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Revealing differential psychotic symptoms in schizophrenia and bipolar I disorder by manifold learning and network analyses

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The field of psychiatry has encountered ongoing challenges in understanding the intricate nature of psychotic symptoms, particularly when they manifest in individuals diagnosed with bipolar disorder or schizophrenia. In this study, we employed manifold and network analyses to investigate whether the pattern of symptom occurrence differs between schizophrenia and bipolar I disorder. We analyzed data collected from 555 individuals, 282 of whom were diagnosed with schizophrenia-related disorders and 273 with bipolar I disorder. In the context of schizophrenia, negative symptoms, particularly avolition, were prominent with manifold and network analyses, identifying avolition as a high central symptom associated with clozapine use, patterns of deterioration, tendency toward remission, and illness severity. Conversely, bipolar I disorder exhibits discernible patterns where positive symptoms play a central role in network analysis. Unexpectedly, manifold analysis revealed two distinct clusters of patients, suggesting variability in psychotic symptom profiles within bipolar I disorder. In conclusion, schizophrenia and bipolar I disorder, while sharing psychotic symptoms, exhibit distinct co-occurrence patterns. Schizophrenia demonstrates negative symptoms, whereas bipolar I disorder exhibits a stronger interconnectivity of psychotic symptoms, highlighting the complexity of psychotic symptom patterns and their relevance for understanding psychiatric disorders. These findings highlight the complexity of psychotic symptom patterns and their relevance for understanding psychiatric disorders.

Translational Psychiatry (2025)15:194 ; https://doi.org/10.1038/s41398-025-03403-6

INTRODUCTION

The distinction between bipolar disorder and schizophrenia has long been a subject of discussion in psychiatry [1, 2]. Emil Kraepelin's pioneering work categorizing major psychosis into manic depression and dementia praecox has been a source of fundamental assumptions in psychiatry since the early 20th century [3–5]. Eugen Bleuler emphasized the central role of negative symptoms in schizophrenia [6]. The overlapping phenomenology and neurobiological basis of schizophrenia and bipolar spectrum disorders, particularly bipolar I disorder, make differentiation challenging [7–10]. Kraepelin recognized the challenges in applying the dichotomy he had suggested [11, 12]. The expanded applications of second-generation antipsychotics as mood stabilizers have increased these challenges [13–16]. Based on the historical context and challenges associated with distinguishing these disorders, their shared and distinct characteristics should be investigated. Distinguishing between the two disorders has significEant clinical implications, including for treatment selection and prognostication [17]. In particular, the disorders share psychotic symptoms, which are important for distinguishing them. Traditional Schneiderian first-rank symptoms for schizophrenia are also common in bipolar disorders [18, 19], and the presence of particular psychotic symptoms lacks diagnostic value. Furthermore, negative symptoms, such as anhedonia and avolition, have been observed in patients with bipolar disorder, and they persist even during periods of mood abnormalities [20–22]. In cases of bipolar disorders with psychotic features, misdiagnosis as schizophrenia is common, which is associated with delayed treatment and a poor prognosis [23–26].

Psychotic symptoms are multi-dimensional phenomena [27–29]. In addition to major categories such as hallucinations, delusions, disorganized behaviors, thought process abnormalities, and negative symptoms, each dimension comprises sub-dimensions. Hallucinations can be categorized according to the perception modalities, including auditory, visual, tactile, olfactory, and gustatory. Delusions also have multiple sub-dimensions distinguished according to the content of thoughts, such as paranoid, persecutory, grandiose, religious, somatic, and erotic.

The patterns of psychotic symptoms differ between schizophrenia and bipolar disorder. For example, delusions of grandiosity and religious themes are highly correlated with manic episodes [30, 31]. The subtypes of negative symptoms also differ between schizophrenia and bipolar disorders [22, 32, 33].

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Received: 18 March 2024 Revised: 28 April 2025 Accepted: 20 May 2025
Published online: 06 June 2025

Moreover, each symptom domain has interconnections that form symptom networks [33–37]. Although the presence of single psychosis-related symptoms may not have diagnostic value for differentiating schizophrenia and bipolar disorder, the analysis of complex patterns between symptoms may reveal differences between these conditions. By examining the interactions between various dimensions and subdimensions of symptomatology, we can gain insight into the distinctive profiles of schizophrenia and bipolar disorder. Understanding the complex symptom networks and their configurations holds promise for enhancing the accuracy of differential diagnosis and our knowledge of the underlying mechanisms of these disorders.

To analyze high-dimensional data, manifold analysis tools [38, 39] from the field of machine learning, such as Uniform Manifold Approximation and Projection (U-MAP) [38], have emerged as valuable resources in recent years. These tools allow the exploration and visualization of complex datasets by reducing their dimensionality while maintaining their underlying structure. U-MAP can reduce the high-dimensional data associated with symptoms and potentially facilitate understanding of the intricate patterns and relationships between symptoms in the context of psychiatric symptomatology. Using such techniques, we can gain insights into the clustering, groupings, and interconnections within the symptom space.

In addition to manifold analysis, our study also utilized network analysis as a complementary method for understanding the interactions and patterns of symptoms in schizophrenia and bipolar disorder. By constructing symptom networks, we aimed to identify key symptoms that play central roles in these disorders and to investigate the relationships between various symptom domains [34, 35]. This combined approach of manifold and network analyses offers a comprehensive framework for elucidating the intricate symptom profiles and illuminating the underlying dynamics of schizophrenia and bipolar disorder. In addition, the clinical implications were determined by examining the associations among core symptoms, symptom patterns, and pertinent outcomes, such as hospitalization dates and medication use.

MATERIAL AND METHODS

Participants and data collection

We recruited patients with schizophrenia, schizoaffective disorder, and bipolar I disorder from Seoul National University Hospital, Korea. The participants fulfilled the Diagnostic and Statistical Manual-IV diagnostic criteria for their respective disorder. During regular meetings between at least three psychiatrists, a final consensus diagnosis was reached. Participants were individually interviewed by trained nurses using the Korean version of the Diagnostic Interview for Genetic Studies (DIGS) [40, 41], which has poly-diagnostic capability and provides detailed assessments of psychotic and mood syndromes in terms of chronology and comorbidity with other psychiatric illnesses. In particular, we utilized the DIGS data to compare the symptomatic characteristics of bipolar disorder and schizophrenia, including clinical outcomes such as the number of suicide attempts, deterioration pattern, and remission rate, in addition to ratings of psychotic symptoms that are not associated with the diagnosis.

The Korean version of DIGS evaluates multiple domains of psychiatric symptoms through a structured interview format [40] For psychotic symptoms, participants were asked whether they had ever experienced specific symptoms, which includes paranoid delusion, persecutory delusion, auditory hallucination, thought form disorder, as listed in Table 1. If they reported experiencing a symptom, they were further asked whether it occurred during the current or past episodes, which enable us to identify whether each symptom occurred during entire course of disease. Similarly, other symptom domain such as anxiety or mood symptoms were assessed using the same lifetime framework, instead asking whether they experienced these symptoms during their most severe mood episode.

Participants with a history of organic brain disease, substance or drug abuse, or other physical conditions that can cause psychiatric symptoms were excluded. The study included 555 patients with schizophrenia, schizoaffective disorder, or bipolar I disorder (287 males, 268 females; mean [SD] age, 33.4 [10.7]). Among these participants, 282 were diagnosed with schizophrenia or schizoaffective disorder and 273 with bipolar I disorder.

Notably, the sample size of 555 participants is comparable to those used in similar studies employing network analysis in psychiatry. The sample size ensures sufficient representation of schizophrenia and bipolar I disorder populations, allowing for robust modeling of complex symptom patterns and reliable subgroup analyses.

All methods were carried out in accordance with relevant guidelines and regulations. The study protocol was approved by the Ethics Committee of Seoul National University Hospital (approval no.: 0106-080-002), and all participants provided written informed consent prior to participation. The procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

Table 1. Leave-one-out cross-validation accuracy for each symptom using the 2D coordinates in the U-MAP.

Symptoms	Accuracy (%)
Grandiose Delusion	65.60
Thought Form Disorder	66.31
Obsession & Compulsion	69.86
Visual Hallucination	74.11
Paranoid Delusion	78.01
Erotic Delusion	78.72
Thought Broadcasting	79.79
Religious Delusion	80.85
Delusion of Reference	81.21
Delusion of Being Controlled	81.91
Auditory Hallucination	81.91
Avolition	81.91[a]
Delusion of Guilt	82.98
Disorganized Behavior	84.40
Thought Insertion	84.40
Anhedonia	91.84[a]
Phobia	92.20
Mutism	92.55[a]

[a]Symptoms with high accuracy in leave-one-out cross-validation, while having balanced number of samples (over 35 percent for the smaller group) for both classes.

Data processing

We collected the information for data analysis from DIGS. We evaluated symptoms that were observed in ≥5% of individuals diagnosed with both schizophrenia and bipolar disorder. Eighteen symptoms related to psychosis or anxiety were selected based on these criteria.

Within the realm of delusional symptoms, we documented a range of manifestations, including paranoid delusions, delusions of reference, grandiose delusions, religious delusions, erotic delusions, and guilt delusions. With regard to hallucinatory symptoms, only auditory and visual hallucinations were recorded, as olfactory, gustatory, and tactile hallucinations were seldom reported. Delusional self-experience [42], encompassing delusions of being controlled, thought broadcasting, and thought insertion, was also recorded. Negative symptoms were also recorded, including avolition, anhedonia, and mutism. Furthermore, we collected information on thought form disorders and disorganized behaviors. Obsessions and compulsions were considered as a composite symptom entity, and phobia was integrated into the assessment.

The evaluation of symptoms was based on lifetime occurrences rather than present status. This approach allowed for binary data collection, categorizing symptoms as present or absent.

Statistical analysis

We collected information on 18 psychotic and anxiety-related symptoms from each participant. To effectively manage the complex and multi-dimensional nature of symptom data, we implemented an advanced

dimensionality reduction technique known as U-MAP. This algorithm functions by generating a high-dimensional graph for the data, which is subsequently projected optimally into a lower-dimensional space. This approach preserves the local and global structure of data, while facilitating visualization and analysis of the symptom distribution in a reduced dimensional space, thereby facilitating manifold learning [38]. The advantage of U-MAP lies in its ability to facilitate the interpretation of intricate psychiatric symptom patterns by identifying clusters or groupings of symptoms that may not be readily observable in spaces with a higher number of dimensions.

Furthermore, to delve deeper into the patterns identified through U-MAP, we utilized support vector machine (SVM) analysis [43], which is a robust supervised machine learning algorithm that is particularly suitable for classification tasks. We utilized SVM to classify participants according to their symptom profiles. The algorithm accomplishes this by identifying the hyperplane that effectively divides the data into separate classes with the largest possible margin. This enables us to detect distinct patterns and potential diagnostic categories within the manifold identified by U-MAP. The performance of the SVM model was assessed using a standard metric, i.e., accuracy. The Python programming language was used to implement the U-MAP and SVM algorithms.

For network analysis, we used the eLasso method included in the IsingFit package in R [44]. By constructing a symptom network structure, this method enables us to examine the interconnections and interactions among symptoms within the network structure, thus unveiling their connectivity and centrality. This method facilitates a comprehensive understanding of the intricate relationships between symptoms by clarifying these network properties. The impact of each symptom on the network was assessed using centrality metrics, such as betweenness, closeness, and strength. Nodes with high-betweenness centrality serve as connectors in the network. Closeness centrality assesses the proximity of a symptom to all other symptoms in the network, whereas strength measures the overall level of connectivity between a symptom and other symptoms in the network. Although we explored these conventional centrality indices to gain a broad understanding of symptom interrelationships, our primary focus was on Katz centrality [45]. Katz centrality expands upon the notion of degree centrality by considering not only the direct connections of a symptom but also the connections of its neighboring symptoms, thus providing a more nuanced perspective on the potential influence of each symptom within the network. In addition to examining Katz centrality in detail, the inclusion of betweenness and closeness metrics allowed us to investigate the network's structure from multiple angles, offering insights that might not be fully captured by a single centrality measure alone. We utilized the walktrap algorithm to identify symptom communities within the network. Identifying these communities provided insights into the modular structure of the symptom network [46].

To compare the symptom networks of schizophrenia and bipolar I disorder, we conducted the network comparison test (NCT) from the NetworkComparisonTest package in R [47]. This permutation-based method evaluates differences in network structure, global strength (total connectivity), and individual edge weights between two networks. The structure invariance test assessed whether the overcall network configuration differed, while the global strength test compared the sum of absolute edge weights. Edge and centrality difference tests assessed symptom connections and centrality measures; however, Katz centrality was excluded due to its lack of implementation in this method. Statistical significance for all tests was determined using 2500 permutations.

To evaluate the clinical implications of symptom dimensions, we compared the clinical outcomes of groups with and without certain symptom dimensions using the chi-square test. This allowed us to evaluate the potential impact of particular symptom dimensions on a variety of clinical parameters.

RESULTS

Manifold analysis of schizophrenia

Manifold analysis tools facilitate the recognition of patterns in high-dimensional data. Using U-MAP, we reduced data into psychotic and anxiety-related symptoms. The color of the data points was encoded with the number of symptoms the patient had ever experienced. The number of symptoms gradually increases along the first axis of U-MAP (Fig. 1a). To interpret this pattern, we trained SVM to predict whether a patient has ever experienced each symptom based on their 2D U-MAP coordinates. Avolition, mutism, and anhedonia are 3 of the 18 psychotic and anxiety-related symptoms that SVM predicted correctly (Fig. 1c, Table 1, Fig. S1).

Positive, negative, and dissociative symptoms, as well as anxiety symptoms such as phobia and obsessions and compulsions, were analyzed. Based on the intriguing fact that only negative symptoms could be divided with an SVM, we counted the number of negative symptoms for each patient and encoded them according to the color of data points on the 2D U-MAP. The number of negative symptoms mirrored the patient's total number of symptoms (Fig. 1b; Pearson's correlation: 0.606, $p < 0.001$).

Manifold analysis for bipolar I disorder

Using the same methodology, we reduced the feature space of bipolar I disorder symptoms. In contrast to schizophrenia, patients were organized into two clusters in the reduced manifold space (Fig. 2a). One cluster had a lower prevalence of the majority of psychotic symptoms (cluster 2), whereas the other cluster had a higher prevalence of all psychotic symptoms (cluster 1). None of the individual symptoms could distinguish between the two clusters.

The feature space was independently reduced for both clusters. Cluster 1 was characterized by a low prevalence of psychotic and anxiety symptoms (Fig. 2b), displaying a greater prevalence of psychotic and anxiety-related symptoms. Unlike schizophrenia, the distribution of symptoms along the reduced manifold space did not show any particular pattern (Fig. 2c).

Network analysis of symptoms in schizophrenia and bipolar I disorder

To gain a better understanding of the relationships between symptoms in schizophrenia and bipolar I disorder, we performed network analyses using the eLasso method.

Using random walk clustering, we found that the 18 symptoms of schizophrenia formed nine distinct communities (Fig. 3a). Phobia, delusions of guilt, and obsessions/compulsions were distinct and unrelated to other symptoms. Delusional self-experience, such as the delusion of being controlled, thought broadcasting, and insertion, were categorized together based on their shared association with self-destruction. Hallucinatory symptoms, such as auditory and visual hallucinations, were categorized together and were considered distinct from the other psychotic symptoms, with auditory hallucination having a weak connection with delusions of being controlled, avolition, and thought form disorder. Thought form disorder and disorganized behavior were also grouped together and connected to avolition but not to thought broadcasting or insertion. Notably, the three negative symptoms (avolition, mutism, and anhedonia) were categorized into the same community, which is consistent with our manifold analysis, demonstrating that these symptoms had well-defined support vector borders and high leave-one-out validation accuracy (Table 1). To determine the contribution of each symptom to other symptoms, we measured the Katz, betweenness, closeness, and strength of centrality of the symptom network. In patients with schizophrenia, avolition had the highest Katz, betweenness, and closeness centrality scores, ranked second for strength centrality, and thus had a high ranking in all four centrality measures. Other negative symptoms categorized with avolition (anhedonia and mutism) were not highly ranked for most centrality measures, with the exception of anhedonia, which received the highest score for strength centrality. Disorganized behavior ranked second for centrality on the betweenness and closeness scale and sixth for strength. This was in line with the network results, as disorganized behavior serves as a hub between various symptom communities; however, its strength appears to be weaker than that of avolition. Other symptoms that were ranked highly in certain centrality

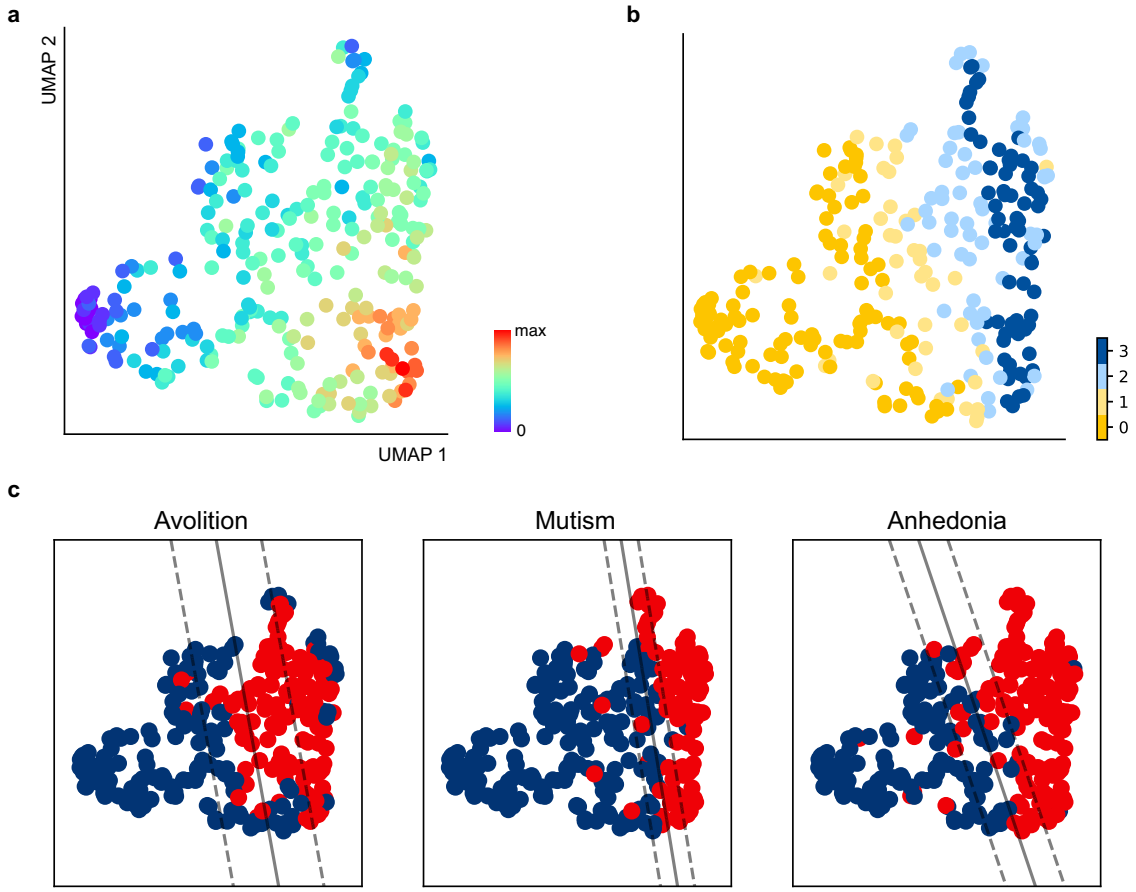

Fig. 1 Low-dimensional symptom manifolds reveal heterogeneity in schizophrenia. a Symptom manifolds projected into 2D space in schizophrenia patients. The color shows the normalized number of symptoms that the patient has ever experienced. **b** Scatter plot of people with schizophrenia, with each color representing the number of negative symptoms (avolition, mutism, and anhedonia). The number of negative symptoms is comparable between the total number of psychotic and anxiety symptoms. **c** Using the coordinates in the 2D U-MAP space, a support vector machine was trained to predict the presence of negative symptoms. Each of the three symptoms had a well-defined vector support border. Therefore, the presence or absence of these symptoms indicated the diversity of schizophrenia patients.

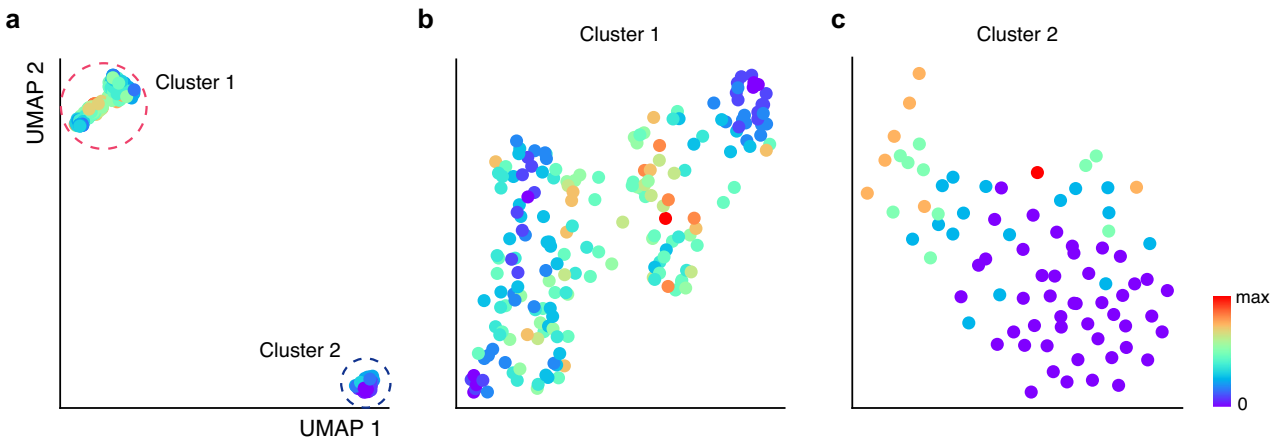

Fig. 2 Symptom manifolds reveal distinct clustering patterns in bipolar I disorder. a Symptom manifolds projected into two-dimensional space for bipolar I disorder patients. The color indicates the patient's normalized lifetime symptom count. In the reduced feature space, unlike schizophrenia, patients are clustered into two distinct groups. **b** A manifold reduction was performed on cluster 1, which is the group of patients located at the top left. Greater numbers of psychotic and anxiety-related symptoms were experienced by the majority of patients. **c** For cluster 2, the group of patients located in the lower right-hand corner, a manifold reduction was performed. Unlike cluster 1, patients in this cluster exhibited fewer psychotic and anxiety-related symptoms.

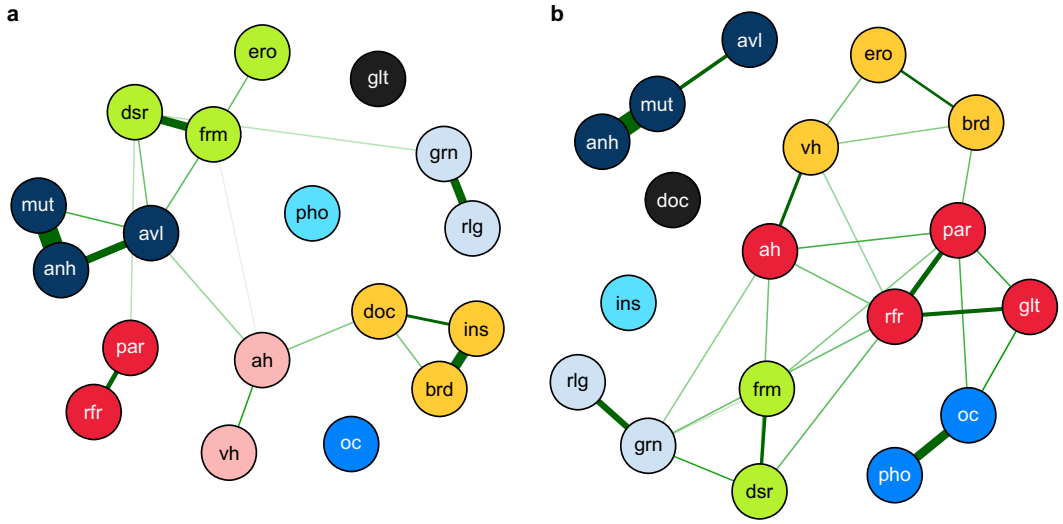

Fig. 3 Network structure of psychotic and anxiety-related symptoms in schizophrenia and bipolar I disorder. a, **b** Network analysis of psychotic and anxiety-related symptoms in schizophrenia (left) and bipolar I disorder (right) par; paranoid delusion, rfr; delusion of reference, doc; delusion of being controlled, ah; auditory hallucination, vh; visual hallucination, dsr; disorganized behavior, frm; thought form disorder, grn; grandiose delusion, rlg; religious delusion, ero; erotic delusion, glt; delusion of guilt, avl; avolition, anh; anhedonia, mut; mutism, brd; thought broadcasting, ins; thought insertion, oc; obsession/compulsion, pho; phobia.

measurements had inconsistent rankings in other centrality assessments (Fig. 4a).

The 18 symptoms of bipolar I disorder formed eight distinct communities (Fig. 3b). Obsession/compulsion and phobia formed a single community linked to positive symptoms via paranoid and guilt delusions. In contrast to schizophrenia, psychotic symptoms, such as paranoid delusion, guilt delusion, auditory hallucination, and delusion of reference, formed a single community. Interestingly, auditory and visual hallucinations were categorized into distinct categories within the context of bipolar disorder. Consistent with schizophrenia, religious and grandiose delusions were grouped together, having connections with the thought form disorder and disorganized behavior community. The three negative symptoms (avolition, anhedonia, and mutism) formed a community similar to the network for schizophrenia. However, unlike schizophrenia, the negative symptom community did not form connections with other symptoms. Instead, thought broadcasting formed a community group that included erotic delusion and visual hallucinations. In general, the connections between the nodes in the symptom network of bipolar I patients were stronger. This is also evident when comparing the centrality values of patients with schizophrenia and bipolar I: the symptom network of patients with bipolar I disorder had, on average, higher values for most centrality measures (except betweenness). In bipolar I disorder patients, delusions of reference and paranoid delusions exhibited high centralities across all four measures.

These network analyses provide additional insights into the complex relationships between symptoms in schizophrenia and bipolar I disorder, highlighting both similarities and differences between the network structures of these two disorders. To assess the stability of the network obtained from the data, we employed the bootstrapping technique. Strength exhibited strong resilience to subsampling, whereas betweenness and closeness showed greater susceptibility to bootstrapping. The centrality stability (CS) coefficients for schizophrenia were 0.472 for strength and 0 for closeness and betweenness. The strength value for bipolar I disorder was 0.366, whereas the values for closeness and betweenness were 0 (Fig. S2). The bootstrap confidence intervals for the edge weights exhibited significant overlap (Fig. S3).

The network comparison test revealed significant differences in the symptom network structure between schizophrenia and bipolar I disorder (Table 2). The network structure invariance test indicated that the structure of the symptom networks different significantly between the two disorders (Table 2, $p = 0.012$). Although the bipolar I disorder network had higher global strength compared to the schizophrenia network, this difference was not statistically significant ($p = 0.244$).

Furthermore, while some symptoms exhibited differences in their connections with other symptoms (Fig. S4), the edge difference and centrality tests revealed no significant individual differences between the two networks. This suggests that, despite differences in overall network structure, the relative importance and connectivity of individual symptoms remain comparable between schizophrenia and bipolar I disorder.

Clinical characteristics of schizophrenia patients depending on avolition

On the basis of observations derived from manifold and network analyses, avolition emerged as a primary symptom of schizophrenia, encompassing a constellation of lifelong psychotic and anxiety-related manifestations. Consequently, it can be regarded as the primary "gate symptom" that leads to the emergence of additional symptoms in affected individuals. To demonstrate the clinical significance of avolition, we compared the clinical characteristics of schizophrenia patients who have and have not experienced avolition. Comparative clinical characteristics included patterns of deterioration, types of remission, illness severity, suicide attempts, and clozapine use.

Among various clinical characteristics, clozapine use, deterioration, remission pattern, and severity demonstrated statistically significant differences between the two entities (Table 3; all $p < 0.01$). In particular, schizophrenia patients with avolition had a higher rate of clozapine use, a more severe pattern of deterioration, and a lower remission rate. However, the suicide rate did not differ significantly between the two groups (Table 3).

DISCUSSION

Our study primarily examined the differential symptom patterns concerning psychotic and anxiety-related symptoms in schizophrenia and bipolar I disorder. The manifold analysis focused mainly on the variation of gross symptom patterns, whereas network analysis offered an in-depth view of the interactions among symptoms. In schizophrenia, the U-MAP findings indicated

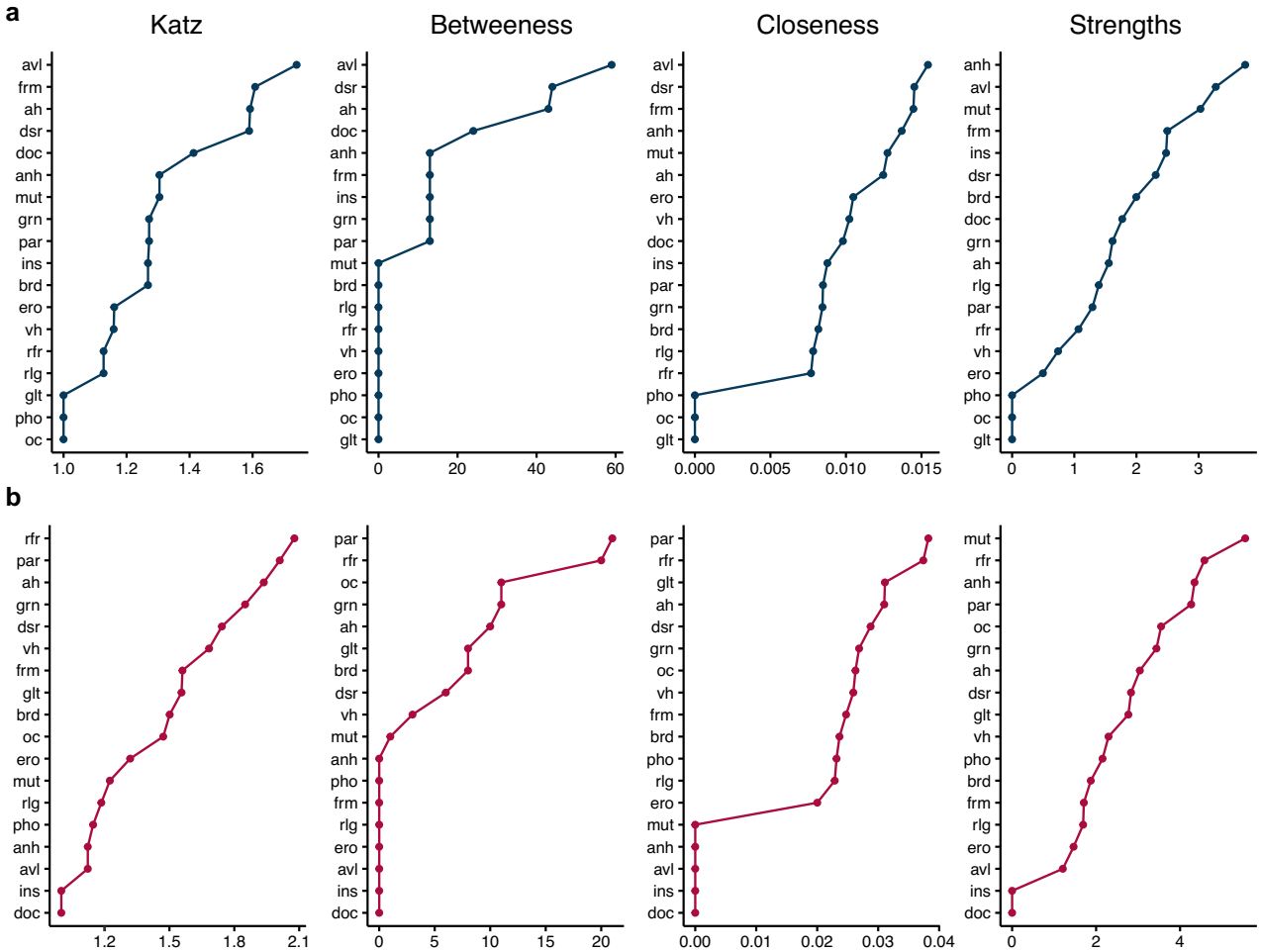

Fig. 4 Centrality profiles of psychotic and anxiety-related symptoms in schizophrenia and bipolar I disorder networks. a, **b** Centrality measures of psychotic and anxiety-related symptoms for the schizophrenia network (upper panel) and bipolar I disorder network (lower panel). Four different centralities were measured: Katz, betweenness, closeness, and strength. par; paranoid delusion, rfr; delusion of reference, doc; delusion of being controlled, ah; auditory hallucination, vh; visual hallucination, dsr; disorganized behavior, frm; thought form disorder, grn; grandiose delusion, rlg; religious delusion, ero; erotic delusion, glt; delusion of guilt, avl; avolition, anh; anhedonia, mut; mutism, brd; thought broadcasting, ins; thought insertion, oc; obsession/compulsion, pho; phobia.

Table 2. Network comparison test Results between schizophrenia and bipolar I disorder symptom networks.

Measure	Schizophrenia	Bipolar I disorder	Compared value	P value
Network Structure (M)			2.154	0.012*
Global Strength (S)	12.585	17.025	4.44	0.244

*Statistically significant results (P value < 0.05).

a singular cluster among individuals, with network analysis revealing that negative symptoms were predominantly the central symptom. Conversely, manifold analysis results in patients with bipolar I illness have indicated two different clusters, with positive symptoms, including paranoid delusions, as the central symptom in network analysis.

A unique contribution of our study is the application of manifold analysis to further explore the critical role of negative symptoms in schizophrenia. Through this approach, we demonstrated that negative symptoms could be accurately predicted based on 2D U-MAP coordinates using SVM classification (Table 1, Fig. 1c). This finding highlights the distinct patterns these symptoms exhibit within the manifold space. Notably, we observed a positive correlation between the number of negative symptoms and the cumulative count of psychotic symptoms, which demonstrated a gradual and consistent increase along a specific trajectory (Fig. 1a, b). This finding suggests that the presence of negative symptoms may be linked to more severe overall symptomatology.

In parallel, our analysis revealed distinct clustering of bipolar I disorder patients into two groups in the U-MAP projection space. Notably, cluster 1 (Fig. 2c) characterized by a high prevalence of psychotic symptoms. This observation aligns with the DSM-5 specifier that differentiates between bipolar I disorder with and without psychotic features [48], suggesting that psychotic features may have a significant impact on the symptom profile of the disorder (Fig. 2b, c). However, interpretations based on manifold analysis should be

Table 3. Comparison of clinical characteristics between schizophrenia patients with and without avolition.

	Symptom dimension				χ^2(df)	P value
	Avolition (+)		Avolition (−)			
	N	(%)	N	(%)		
Suicide					0.92(1)	0.337
Yes	26	21.0	25	15.8		
No	98	79.0	133	84.2		
Clozapine use					21.7(1)	0.000[a]
Yes	72	58.1	47	29.7		
No	52	41.9	111	70.3		
Deterioration					43.8(1)	0.000[a]
Yes	54	43.5	14	8.9		
No	79	56.5	144	91.1		
Remission					7.74(1)	0.005[a]
Yes	36	36.4	32	61.5		
No	63	63.6	20	38.5		
Severity					6.83(1)	0.009[a]
Severe	53	54.6	16	30.8		
Not severe	44	45.4	36	69.2		

[a]Statistically significant results (P value < 0.01).

approached with caution, as projection methods like U-MAP can potentially distort the original coordinate relationships [38].

While manifold analysis provided an overview of symptom co-occurrence pattern, network analysis offered detailed insights into symptom-level interactions. Our network analysis confirmed the well-established impact of negative symptoms in schizophrenia. Using the walk trap algorithm, we identified three core negative symptoms – avolition, anhedonia, and mutism – that formed a distinct and cohesive community (Fig. 3a). Among these, avolition stood out as particularly influential, ranking second in strength and showing the highest Katz centrality in the network (Fig. 4a).

NCT results indicated the distinct topology in symptoms networks between schizophrenia and bipolar I disorder patients. Being more specific, for negative symptoms, unlike schizophrenia, bipolar I disorder showed no links with other symptom communities. While negative symptoms are also present in bipolar disorder [21, 22, 33], as shown in our analysis, they do not constitute core symptoms in this condition. Rather, paranoid delusions and delusions of reference were highly ranked in Katz centrality (Fig. 4b), indicating their critical influence within the bipolar symptom network. Additionally, in bipolar I disorder, positive symptoms adjoined to form communities which are different from ones identified in schizophrenia. Strong intra-community links suggest that bipolar I disorder may exhibit a tendency for symptom co-occurrence within clusters, particularly emphasizing the strong co-occurrence of positive symptoms – a pattern also indicated in the manifold analysis (Fig. 2a). However, cross-group comparisons should be interpreted with caution as quantitative comparison between node centrality did not have statistical difference in NCT.

Moreover, it is important to note that in schizophrenia, similar symptoms formed distinct communities that aligned with conventional categories — such as delusions grouped together or thought disorders grouped together — whereas in bipolar I disorder, the symptoms were interconnected and blended across these communities. Although the effect of mood symptoms on the symptom network of bipolar disorder [49] has not been considered, our findings of interconnected features of psychotic and anxiety symptoms during the entire disease course could provide psychopathological and therapeutic insights.

Since the disorder's initial description, negative symptoms have been regarded as a central feature of schizophrenia [6, 50, 51]. Prior research has frequently reported the presence of negative symptom-like traits, such as social withdrawal and anhedonia, in children and adolescents with schizophrenia [52, 53], and greater severity of these symptoms has been linked to a longer duration of untreated psychosis [54]. Numerous network studies also underscore the importance of negative symptoms in shaping cognition and global functioning [33, 34, 55]. Our findings similarly highlight avolition as a symptom with a strong influence on multiple clinical dimensions and treatment approaches, although other work points to anhedonia as having the highest expected influence [34]. Such discrepancies may reflect differences in centrality metrics and study methodologies. Moreover, because DIGS evaluates whether a given symptom persists throughout the entire illness course, our observations suggest that a history of avolition could have lasting clinical significance.

Extending the observation that negative symptoms are important in schizophrenia, we focused on avolition in particular within our cohort, building on prior research highlighting the impact of negative symptoms on patient functioning and clinical outcomes [50, 56, 57]. Recent studies further underscore the centrality of avolition among negative symptoms and its relevance as a key target for treatment development [58, 59]. Hence, we examined whether the presence of avolition could impact the course and prognosis of the illness in schizophrenia. Using DIGS data intended to assess the course and prognostic outcome, we found that group who had experienced avolition exhibited a higher rate of clozapine use, a greater tendency for deterioration, a decreased remission rate, and a larger proportion of severe cases (Table 3). In particular, substantial disparity in clozapine use was found between patients with and without avolition. These findings could reflect a higher possibility of treatment resistance in patients with negative symptoms, as evidenced by previous reports [55, 60, 61]. On the other hand, it could be related to the superior efficacy of clozapine not only for positive symptoms but also negative symptoms of schizophrenia

[62]. Through a comprehensive analysis, we determined the predictive significance of avolition, supporting the results of prior investigations.

Beyond avolition, our analyses also revealed important contrasts in the overall connectivity of symptom networks between schizophrenia and bipolar disorder, which hold further therapeutic implications. The reduced connectivity of symptom network in schizophrenia suggests resistance to treatment, as individual symptoms may operate independently and persist without the interconnections necessary for overall improvement [63]. In schizophrenia, each symptom might have distinct pathophysiological mechanisms and thus should be considered as an independent treatment target. Achieving overall improvements in the broad construct may not be realistic due to the loosely connected network and the independence of individual domains in schizophrenia. Clinical trials should focus on specific domains instead of the overall construct. The higher density and interconnectedness in our bipolar disorder symptom network suggest a shared underlying cause. This calls for a holistic treatment approach addressing these co-occurring symptoms. Furthermore, a newly formed symptom community based on different subdomains could be a focus for treatment in bipolar disorder.

There were several limitations in our study. First, our research largely focused on examining the long-term development of symptoms in individuals, offering a thorough understanding of their symptomatology. However, it is crucial to acknowledge that our study was cross-sectional in design, and we did not perform a direct longitudinal analysis of symptom progression. Nevertheless, the cumulative nature of the DIGS data provides indirect but valuable insights into lifetime symptom occurrence, allowing for cautious inferences about symptom progression. Second, we collected symptoms in a binary manner, categorizing them as present or absent without taking into account their level of severity. Our bootstrap analysis indicated that centrality measurements and connectedness may exhibit variability in terms of their reliability. The binary nature of our data might not provide the granularity needed to fully capture the complexity of connections provided by continuous data. This lack of granularity could affect the accuracy of our interpretations. Third, the DIGS interview, which served as our primary symptom assessment tool, did not include several key negative symptoms, such as alogia, asociality, and blunted affect. The absence of these critical symptoms may have limited the comprehensiveness of our negative symptom analysis. Addressing this limitation in future research could provide a more detailed understanding of the role of negative symptoms in the disorder and further refine symptom network interpretations. Finally, as a result of the constraints imposed by our limited sample size, we were unable to perform a comprehensive analysis to differentiate between schizophrenia and schizoaffective illness. Subsequent investigations utilizing more extensive datasets could enhance our comprehension of these aforementioned conditions. In brief, this work makes significant contributions to the field, although it is crucial to acknowledge the limitations that may impact the interpretation of our findings.

Building upon a growing body of evidence underscoring negative symptoms in schizophrenia [50, 64, 65], our findings demonstrate their pivotal role in shaping the disorder's overall symptom profile. By contrast, bipolar I disorder is marked by a higher centrality of positive symptoms and stronger interconnections among psychotic features. The distinctive pattern of psychotic symptom centrality between schizophrenia and bipolar I disorder may be better understood through a more detailed analysis of their interactions with mood symptoms, an area that remains crucial for future research. Exploring these interactions could provide valuable insights into the shared and unique features of these disorders. Additionally, the overlapping symptom profiles of bipolar I disorder with psychotic features and schizophrenia spectrum disorders underscore the limited stability of strict diagnostic categories, raising questions about their clinical utility [31, 66–69]. This calls for a reconsideration of symptom-based clustering, which may offer better prognostic value than traditional diagnoses [25, 70–72]. By emphasizing symptom patterns and their clinical implications, we can further advance our understanding of these complex conditions. Ultimately, such a shift toward symptom-focused approaches may enhance both our conceptualization and management of challenging psychiatric disorders.

DATA AVAILABILITY

The data that support the findings of this study are not publicly available due to confidential concerns. However, de-identified individual participant data are available from the corresponding author upon reasonable request and with approval from the Institutional Review Board, in accordance with institutional and regulatory guidelines.

CODE AVAILABILITY

All codes used in the analysis are available in https://github.com/aktivhoon/scz_bip_manifold.

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ACKNOWLEDGEMENTS

We would like to thank the participants who took part in this study.

AUTHOR CONTRIBUTIONS

YHK, JJ, NK, JHJ, JK, YMA, YSK, and SHK contributed to the study concept and the overall design. JJ, NK, JHJ, YMA, YSK, and SHK collected the clinical data. YHK, JK performed the statistical analysis. YHK, YSK, SHK drafted this manuscript. All authors critically reviewed the manuscript and approved the final version.

FUNDING

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (no. HL19C0026).

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of Seoul National University Hospital (approval no.: 0106-080-002), and all participants provided written informed consent in accordance with the Declaration of Helsinki and relevant institutional guidelines. All methods were performed in accordance with the relevant guidelines and regulations.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41398-025-03403-6.

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