Revealing Differential Psychotic Symptom  
patterns in Schizophrenia and Bipolar I Disorder  
by Manifold Learning and Network Analysis

Abstract

The field of psychiatry has encountered ongoing challenges in understanding the intricate nature of psychotic symptoms, particularly when they manifest in individuals diagnosed with either bipolar disorder or schizophrenia. Here, we utilize manifold and network analyses to investigate whether the symptom occurrence pattern between schizophrenia and bipolar I disorder would differ. The analysis conducted in this study utilizes data collected from a sample of total 555 individuals, with 282 diagnosed with schizophrenia-related disorders and 273 diagnosed with bipolar I disorder. Within the context of schizophrenia, the manifold analysis demonstrated that negative symptoms, specifically avolition, exert a prominent influence over the array of symptoms experienced by individuals. The findings from network analysis provide further support for the notion that avolition exhibits a high degree of centrality. Avolition is a clinically relevant phenomenon that has been found to be associated with the use of clozapine, patterns of deterioration, tendencies towards remission, and the severity of illness. In contrast, bipolar I disorder exhibits discernible patterns wherein positive symptoms assume a central role in network analysis. The application of manifold analysis reveals an unexpected partitioning of patients into two distinct clusters. In conclusion, schizophrenia and bipolar I disorder, while sharing psychotic symptoms, exhibit distinct co-occurrence patterns. Schizophrenia emphasizes negative symptoms, whereas bipolar I disorder highlights positive symptoms, and the strength of associations between these symptoms varies, with bipolar I disorder displaying stronger connections between psychotic symptoms. These findings underscore the complexity of psychotic symptom patterns and their relevance for understanding psychiatric disorders.

**1. Introduction**

The distinction between bipolar disorder and schizophrenia has long been a subject of discussion in psychiatry. [1, 2] Emil Kraepelin’s pioneering work to classify the major psychosis into “manic-depression” and “dementia praecox” has been a fundamental assumption in psychiatry since the early 20th century. [3–5] Eugen Bleuler added to the discussion by emphasizing the central role of negative symptoms in schizophrenia. [6] The overlapping phenomenology and neurobiological basis of schizophrenia and bipolar spectrum disorders, especially bipolar I disorder, have made differentiation challenging. [7–10] Kraepelin himself recognized the difficulties in applying the dichotomy he had suggested. [11, 12] The expanded application of second generation antipsychotics as mood stabilizers has added to the difficulty of the task. [13–16] Understanding the historical context and difficulties associated with distinguishing these disorders sets the stage for investigating their shared characteristics and the complexities of their distinction. Nevertheless, the distinction between the two disorders has significant clinical implications, including treatment selection and prognostic values. [17] Specifically, they share psychotic symptoms, which represent the boundary between two distinct disorders. Traditional Schneiderian first-rank symptoms for schizophrenia are also common in bipolar disorders, [18, 19] and the presence of particular psychotic symptoms therefore, lacks diagnostic value. Furthermore, negative symptoms such as anhedonia and avolition have been observed in patients with bipolar disorder, persisting even during periods devoid of mood episodes. [20–22] In the case of bipolar disorders with psychotic features, misdiagnosis as schizophrenia frequently occurs, which delays adequate treatment and worsens the prognosis. [23–26] Psychotic symptoms consist of multi-dimensional phenomena. [27–29] Beyond the major categories such as hallucination, delusion, disorganized behaviors, thought process abnormalities, and negative symptoms, each dimension has sub-dimensions. Hallucinations can be divided according to the perception modalities, including auditory, visual, tactile, olfactory, and gustatory. Delusion also has multiple sub-dimensions according to its thought content topics, such as paranoid, persecutory, grandiose, religious, somatic, erotic, and so on.

Patterns of multiple psychotic symptoms could be different between disorders. For example, delusions of grandiosity and religious themes appear to be highly correlated with manic episodes. [30, 31] The appearance of sub-symptoms in negative symptoms are, as well, different between schizophrenia and bipolar disorders. [22, 32, 33] Moreover, each symptom domain has interconnections, and links between them form symptom networks. [33-37] Although the presence of single psychosis-related symptoms may not have diagnostic value to differentiate schizophrenia from bipolar disorder, the analysis of complex patterns between symptoms may reveal differences between the two conditions. By examining the interaction 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.

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

In addition to manifold analysis, our study also utilized network analysis as a complementary method for comprehending 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 the various symptom domains. [34, 5] This combined approach of manifold analysis and network analysis offers a comprehensive framework for elucidating the intricate symptom profiles and illuminating the underlying dynamics of schizophrenia and bipolar disorder. In addition, we examined the clinical implications by examining the associations between core symptoms, symptom patterns, and pertinent outcomes, such as hospitalization dates and medication use.

**2. Material and methods**

2.1 Participants and Data collection

From the Seoul National University Hospital in Korea, we recruited patients with schizophrenia, schizoaffective disorder, and bipolar I disorder. Each participant met the DSM-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] DIGS is distinguished by its poly-diagnostic capability and detailed assessment 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, as it comprises clinical outcomes such as the number of suicidal attempts, deterioration pattern, and remission rate, in addition to ratings of psychotic symptoms that are not associated with the diagnosis.

The participants with a history of any kind of organic brain disease, substance or drug abuse, or other physical conditions which can cause psychiatric symptoms were excluded. The total number of subjects which were included in this study was 555 patients with schizophrenia, schizoaffective disorder, or bipolar I disorder (287 male, 268 female; mean [SD] age, 33.4 [10.7]). Among these participants, 282 were diagnosed as schizophrenia or schizoaffective disorder, and 273 met the criteria for bipolar I disorder.

In this research, all individuals who took part in the study granted their consent in writing after being adequately informed. The protocol for the study was approved by the ethics committee of Seoul National University Hospital, under the Institutional Review Board (IRB) approval number 0106-080-002.

2.2 Data Processing

In the data processing phase of our study, we obtained information we collected through DIGS. In our study, symptoms were included in the analysis if they were observed in a minimum of five percent of individuals diagnosed with both schizophrenia and bipolar disorder. Eighteen symptoms related to psychosis or anxiety were selected based on these specific 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. Hallucinatory symptoms were collected as well, specifically auditory and visual hallucinations, as olfactory, gustatory and tactile hallucinations were seldom reported. Delusional self experience, [42] covering delusion of being controlled, thought broadcasting, and thought insertion was collected as well. Negative symptoms were gathered, which included avolition, anhediona, and mutism. Furthermore, we procured information on thought form disorders and disorganized behaviors. Obsessions and compulsions were considered as a composite symptom entity (obsession & compulsion), and phobia were also integrated into the assessment.

The evaluation of all symptoms was centered on their lifetime occurrences rather than their present state. This approach allowed for a binary data collection method, categorizing symptoms as present or absent.

2.3 Statistical Analysis

In this study, we collected information on a total of eighteen psychotic and anxiety-related symptoms from each participant. In order to effectively manage the complex and multidimensional nature of the symptom data, we implemented an advanced dimensionality reduction technique known as Uniform Manifold Approximation and Projection (U-MAP). The U-MAP algorithm functions by initially generating a high-dimensional graph representing the data, which is subsequently projected optimally into a lower-dimensional space. By employing this approach, which preserves the local and global structure of the data while facilitating visualization and analysis of the symptom distribution in a reduced dimensional space, manifold learning is especially well-suited for this purpose. [38] The significance of this aspect 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.

Further, to delve deeper into the patterns identified through U-MAP, we utilized Support Vector Machine (SVM) analysis. [43] The SVM 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 in our study. 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, specifically accuracy. The Python programming language was used to implement the U-MAP and SVM algorithms.

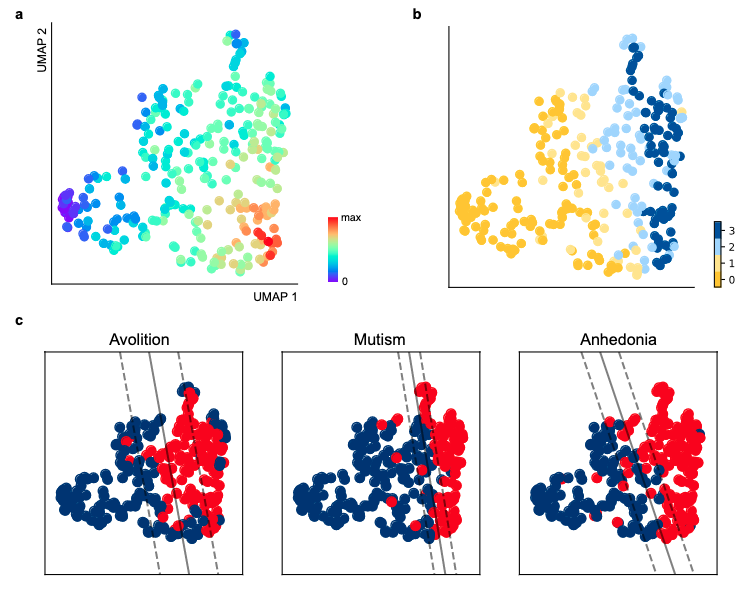
For network analysis, we used the eLasso method that the IsingFit package in R. [44] Through the construction of a symptom network structure, this method enabled us to examine the interconnections and interactions among symptoms within the network structure, thus unveiling their connectivity and centrality. The eLasso method allowed us to gain a more comprehensive understanding of the intricate relationship 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 strengths. 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. In addition, we employed the Katz centrality, a measure that 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. Using Katz centrality, we were able to pinpoint symptoms in our study that, although not necessarily linked in the most direct way, were influential due to longer pathways in the symptom network.

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 statistical test allowed us to evaluate the potential impact of particular symptom dimensions on a variety of clinical parameters.

**3. Results**

3.1 Manifold analysis for schizophrenia

Manifold analysis tools are potent tools that enable us to recognize patterns in high-dimensional data. Using U-MAP, we reduced into two dimensions the feature space of psychotic and anxiety-related symptoms in schizophrenia patients. The data point's color was then encoded with the number of symptoms the patient has ever experienced. Following along the first axis of U-MAP, the number of symptoms increases gradually. (Fig. 1a) In order to comprehend this pattern, we trained support vector machines (SVM) to predict whether a patient has ever experienced each symptom based on their 2D U-MAP coordinates. Avolition, mutism, and anhedonia are three of the eighteen psychotic and anxiety-related symptoms that SVM appears to predict correctly. (Fig. 1c, Table 1, Fig. S1)



**Fig. 1 a** Symptom manifolds that are projected into 2D space in schizophrenia patients. The colorshows the normalized number of symptoms that the patient has ever had. **b** Scatter plot of peoplewith schizophrenia, with each color representing the number of negative symptoms (avolition, mutism,and anhedonia). The number of negative symptoms is spread out in a comparable way as the totalnumber of psychotic and anxiety symptoms. **c** Using the coordinates in the 2D U-MAP space, asupport vector machine was trained to predict the presence of negative symptoms. Each of the threesymptoms had a well-defined vector support border. Therefore, the presence and absence of thesesymptoms are quite indicative of the diversity of schizophrenia patients.

Positive, negative, and dissociative symptoms, as well as anxiety symptoms such as phobia, obsessions & compulsions, were included in the analysis of psychotic and anxiety-related symptoms. 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 as the color of data points on the 2D U-MAP. The number of negative symptoms mirrored the pattern of the patient's total number of symptoms (Fig. 1b; Pearson's correlation: .606, P value < .001).

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

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3.2 Manifold analysis for bipolar I disorder

Using the same methodology, we reduced the feature space of bipolar I disorder patients' 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 symptoms could, on their own, distinguish between the two clusters.

A diagram of a cluster

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**Fig. 2 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 wasperformed on cluster 1, which is the group of patients located at the top left. Greater number ofpsychotic and anxiety-related symptoms have been experienced by the majority of patients. **c** For cluster 2, the group of patients located in the lower right-hand corner, a manifold reduction hasbeen performed. Unlike cluster 1, patients in this cluster have exhibited a relatively lesser number ofpsychotic and anxiety-related symptoms.

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

3.3 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. In this section, we focus on the results of the network analyses for both disorders.

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**Fig. 3 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

Using random walk community clustering, we discovered that for schizophrenia, the 18 symptoms 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 delusion of being controlled, thought broadcasting and insertion were grouped together, which is consistent with their shared association with the destruction of the self. Hallucinatory symptoms, such as auditory and visual hallucinations, were grouped together, were separated from the other psychotic symptoms, with auditory hallucination having a weak connection with delusional 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 and insertion. Notably, the three negative symptoms (avolition, mutism, and anhedonia) were grouped into the same community, which is consistent with our manifold analysis, which demonstrated 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 strengths centralities of the symptom network. In patients with schizophrenia, avolition had the highest Katz, betweenness, and closeness centrality scores and was ranked second for strengths centrality, demonstrating a high ranking in all four centrality measures. Other negative symptoms grouped 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, but sixth for strengths. This can be confirmed by examining the network, as disorganized behavior serves as a hub between various symptom communities, although its strength appears to be weaker than avolition. Other symptoms, which ranked highly in certain centrality measurements, were inconsistent in other centrality assessments. (Fig. 4a)

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**Fig. 4 a, b** Centrality measure of psychotic and anxiety related symptoms, for the schizophrenia network (upper panel) and bipolar I disorder network (lower panel). Four different centralities weremeasured: Katz, betweenness, closeness, strenghts.  
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

The 18 symptoms of bipolar I disorder formed eight distinct communities. (Fig. 3b) Obsession/compulsion and phobia formed a community, with obsession/compulsion linked to positive symptom group via paranoid and guilt delusion. 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 classified into distinct categories within the context of bipolar disorder. Consistent with schizophrenia, religious and grandiose delusion 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 in a manner comparable to the network for schizophrenia as well. 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 hallucination. 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 has, on average, higher values for most centrality measures (except betweenness). In bipolar I disorder patients, delusion of reference and paranoid delusion exhibited high centralities across all four measures.

These network analyses provide additional insight 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. In order to assess the stability of the network estimated from the data, we employed the bootstrapping technique. Strength exhibited strong resilience to subsampling, whereas betweenness and closeness shown greater susceptibility to bootstrapping. The 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 both zero. (Fig. S2) The bootstrap confidence intervals for the edge weights exhibited significant overlap. (Fig. S3)

3.4 Clinical characteristics of schizophrenia patients depending on avolition

**Table 2** Comparison of clinical characteristics between schizophrenia patients with and without avolition.

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On the basis of observations derived from manifold analysis and network analysis, avolition emerges as a primary symptom of schizophrenia, encompassing a constellation of lifelong psychotic and anxiety-related manifestations. Consequently, avolition 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 use of clozapine.

Among various clinical characteristics, clozapine use, deterioration, remission pattern, and severity have statistically significant differences between the two (Table 2; all P values <.01). More specifically, schizophrenia patients with avolition had a higher rate of clozapine use, a worse pattern and severity of deterioration, and a lower remission rate. However, the suicide rate did not differ significantly between the two groups (Table 2).

**Discussion**

Since the disorder's initial description, negative symptoms have been regarded as a central feature of schizophrenia. Prior research has frequently reported the presence of negative symptom-like traits, such as social withdrawal and anhedonia, in children and adolescents with schizophrenia. [45, 46] The severity of negative symptoms correlates with the duration of untreated psychosis, [47] and the association between negative symptoms and cognition or global functioning, has been examined in several studies utilizing network analysis. These investigations have consistently revealed the importance of negative symptoms, such as avolition or anhedonia, as central features within the symptom network of schziophrenia. [33, 34, 38]

The significant position of negative symptoms within the symptom profile of schizophrenia is supported by our manifold analysis. The presence of negative symptoms, namely avolition, mutism, and anhedonia, could be accurately predicted based on the 2D U-MAP coordinates in SVM analysis. (Table 1, Fig. 1c) This suggests that these symptoms have distinct patterns in the manifold space, and therefore their presence or absence can provide valuable information regarding the diversity of schizophrenia patients. The cumulative count of psychotic symptoms exhibited by individuals diagnosed with schizophrenia demonstrated a gradual and consistent increase in a specific trajectory, with a positive correlation observed between the number of negative symptoms and this cumulative count. (Fig. 1a, b) Hence, it is plausible to propose that the existence of negative symptoms could be linked to a greater severity of symptomatology among individuals diagnosed with schizophrenia.

Based on the findings, we were able to derive the hypothesis that negative symptoms could potentially act as influential factors in the interconnected symptom clusters in schizophrenia, and we validated our hypothesis through the application of network analysis. Looking at the symptom community derived through the utilization of the random-walk algorithm, three negative symptoms, including avolition, anhedonia, and mutism were closely associated and formed a single community. (Fig. 3a) In addition, avolition ranked second for strength and possessed the highest centrality with respect to Katz, betweenness, and closeness. Integrating the results from both manifold and network analysis, it appears that negative symptoms might potentially influence the emergence and evolution of other symptom dimensions in individuals with schizophrenia. (Fig. 4a)

Extending the observation that negative symptoms are important, we focused on avolition in particular within our cohort, building on prior research that highlights the impact of negative symptoms on patient functioning and clinical outcomes. [49-51] Here, we could examine 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 those who had experienced avolition exhibited a higher prevalence of clozapine use, a greater tendency for deterioration, a decreased remission rate, and a heightened proportion of severe cases. (Table 2) In particular, substantial disparity in the utilization of clozapine was found between patients with and without avolition. The findings could reflect the relationship between the higher possibility of treatment-resistance in the patients with negative symptom as evidenced by previous reports. [48, 52, 53] On the other hand, it could be related to the clozapine's superior efficacy to not only positive symptoms, but also negative symptoms in schziophrenia. [54] Through a comprehensive analysis, we also have determined the predictive significance of avolition, supporting the results of various prior investigations.

Previous research has identified avolition as a significant negative symptom in schizophrenia. [6, 33, 48, 49, 55] These findings align with our own findings, which highlight the significant influence of avolition on patient clustering, multiple symptom dimensions, patient outcomes, and treatment approaches. One recent network analysis also reported the high centrality of negative symptoms and their connections with multiple functional domains. However, anhedonia demonstrated the highest expected influence value, followed by avolition in the psychotic symptom network [34] This discrepancy in the most influential negative symptom within the symptom network may be explained by methodological differences, such as the choice of centrality metric used. Furthermore, DIGS assesses if a specific symptom has consistently manifested throughout the illness's entire duration. Hence, our findings can suggest that a history of avolition may have clinical significance in shaping the long-term progression of the disease, rather than merely its presence in a cross-sectional context. Further investigation will be necessary to delve into the specific clinical implications of avolition, a motivational deficit, in contrast to anhedonia, an affective dysfunction, within the context of schizophrenia.

In contrast to schizophrenia, in bipolar disorder symptom network, a community of negative symptoms, including anhedonia, mutism, avolition, showed missed link from other symptom communities. Intriguingly, our analysis reveals that it is the positive symptoms that assume a central role in the symptom network of bipolar disorder. To be more specific, paranoid delusion and delusion of reference were highly ranked in the betweenness, closeness, and Katz centrality measures. (Fig. 4b) Formation of fewer symptom communities and stronger connectivity between positive psychotic symptoms in the bipolar I disorder was demonstrated, in comparison to schizophrenia. The connection between anxiety-related symptoms and psychotic symptoms is another notable consequence of bipolar I disorder. The intra-connectivity between community was high, as was their inter-connectivity with the positive symptom, which indicates that these symptoms co-occur frequently with positive symptoms. We could cautiously suggest that bipolar I disorder tends to exhibit symptoms witha notable likelihood of symptom co-occurrence within each cluster, particularly highlighting the high co-occurrence of positive symptoms based on this observation. (Fig. 2a)

The distinct clustering of bipolar I disorder patients in the U-MAP projection space also supported the symptom co-occurrence pattern. It appears to be consistent with the DSM-5 specifier that differentiates between bipolar I disorder with and without psychotic features, [56] meaning that psychotic features may have a significant impact on the symptom profile of the disorder. (Fig. 2b, c) Indeed, cluster 1 in the U-MAP analysis (Fig. 2c) of bipolar I disorder, which has a high prevalence of psychotic symptoms, appears to be located on the boundary of both the psychosis spectrum and the bipolar spectrum. Given the overlap in symptomatology, as evidenced by this observation the findings could support the continuum spectrum from bipolar disorder to schizophrenia as unitary psychosis. [57-59]

DIGS has advantage to evaluate the detailed multi-dimensional psychiatric symptoms for the entire period of illness, enabling us to compare how these detailed symptoms are clustered in schizophrenia and bipolar I disorder. [41] In schizophrenia, similar symptoms formed distinct communities, while in bipolar disorder, these symptoms were interconnected and blended into communities. For example, auditory and visual hallucinations formed a community in schizophrenia, but were separated in bipolar disorder. Obsessive-compulsive symptoms was outside the psychotic symptom network in schizophrenia, but was linked to other delusions in bipolar disorder. Delusional self-experiences like thought insertion, thought broadcasting, and delusion of being controlled form a community in schizophrenia, but are scattered in bipolar disorder. Although mood symptom affecting the symptom network of bipolar disorder has not been considered, [60] the present findings of interconnected feature of psychotic and anxiety symptoms during the whole course of illness could provide the psychopathological and therapeutic insight.

The density and interconnectedness difference in symptom network between schizophrenia and bipolar disorder have therapeutic implications. The reduced connectivity observed in schizophrenia suggests resistance to treatment, as individual symptoms may operate independently and persist, without the necessary interconnections for overall improvement. [61] In schizophrenia, each symptom might have distinct pathophysiological mechanisms and thus should be considered as independent treatment targets. 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 may benefit by focusing on specific domains instead of the overall construct. The higher density and interconnectedness in our study's 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 are 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. Nevertheless, it is crucial to acknowledge that we did not do a cross-sectional analysis of symptom incidence. However, the utilization of a longitudinal strategy provides a distinct and valuable viewpoint on the progression of symptoms. Secondly, we gathered symptoms in a binary manner, classifying them as either present or absent, without taking into account their level of severity. Although this simplification may fail to capture certain nuances, it also serves to clarify underlying patterns in psychiatric conditions such as schizophrenia and bipolar disorder. Furthermore, our bootstrap research has indicated that centrality measurements and connectedness may exhibit variability in their reliability as outcomes. The binary nature of our data could be a factor, as it might not provide the granularity needed to fully capture the complexity of connections, compared to continuous data. This lack of granularity could affect the accuracy of our interpretations. Therefore, while our findings shed light on networks associated with schizophrenia and bipolar disorder, we see value in pursuing further studies using different analytical methods for a more nuanced understanding. Finally, as a result of the constraints imposed by our limited sample size, we were unable to do a comprehensive study to differentiate between schizophrenia and schizoaffective illness. Subsequent investigations utilizing more extensive datasets have the potential to enhance our comprehension of these aforementioned circumstances. In brief, this work provides significant contributions to the field, although it is crucial to acknowledge the limitations that may impact the interpretation of our findings

Our findings add to the growing body of evidence demonstrating the importance of negative symptoms in schizophrenia by highlighting their central role in shaping the overall symptom profile of the disorder. This lends credibility to the notion that schizophrenia's negative symptoms are fundamental and influence many different aspects of the disorder. [50, 62, 63] The potential clinical implications of taking these symptoms into account in diagnosis and treatment are also highlighted by our study. Furthermore, the relatively low centrality of negative symptoms in bipolar I disorder highlights the significance of negative symptoms in schizophrenia. In contrast, bipolar I disorder is characterized by a greater centrality of positive symptoms as well as a strong connection between psychotic symptoms. Importantly, we assessed the co-occurrence of symptoms longitudinally, as opposed to cross-sectionally. For many cases of bipolar I disorder with psychotic features and schizophrenia spectrum disorders, diagnostic stability is known to be inadequate, calling into question the utility of strict distinctions. [31, 64-67] Instead, symptom-based clustering beyond the diagnosis may have better clinical implications, including prognostic value. [57, 68, 69] By examining symptom patterns and their clinical implications, we can acquire a deeper understanding of these complex disorders. We hope to improve our understanding and management of these challenging psychiatric disorders by focusing on symptom patterns rather than diagnostic categories.

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**Fig. S1** In this analysis, a support vector machine utilized 2D U-MAP coordinates to classify individuals based on the presence of negative symptoms, with red dots representing symptomatic schizophrenia patients and blue dots indicating those without symptoms.

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**Fig. S2** Bootstrapping result of edge weight accuracy with 95% confidence interval for **a** schizophrenia and **b** bipolar I disorder.

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**Fig. S3** Bootstrapping result of the centrality measures in a schizophrenia and b bipolar I disorder. Lacking variance, closeness is not visually represented.