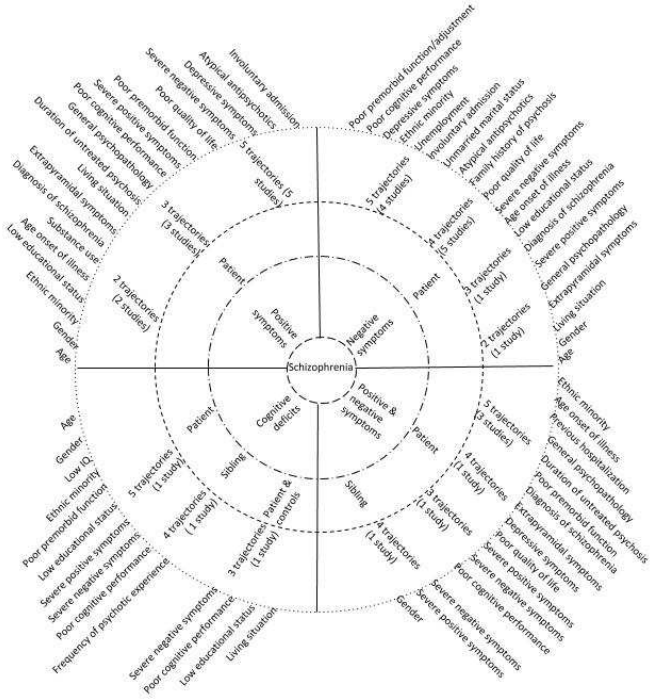

Figure 3: Schizophrenia spectrum circle illustrating predictors of symptomatic trajectories.

Predictors of symptomatic clusters

As illustrated in Figure 4, severe positive and/or negative symptoms cluster(s) were predicted by male gender, ethnic minority, low educational status, early age onset of illness, low IQ, severe general psychopathology, , and poor cognition, premorbid adjustment and global functioning.[29,35,97,99,100] Severe positive and/or negative schizotypy cluster(s) in unaffected first degree relatives of patients with schizophrenia were predicted by poor experience of pleasure and emotional expression, and low neurocognitive performance.[67] In the non-clinical population, severe positive and/or negative schizotypy cluster(s) were predicted by male gender, severe paranoid and schizoid symptoms, major depressive episode, substance abuse, medication use, poor social adjustment, severe somatic and anxiety symptoms, and poor neurocognitive and social functioning.[101,102]

In addition, poor cognitive impairment cluster(s) were predicted by age, gender, non-Caucasian ethnicity, low socioeconomic and educational status, poor premorbid adjustment, low premorbid and current IQ, early age of illness onset, long duration of illness, severe positive and negative symptoms, poor social cognition, high antipsychotics dosage, use of second generation antipsychotics, and poor functioning and poor quality of life.[32,37,65,66,79-96] Siblings subgroups with impaired neurocognitive function were predicted by young age, low educational status, low IQ, poor premorbid adjustment, and severe positive schizotypy (Figure 4).[66]

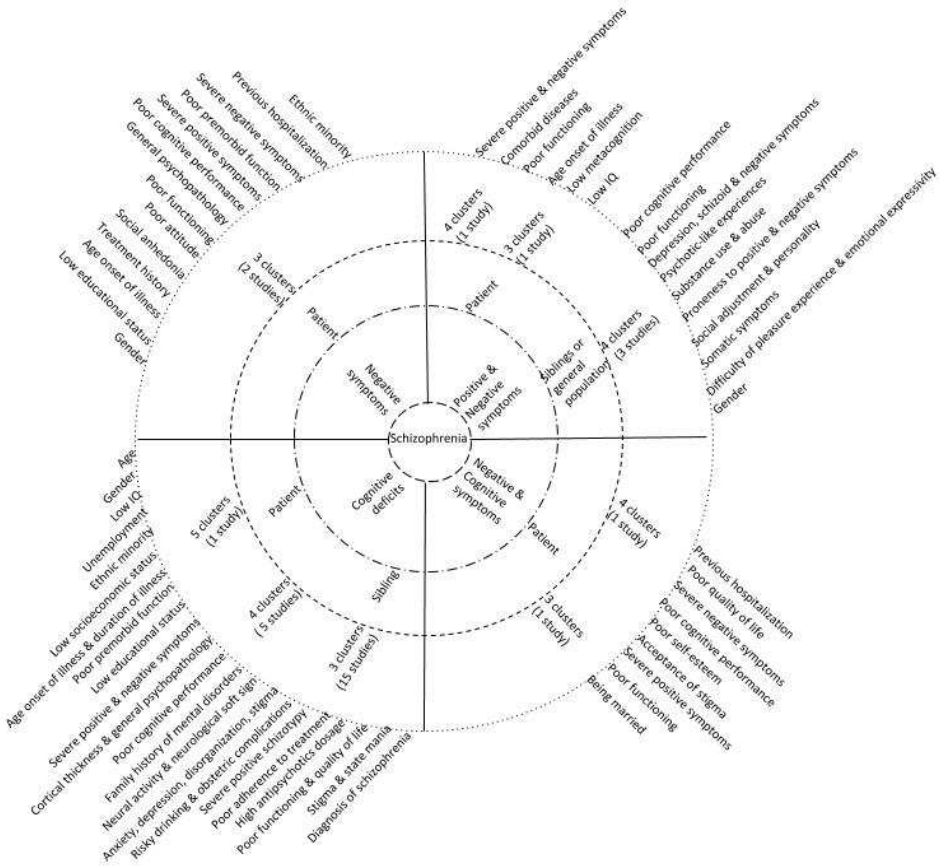

Figure 4: Schizophrenia spectrum circle illustrating predictors of symptomatic clusters.

Overall, as shown in Table 3, 57 predictors of clusters or trajectories were identified by longitudinal and cross-sectional studies across all study participants and symptom dimensions. The most common predictors were old age, male gender, non-Caucasian ethnicity, low educational status, late age of illness onset, diagnosis of schizophrenia, several general psychopathology and depressive symptoms, severe positive and negative symptoms, low cognitive performance, and poor premorbid functioning, quality of life and global functioning.

Table 3: Summary of clusters and trajectories and predictors

	Participants					Symptom dimensions					Type of study		
	Patients	Siblings	Healthy subjects	Patients and siblings	Patients and healthy controls	Cognitive impairment	Negative symptoms	Positive symptoms	Negative and positive symptoms/ schizotypy	Negative symptoms and cognitive impairment	Longitudinal study		Cross-sectional study
											< 2 years follow-up	≥ 2 years follow-up	
Clusters/Trajectories													
2			√				√	√				√	√
3	√	√		√	√	√	√	√	√	√	√	√	√
4	√	√	√			√	√		√	√	√	√	√
5	√					√	√	√	√		√	√	√
Predictors													
Sociodemographic													
Age	√	√				√	√	√			√	√	√
Gender	√	√	√			√	√	√	√		√	√	√
Summer season of birth	√						√						√
Ethnic minority	√	√				√	√	√	√		√	√	√
Un married marital status	√						√			√		√	√
Low educational status	√	√		√	√	√	√	√				√	√
Low premorbid or current IQ	√	√		√		√			√			√	√
Family history of psychosis or any mental disorders	√					√	√						√
Poor living situation	√				√		√	√				√	
Unemployment	√					√	√					√	√
Low socioeconomic status	√					√							√
Clinical													
Cannabis use	√							√			√		
Substance abuse	√		√					√	√			√	
Risky drinking	√					√							√

Acceptance of stigma ()	√					√					√				√
Low self-esteem	√										√				√
Lack of pleasure experiences		√	√							√					√
Difficulty of emotional expression		√	√							√					√
Obstetric complications	√					√									√
Low cortical thickness	√					√									√
Neural activity	√					√									√
Late age onset of illness	√					√	√	√	√			√			√
Diagnosis of schizophrenia	√			√		√	√	√	√			√	√		√
Long duration of untreated psychosis	√						√	√				√	√		
Long duration of illness	√					√			√			√			√
Frequent of psychotic experiences		√				√							√		
Previous hospitalizations	√						√		√		√	√			√
Involuntary admission	√						√	√					√		
Extrapyramidal symptoms	√						√	√	√			√			
Severe depressive symptoms	√		√			√	√	√	√			√	√		√
Severe disorganized symptoms	√					√	√						√		√
State mania	√					√									√
Poor attitude	√						√								√
Personality			√						√						√
Social anhedonia	√						√								√
Neurological soft signs	√					√									√
Severe general psychopathology	√					√	√	√	√			√			√
Severe Psychotic-like experiences			√						√						√

Somatic symptoms			√						√				√
Comorbid diseases	√								√				√
Atypical antipsychotic medication	√						√	√			√		
High antipsychotics dosage	√			√		√							√
Poor adherence to treatment	√					√							√
Treatment history	√						√						√
Severe positive and negative symptoms/schizotypy	√	√	√		√	√	√	√	√	√	√	√	√
Severe positive schizotypy		√				√							√
Low cognitive performance	√	√	√	√		√	√	√	√	√	√	√	√
Low meta-cognition	√								√				√
Poor premorbid functioning	√	√				√	√	√	√		√	√	
Poor premorbid adjustment	√	√				√	√				√	√	√
Poor social adjustment			√						√				√
Poor quality of life	√					√	√	√	√	√	√	√	√
Poor social functioning	√		√				√		√	√		√	√
Poor community functioning	√					√							√
Poor socio-occupational functioning	√					√							√
Poor psychosocial functioning	√						√						√
Poor global functioning	√				√	√	√	√	√			√	√

Discussion

To our knowledge, this is the first comprehensive systematic review on recent cluster- and trajectory-based studies of positive symptoms, negative symptoms and cognitive deficits in patients with schizophrenia spectrum disorders, their siblings and healthy people. Our review has three key findings. First, longitudinal trajectory-based studies distinguished two to five trajectory groups in patients based on positive and negative symptoms, and four to five trajectory groups in patients and siblings based on cognitive deficits. Second, cross-sectional cluster-based studies discovered three clusters of patients based on positive and negative symptoms, and four clusters of siblings based on positive and negative schizotypy. In addition, three to five clusters of patients and their unaffected siblings were discovered based on cognitive deficits. Third, poor symptomatic-outcome trajectories and clusters were predicted by numerous sociodemographic and clinical factors.

We showed that longitudinal studies with patients and siblings have inconsistently identified two to five trajectories across the schizophrenia symptoms. Several shortcomings may cause this inconsistency. Only one-third of the reviewed studies were longitudinal and only two studies[30,64] investigated the trajectories of cognitive deficits. This paucity of longitudinal studies on cognitive function may be caused by the fact that neuropsychological assessment is resource intensive, time-consuming, requires specialized data collection training and commitment by study participants. For example, some studies[37,85,93] administered up to 18 psychometric tests, which took more than four hours per wave of assessment. Utterly, none of the reviewed longitudinal studies validated their model against empirical methods or comparable statistical method, and used complex trajectory modelling analysis. Our review showed that growth mixture modelling (GMM)[31,69,74], latent class growth analysis (LCGA)[30,33,34,70,73,76,77], mixed mode latent class regression modelling[36,68,72] and group-based trajectory modelling (GBTM) were applied.[64,71,75] The difference in patient characteristics may also affect the number of clusters. For example, a studies that included only first-episode psychosis or chronic patients may identify smaller clusters than studies that included a mixture of patients with first-episode and chronic psychosis. Moreover, the difference in frequency and duration of follow-up may lead to subtle difference in results.

Given the scarcity of longitudinal studies, conducting cross-sectional studies and identifying meaningful clusters is the reasonable alternatives. Cluster analysis, which includes K-means clustering and Ward's method, is data-driven approach for classifying individuals into homogeneous groups by determining clusters of participants that display less within-cluster variation relative to the between-cluster variation.[89] K-means cluster analysis is a non-hierarchical form of cluster analysis, which is appropriate if previous evidence or hypotheses exist regarding the number of clusters in a sample. It produces the number of clusters initially called for by minimizing variability within clusters and maximizing variability between clusters.[103] Ward's method is a hierarchical cluster analysis aiming to determine group assignment without prior hypothesis.[103] K-means iterative cluster analyses handle larger data sets better than Ward's method.[102] To this end, even though they do not to show variability over time, cross-sectional studies are capable of unraveling the heterogeneity of schizophrenia symptoms if appropriate statistical procedures are followed. To date, 33 cross-sectional studies were conducted that found three to five clusters in patients and four in siblings across schizophrenia symptoms. Cognitive deficit was the most commonly examined symptom dimension in cross-sectional studies, whereby 26 studies identified clusters used either K-means[35,65,67,88,90,93,95,100-103] or Ward's method clustering analysis.[82,83,87,89,92,98] Nine cross-sectional studies[32,37,66,80,85,91,94,97,104] cross-validated their model using K-means and Ward's clustering analysis. Another study[81] used a combination of clustering and clinical experience to identify homogeneous subgroups.

Longitudinal and cross-sectional studies consistently found several predictors of poor symptomatic trajectories or clusters among patients, unaffected siblings, and general population, including age, gender, ethnic minority, low educational status, late age of illness onset, diagnosis of schizophrenia, severe general psychopathology and depressive symptoms, severe positive and negative schizotypy/symptoms, low cognitive performance, and poor premorbid functioning, quality of life and global functioning. These factors may be used to develop risk prediction model for clinical practice and study disease pathway.

We showed that previous studies included various groups of study population, such as patients with first-episode psychosis or chronic schizophrenia, antipsychotic naïve patients or

patients who were on antipsychotic treatment for a month or longer, patients from different age groups and ethnicities, and healthy siblings and controls. While the comparison of patient clusters and trajectories with healthy siblings or controls could provide an accurate means of disentangling the heterogeneity and causes of heterogeneity of schizophrenia symptoms, only four studies (three were cross-sectional studies) examined clusters in siblings. Likewise, most studies used healthy controls to standardize patients neurocognitive composite scores, and few other studies used controls to compare the distribution of patient clusters or trajectory groups. Substantial differences between studies were also noted in constructing composite scores, use of model selection criteria and method of parameter estimation. Moreover, we observed several ways of subtyping and nomenclature for clusters or trajectories, which may be difficult for clinicians to translate the evidence in diagnosing and treating diseases. This is due to the lack of standardized reporting procedures for data analysis plans or results.[54]

The results of statistical subtyping approaches, such as cluster or trajectory analysis depend on mathematical assumptions, type of data, number of variables or tests, sample size and sampling characteristics. Therefore, the models can be unstable and parameter estimates of clinical symptoms may not converge to a consistent set of subgroups and lack a direct relationship to clinical reality.[73,91,105] For example, intermediate clusters and trajectories substantially vary between studies.[91] We advocate that study results should be applicable, comparable, generalizable and interpretable into clinical practice. We also propose to validate models using additional comparable statistical methods, combine statistical methods of subtyping with empirical methods, and work together with clinicians to create a common understanding and clinically relevant clustering or trajectories nomenclature. Furthermore, it is relevant to replicate clusters or trajectory groups using independent samples, different assessment tools that measure the same construct and different linkage methods.[37,106] Finally, further studies are required that focus on longitudinal study design, unaffected siblings and genetic markers as a predictor.

Conclusions

Our study reveals that schizophrenia symptoms are more heterogeneous than currently recognized and clinically divergent. Future clinical approaches may benefit from the

subgrouping of patients to implement person-based therapy. Uncovering the biological basis of individual symptoms may be more helpful in understanding the pathophysiology of the illness than forcing a constellation of co-occurring symptoms.[1] The identified predictors could be used for developing clinical risk prediction and network modelling, deep endophenotyping, and machine learning to understand symptom pathways. This study showed evidence for clinicians to optimize the efficacy of personalized psychiatric care by predicting individual susceptibility to disease, providing accurate assessment, initiating early intervention strategies, and selecting treatments targeting subgroups of patients with similar phenotypic or psychosocial characteristics.[107] Therefore, using clustering and trajectory analysis methods will help in implication of precision medicine, in treating subgroups of patients with poor outcome and diagnosing prodromal symptoms in their relatives. Finally, given that personalized psychiatry is at the infancy stage, findings from our review could assist in informing personalized and preventive strategies for clinical practice.[1,108]

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References

1. Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: Problems and promises. *BMC medicine*. 2013;11(1):132.

2. Jablensky A. The diagnostic concept of schizophrenia: Its history, evolution, and future prospects. *Dialogues Clin Neurosci*. 2010;12(3):271-287.

3. Owen MJ, Sawa A, Mortensen PB. Schizophrenia. *The Lancet*. 2016;388(10039):86-97.

4. Gejman PV, Sanders AR, Duan J. The role of genetics in the etiology of schizophrenia. *Psychiatr Clin North Am*. 2010;33(1):35-66.

5. Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet*. 2018;50(3):381.

6. American Psychiatric Association, ed. *Diagnostic and statistical manual of mental disorders : DSM-5.* 5th ed. American Psychiatric Publishing, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 222093901.; 2013.

7. Kern RS, Nuechterlein KH, Green MF, et al. The MATRICS consensus cognitive battery, part 2: Co-norming and standardization. *Am J Psychiatry*. 2008;165(2):214-220.

8. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203-213.

9. Andreasen NC. The scale for the assessment of negative symptoms (SANS): Conceptual and theoretical foundations. *The British Journal of Psychiatry*. 1989;155(S7):49-52.

10. Kay SR, Fiszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

11. Kumari S, Malik M, Florival C, Manalai P, Sonje S. 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). *J Addict Res Ther*. 2017;8(3):10.4172/2155-6105.1000324. Epub 2017 May 11.

12. Overall JE, Gorham DR. The brief psychiatric rating scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacol Bull*. 1988.

13. Xavier RM, Vorderstrasse A. Genetic basis of positive and negative symptom domains in schizophrenia. *Biol Res Nurs*. 2017;19(5):559-575.

14. Pai NB, Vella SC. Negative symptoms in schizophrenia: The prevailing challenges. . 2015.

15. Mäkinen J, Miettunen J, Isohanni M, Koponen H. Negative symptoms in schizophrenia—a review. *Nordic Journal of Psychiatry*. 2008;62(5):334-341.

16. Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? *Neuropsychol Rev*. 2009;19(3):365-384.

17. Petrova N, Dorofeikova M. Cognition in schizophrenia: Selective impairment and factors that influence it. *Eur Psychiat*. 2017;41:S193.

18. Shmukler AB, Gurovich IY, Agius M, Zaytseva Y. Long-term trajectories of cognitive deficits in schizophrenia: A critical overview. *Eur Psychiatry*. 2015;30(8):1002-1010.

19. Faraone SV, Kremen WS, Lyons MJ, Pepple JR. Diagnostic accuracy and linkage analysis: How useful are schizophrenia spectrum phenotypes? *Am J Psychiatry*. 1995;152(9):1286-1290.

20. Faraone SV, Tsuang MT, Tsuang DW. *Genetics of mental disorders: A guide for students, clinicians, and researchers.* New York: Guilford Press; 1999.

21. Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV. Neuropsychological risk indicators for schizophrenia: A review of family studies. *Schizophr Bull*. 1994;20(1):103-119.

22. Chen WJ, Faraone SV. Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *Am J Med Genet*. 2000;97(1):52-57.

23. Trandafir A, Méary A, Schürhoff F, Leboyer M, Szöke A. Memory tests in first-degree adult relatives of schizophrenic patients: A meta-analysis. *Schizophr Res*. 2006;81(2):217-226.

24. Krukow P, Karakuła-Juchnowicz H, Juchnowicz D, Morylowska-Topolska J, Flis M, Jonak K. Processing speed is associated with differences in IQ and cognitive profiles between patients with schizophrenia and their healthy siblings. *Nord J Psychiatry*. 2017;71(1):33-41.

25. Walker AE, Spring JD, Travis MJ. Addressing cognitive deficits in schizophrenia: Toward a neurobiologically informed approach. *Biol Psychiatry*. 2017;81(1):e1-e3.

26. Ohi K, Sumiyoshi C, Fujino H, et al. Genetic overlap between general cognitive function and schizophrenia: A review of cognitive GWASs. *International journal of molecular sciences*. 2018;19(12):3822.

27. Seiler N, Maguire J, Nguyen T, et al. Prevalence of subthreshold positive symptoms in young people without psychotic disorders presenting to a youth mental health service. *Schizophrenia Research*. 2019. doi: https://doi.org/10.1016/j.schres.2019.10.041 ".

28. Smith MJ, Barch DM, Thompson PA, Csernansky JG. Subclinical expression of schizophrenia-like symptoms in non-psychotic siblings of individuals with schizophrenia. *Schizophrenia Research*. 2008;103(1):324-325. doi: https://doi.org/10.1016/j.schres.2008.04.028 ".

29. Ahmed AO, Strauss GP, Buchanan RW, Kirkpatrick B, Carpenter WT. Schizophrenia heterogeneity revisited: Clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups. *J Psychiatr Res*. 2018;97:8-15.

30. Thompson WK, Savla GN, Vahia IV, et al. Characterizing trajectories of cognitive functioning in older adults with schizophrenia: Does method matter? *Schizophr Res*. 2013;143(1):90-96.

31. Case M, Stauffer VL, Ascher-Svanum H, et al. The heterogeneity of antipsychotic response in the treatment of schizophrenia. *Psychol Med*. 2011;41(6):1291-1300.

32. Lewandowski K, Sperry S, Cohen B, Öngür D. Cognitive variability in psychotic disorders: A cross-diagnostic cluster analysis. *Psychol Med*. 2014;44(15):3239-3248.

33. Austin SF, Mors O, Budtz-Jørgensen E, et al. Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10year follow-up study in the OPUS cohort. *Schizophr Res*. 2015;168(1):84-91.

34. Abdin E, Chong SA, Vaingankar JA, et al. Trajectories of positive, negative and general psychopathology symptoms in first episode psychosis and their relationship with functioning over a 2-year follow-up period. *PloS one*. 2017;12(11):e0187141.

35. Craddock KES, Zhou X, Liu S, Gochman P, Dickinson D, Rapoport JL. Symptom dimensions and subgroups in childhood-onset schizophrenia. *Schizophr Res*. 2017.

36. Levine SZ, Rabinowitz J. Trajectories and antecedents of treatment response over time in early-episode psychosis. *Schizophr Bull*. 2010;36(3):624-632.

37. Sauvé G, Malla A, Joober R, Brodeur MB, Lepage M. Comparing cognitive clusters across first-and multiple-episode of psychosis. *Psychiatry Res*. 2018;269:707-718.

38. Shmukler AB, Gurovich IY, Agius M, Zaytseva Y. Long-term trajectories of cognitive deficits in schizophrenia: A critical overview. *Eur Psychiatry*. 2015;30(8):1002-1010.

39. Szoke A, Trandafir A, Dupont ME, Meary A, Schurhoff F, Leboyer M. Longitudinal studies of cognition in schizophrenia: Meta-analysis. *Br J Psychiatry*. 2008;192(4):248-257.

40. Alfimova MV, Kondratiev NV, Golimbet VE. Results and promises of genetics of cognitive impairment in schizophrenia: Molecular-genetic approaches. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2016;116(11):137-144.

41. Misiak B, Stanczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. *Schizophr Res*. 2018;192:16-29.

42. Bortolato B, Miskowiak KW, Kohler CA, Vieta E, Carvalho AF. Cognitive dysfunction in bipolar disorder and schizophrenia: A systematic review of meta-analyses. *Neuropsychiatr Dis Treat*. 2015;11:3111-3125.

43. Mesholam-Gately RI, Giuliano AJ, Goff KP, Faraone SV, Seidman LJ. Neurocognition in first-episode schizophrenia: A meta-analytic review. *Neuropsychology*. 2009;23(3):315-336.

44. Snitz BE, MacDonald III AW, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophr Bull*. 2005;32(1):179-194.

45. Bozikas VP, Andreou C. Longitudinal studies of cognition in first episode psychosis: A systematic review of the literature. *Aust N Z J Psychiatry*. 2011;45(2):93-108.

46. Ventura J, Wood RC, Hellemann GS. Symptom domains and neurocognitive functioning can help differentiate social cognitive processes in schizophrenia: A meta-analysis. *Schizophr Bull*. 2011;39(1):102-111.

47. Fett AJ, Viechtbauer W, Dominguez M, Penn DL, van Os J, Krabbendam L. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2011;35(3):573-588. doi: https://doi.org/10.1016/j.neubiorev.2010.07.001.

48. Buchanan RW. Persistent negative symptoms in schizophrenia: An overview. *Schizophr Bull*. 2006;33(4):1013-1022.

49. Boutros NN, Mucci A, Diwadkar V, Tandon R. Negative symptoms in schizophrenia: A comprehensive review of electrophysiological investigations. *Clinical schizophrenia & related psychoses*. 2013;8(1):28-35B.

50. Waters F, Fernyhough C. Hallucinations: A systematic review of points of similarity and difference across diagnostic classes. *Schizophr Bull*. 2017;43(1):32-43.

51. Habtewold TD, Liemburg EJ, Richard Bruggeman, Alizadeh BZ. Symptomatic trajectories and clusters in patients with schizophrenia, siblings and healthy controls. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018093566. Updated 2018. Accessed 10/15, 2019.

52. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS med*. 2009;6(7):e1000097.

53. Beller EM, Glasziou PP, Altman DG, et al. PRISMA for abstracts: Reporting systematic reviews in journal and conference abstracts. *PLoS Med*. 2013;10(4):e1001419.

54. Frankfurt S, Frazier P, Syed M, Jung KR. Using group-based trajectory and growth mixture modeling to identify classes of change trajectories. *The Counseling Psychologist*. 2016;44(5):622-660.

55. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.

56. Cheah S-, Lurie JK, Lawford BR, Young RM, Morris CP, Voisey J. Interaction of multiple gene variants and their effects on schizophrenia phenotypes. *Compr Psychiatry*. 2016;71:63-70.

57. Cocchi A, Cerati G, Lora A, et al. Patients with first-episode psychosis are not a homogeneous population: Implications for treatment. *Clin Pract Epidemiol Ment Health*. 2014;10:1-8.

58. Hall M-, Smoller JW, Cook NR, et al. Patterns of deficits in brain function in bipolar disorder and schizophrenia: A cluster analytic study. *Psychiatry Res*. 2012;200(2-3):272-280.

59. Kavanaugh BC, Dupont-Frechette JA, Tellock PP, Maher ID, Haisley LD, Holler KA. Neurocognitive phenotypes in severe childhood psychiatric disorders. *J Nerv Ment Dis*. 2016;204(10):770-777.

60. Lim J, Chin R, Ho NF, et al. Elucidation of shared and specific white matter findings underlying psychopathology clusters in schizophrenia. *Asian J Psychiatry*. 2017;30:144-151.

61. Lin S-, Liu C-, Liu Y-, et al. Clustering by neurocognition for fine mapping of the schizophrenia susceptibility loci on chromosome 6p. *Genes Brain Behav*. 2009;8(8):785-794.

62. Nordon C, Rouillon F, Azorin JM, Barry C, Urbach M, Falissard B. Trajectories of antipsychotic response in drug-naive schizophrenia patients: Results from the 6-month ESPASS follow-up study. *Acta Psychiatr Scand*. 2014;129(2):116-125.

63. Silver H, Shmoish M. Analysis of cognitive performance in schizophrenia patients and healthy individuals with unsupervised clustering models. *Psychiatry Res*. 2008;159(1-2):167-179.

64. Islam MA, Habtewold T, van Es F, et al. Long-term cognitive trajectories and heterogeneity in patients with schizophrenia and their unaffected siblings. *Acta Psychiatr Scand*. 2018.

65. Ohi K, Shimada T, Nemoto K, et al. Cognitive clustering in schizophrenia patients, their first-degree relatives and healthy subjects is associated with anterior cingulate cortex volume. *NeuroImage-Clin*. 2017;16:248-256.

66. Quee PJ, Alizadeh BZ, Aleman A, van den Heuvel E, GROUP Investigators. Cognitive subtypes in non-affected siblings of schizophrenia patients: Characteristics and profile congruency with affected family members. *Psychol Med*. 2014;44(2):395-405.

67. Lui SSY, Hung KSY, Wang Y, et al. Clustering of schizotypal features in unaffected first-degree relatives of schizophrenia patients. *Schizophr Bull*. 2018.

68. Levine SZ, Rabinowitz J, Faries D, Lawson AH, Ascher-Svanum H. Treatment response trajectories and antipsychotic medications: Examination of up to 18months of treatment in the CATIE chronic schizophrenia trial. *Schizophrenia Research*. 2012;137(1):141-146. doi: https://doi.org/10.1016/j.schres.2012.01.014.

69. Stauffer V, Case M, Kollack-Walker S, et al. Trajectories of response to treatment with atypical antipsychotic medication in patients with schizophrenia pooled from 6 double-blind, randomized clinical trials. *Schizophrenia Research*. 2011;130(1):11-19. doi: https://doi.org/10.1016/j.schres.2011.03.015.

70. Schennach R, Meyer S, Seemüller F, et al. Response trajectories in "real-world" naturalistically treated schizophrenia patients. *Schizophr Res*. 2012;139(1-3):218-224.

71. Pelayo-Teran J, Diaz FJ, Perez-Iglesias R, et al. Trajectories of symptom dimensions in short-term response to antipsychotic treatment in patients with a first episode of non-affective psychosis. *Psychol Med*. 2014;44(1):37-50.

72. Levine SZ, Rabinowitz J, Case M, Ascher-Svanum H. Treatment response trajectories and their antecedents in recent-onset psychosis: A 2-year prospective study. *J Clin Psychopharmacol*. 2010;30(4):446-449.

73. Jäger M, Weiser P, Becker T, et al. Identification of psychopathological course trajectories in schizophrenia. *Psychiatry Res*. 2014;215(2):274-279.

74. Chen L, Johnston JA, Kinon BJ, et al. The longitudinal interplay between negative and positive symptom trajectories in patients under antipsychotic treatment: A post hoc analysis of data from a randomized, 1-year pragmatic trial. *BMC Psychiatry*. 2013;13.

75. Stiekema AP, Islam MA, Liemburg EJ, et al. Long-term course of negative symptom subdomains and relationship with outcome in patients with a psychotic disorder. *Schizophr Res*. 2017.

76. Chang WC, Ho RWH, Tang JYM, et al. Early-stage negative symptom trajectories and relationships with 13-year outcomes in first-episode nonaffective psychosis. *Schizophr Bull*. 2018.

77. Gee B, Hodgekins J, Fowler D, et al. The course of negative symptom in first episode psychosis and the relationship with social recovery. *Schizophr Res*. 2016;174(1):165-171.

78. Wang Y, Shi H, Liu W, et al. Trajectories of schizotypy and their emotional and social functioning: An 18-month follow-up study. *Schizophrenia Research*. 2018;193:384-390. doi: https://doi.org/10.1016/j.schres.2017.07.038.

79. Smucny J, Iosif A, Eaton NR, et al. Latent profiles of cognitive control, episodic memory, and visual perception across psychiatric disorders reveal a dimensional structure. *Schizophr Bull*. 2019.

80. Uren J, Cotton SM, Killackey E, Saling MM, Allott K. Cognitive clusters in first-episode psychosis: Overlap with healthy controls and relationship to concurrent and prospective symptoms and functioning. *Neuropsychology*. 2017;31(7):787-797.

81. Wells R, Swaminathan V, Sundram S, et al. The impact of premorbid and current intellect in schizophrenia: Cognitive, symptom, and functional outcomes. *NPJ Schizophr*. 2015;1(1).

82. Wu M, Chan F, Wang T-, Chen S-. Neurocognitive profiles of rehabilitation clients with schizophrenia in taiwan. *J Rehabil*. 2010;76(3):10-14.

83. Rodriguez M, Fajnerová I, Sedláková K, et al. Cluster analysis and correlations between cognitive domains: Cognitive performance in a czech sample of first episodes schizophrenia spectrum disorders - preliminary results. *Psychiatrie*. 2017;21(1):4-11.

84. Rocca P, Galderisi S, Rossi A, et al. Social cognition in people with schizophrenia: A cluster-analytic approach. *Psychol Med*. 2016;46(13):2717-2729.

85. Reser MP, Allott KA, Killackey E, Farhall J, Cotton SM. Exploring cognitive heterogeneity in first-episode psychosis: What cluster analysis can reveal. *Psychiatry Res*. 2015;229(3):819-827.

86. Rangel A, Muñoz C, Ocampo MV, et al. Neurocognitive subtypes of schizophrenia. *Actas Esp Psiquiatr*. 2015;43(3):80-90.

87. Prouteau A, Roux S, Destaillats J-, Bergua V. Profiles of relationships between subjective and objective cognition in schizophrenia: Associations with quality of life, stigmatization, and mood factors. *J Cogn Educ Psychol*. 2017;16(1):64-76.

88. Potter AI, Nestor PG. IQ subtypes in schizophrenia: Distinct symptom and neuropsychological profiles. *J Nerv Ment Dis*. 2010;198(8):580-585.

89. Crouse JJ, Moustafa AA, Bogaty SE, Hickie IB, Hermens DF. Parcellating cognitive heterogeneity in early psychosis-spectrum illnesses: A cluster analysis. *Schizophr Res*. 2018;202:91-98.

90. Ochoa S, Huerta-Ramos E, Barajas A, et al. Cognitive profiles of three clusters of patients with a first-episode psychosis. *Schizophr Res*. 2013;150(1):151-156.

91. Lewandowski KE, Baker JT, McCarthy JM, Norris LA, Öngür D. Reproducibility of cognitive profiles in psychosis using cluster analysis. *J Int Neuropsychol Soc*. 2018;24(4):382-390.

92. Gilbert E, Mérette C, Jomphe V, et al. Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms of outcome and response to treatment. *Eur Arch Psychiatry Clin Neurosci*. 2014;264(4):333-343.

93. Geisler D, Walton E, Naylor M, et al. Brain structure and function correlates of cognitive subtypes in schizophrenia. *Psychiatry Res Neuroimaging*. 2015;234(1):74-83.

94. Dawes SE, Jeste DV, Palmer BW. Cognitive profiles in persons with chronic schizophrenia. *J Clin Exp Neuropsychol*. 2011;33(8):929-936.

95. Bell MD, Johannesen JK, Greig TC, Wexler BE. Memory profiles in schizophrenia: Categorization validity and stability. *Schizophrenia Research*. 2010;118(1):26-33. doi: https://doi-org.proxy-ub.rug.nl/10.1016/j.schres.2009.12.037.

96. Bechi M, Spangaro M, Agostoni G, et al. Intellectual and cognitive profiles in patients affected by schizophrenia. *J Neuropsychol*. 2018.

97. Strauss GP, Horan WP, Kirkpatrick B, et al. Deconstructing negative symptoms of schizophrenia: Avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res*. 2013;47(6):783-790.

98. Chang JS, Kim Y, Kim SH, et al. Differences in the internal structure of hallucinatory experiences between clinical and nonclinical populations. *Psychiatry Res*. 2015;226(1):204-210.

99. Talpalaru A, Bhagwat N, Devenyi GA, Lepage M, Chakravarty MM. Identifying schizophrenia subgroups using clustering and supervised learning. *Schizophr Res*. 2019.

100. Trauelsen AM, Gumley A, Jansen JE, et al. Metacognition in first-episode psychosis and its association with positive and negative symptom profiles. *Psychiatry Res*. 2016;238:14-23.

101. Wang Y, Neumann D, Shum DHK, Chan RCK. A cross-validation study of clustering of schizotypy using a non-clinical chinese sample. *Psychiatry Res*. 2012;200(1):55-58.

102. Barrantes-Vidal N, Lewandowski KE, Kwapil TR. Psychopathology, social adjustment and personality correlates of schizotypy clusters in a large nonclinical sample. *Schizophr Res*. 2010;122(1-3):219-225.

103. Lysaker PH, Vohs JL, Tsai J. Negative symptoms and concordant impairments in attention in schizophrenia: Associations with social functioning, hope, self-esteem and internalized stigma. *Schizophr Res*. 2009;110(1-3):165-172.

104. Bell MD, Corbera S, Johannesen JK, Fiszdon JM, Wexler BE. Social cognitive impairments and negative symptoms in schizophrenia: Are there subtypes with distinct functional correlates? *Schizophr Bull*. 2013;39(1):186-196.

105. Marquand AF, Wolfers T, Mennes M, Buitelaar J, Beckmann CF. Beyond lumping and splitting: A review of computational approaches for stratifying psychiatric disorders. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2016;1(5):433-447. doi: https://doi-org.proxy-ub.rug.nl/10.1016/j.bpsc.2016.04.002.

106. Stroebe W, Strack F. The alleged crisis and the illusion of exact replication. *Perspectives on Psychological Science*. 2014;9(1):59-71.

107. Peter F. Buckley & Brian J. Miller. Personalized medicine for schizophrenia. *npj Schizophrenia*. 2017;2.

108. Schubert KO, Clark SR, Van LK, Collinson JL, Baune BT. Chapter 3 - mood trajectories as a basis for personalized psychiatry in young people. . 2020:13-26. doi: https://doi.org/10.1016/B978-0-12-813176-3.00003-1.