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Psychopathological networks in psychosis: Changes over time and clinical relevance. A long-term cohort study of first-episode psychosis

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ABSTRACT

Background: First-episode psychosis is a critical period for early interventions to reduce the risk of poor outcomes and relapse as much as possible. However, uncertainties about the long-term outcomes of symptomatology remain to be ascertained.

Methods: The aim of the present study was to use network analysis to investigate first-episode and long-term stages of psychosis at three levels of analysis: micro, *meso* and macro. The sample was a cohort of 510 patients with first-episode psychoses from the SEGPEP study, who were reassessed at the long-term follow-up (n = 243). We used the Comprehensive Assessment of Symptoms and History for their assessments and lifetime outcome variables of clinical relevance.

Results: Our results showed a similar pattern of clustering between first episodes and long-term follow-up in seven psychopathological dimensions at the micro level, 3 and 4 dimensions at the *meso* level, and one at the macro level. They also revealed significant differences between first-episode and long-term network structure and centrality measures at the three levels, showing that disorganization symptoms have more influence in long-term stabilized patients.

Conclusions: Our findings suggest a relative clustering invariance at all levels, with the presence of two domains of disorganization as the most notorious difference over time at micro level. The severity of disorganization at the follow-up was associated with a more severe course of the psychosis. Moreover, a relative stability in global strength of the interconnections was found, even though the network structure varied significantly in the long-term follow-up. The macro level was helpful in the integration of all dimensions into a common psychopathology factor, and in unveiling the strong relationships of psychopathological dimensions with lifetime outcomes, such as negative with poor functioning, disorganization with high antipsychotic dose-years, and delusions with poor adherence to treatment. These results add evidence to the hierarchical, dimensional and longitudinal structure of psychopathological symptoms and their clinical relevance in first-episode psychoses.

1. Introduction

Schizophrenia spectrum and other psychotic disorders exert a significant burden under current systems of care, and they are among the costliest illnesses worldwide (Rössler et al., 2005). Although mental health systems provide early intervention programs, first-episode psychosis (FEP) patients are at high risk for developing moderate to severe impairments in cognitive and psychosocial functioning over time.

Consistent evidence from recent decades has supported the existence of dimensional phenotypes underlying psychosis that complement traditional categorical diagnoses. Both approaches can be integrated into a hybrid model that provides great advantages for clinical practice and research (Bornovalova et al., 2020; Michelini et al., 2021; Peralta et al., 2021a; Quattrone et al., 2019). Numerous studies have aimed to clarify the relationship between psychotic symptoms, identify underlying psychosis dimensions (Allardyce et al., 2007), and, most recently, identify transdiagnostic dimensions across all mental disorders (Kotov et al., 2018). It is now widely accepted that the psychosis construct is

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multidimensional, comprising underlying layers that differ in number depending on the depth of statistical analysis (Cuesta and Peralta, 2001; Kotov et al., 2018; Peralta et al., 2013).

Network analysis allows for the study of individual interactions between symptoms. It is this interaction between symptoms that is conceptualized in network theory as a mental disorder (Borsboom, 2017). Network analysis can provide information about the visual structure of the network, the presence of clusters or symptoms that tend to be closely related, and the centrality and relative importance of specific symptoms. Therefore, this methodology can facilitate the identification of symptoms that play a relevant role in the network.

To date, five cross-sectional studies (Isvoranu et al., 2017; Peralta et al., 2020; Strauss et al., 2019; van Rooijen et al., 2018; van Rooijen et al., 2017) and one short-term longitudinal study (Piao et al., 2021) have been published that used network analysis methodology to examine the interrelationships of symptoms in psychosis. However, it is unknown to what extent the network structure of psychosis dimensions could change over the long term in first-episode psychosis. Moreover, in three of the five studies, symptoms in network analysis were grouped into predefined clusters, following the test arrangement.

To examine the structural complexity of the dimensional phenotypes of the psychopathology of psychosis and to better account for their integrated relationships, we carried out our study using three levels of analysis of the data: micro-, meso- and macro-analysis. The unit of observation at the micro-level is the symptom. The meso-level corresponds to an intermediate level, indicating the interrelationships of psychopathological dimensions. Finally, the macro-level involves high-order psychopathological dimensions.

We proposed two hypotheses in this study. The first is that the overall network pattern remains unchanged across disease stages and over time. The second hypothesis is that the interrelationships among symptoms, dimensions and domains change depending on the severity at different stages of the disease.

Network analysis is one of the most advanced strategies for a fine analysis of the structure of symptomatology of psychosis. However, to gather a deeper insight into the clinical relevance of the resulting network in the long-term stages of FEP patients, the inclusion of relevant outcome measures is required.

There were three aims in this study. First, we ascertained whether the structure of psychopathological symptoms, dimensions and domains of psychopathology remains invariant over time between first-episode psychosis and long-term follow-up. To achieve this goal, we used network analysis at three levels of analysis: macro, *meso* and micro. Second, we analysed the changes in the interrelationships of psychopathological symptoms, dimensions and domains of psychopathology between FEP and long-term follow-up at three levels. Third, clinical relevance of the resulting networks at macro level was ascertained by examining the interrelationships of psychopathological dimensions and relevant lifetime outcome measures.

2. Methods

2.1. Participants

The current work used data from participants in the SEGPEP study, a longitudinal and naturalistic study of patients with first-episode psychosis. The inclusion criteria consisted of FEP admission patients between 15 and 65 years old with a close relative available to provide background information and to sign a written informed consent form. The exclusion criteria included previous exposure to antipsychotic drugs and prior serious medical or neurological disease or mental disability as defined by an IQ <70. A thorough description of the sample and procedures followed in this study can be found in the study by Peralta et al. (2021b).

Five hundred ten patients were recruited and evaluated during admission due to a first episode of psychosis between 1990 and 2008, referred to here as T1. Two hundred forty-three of the original patients agreed to participate in the second assessment between 2018 and June 2021, assuring that the patients were stabilized and without an acute episode for more than six months, and this cohort was referred to as T2. The main sociodemographic and clinical characteristics of the participants are presented in Table 1.

The subjects underwent a thorough clinical evaluation, including the Comprehensive Assessment of Symptoms and History (CASH)

Table 1
Sociodemographic and clinical characteristics of participants who participated in follow-up vs. those who did not participate.

	Follow-up	Not follow-up	X^2 or t(df)	*p*
Gender Female (%)	106 (43.6)	100 (37.5)	$2.010_{(1)}$	0.156
Male (%)	137 (56.4)	167 (62.5)		
Age at intake	27.5 (9.83)	31.8 (12.6)	$4.197_{(508)}$	<0.001*
Socioeconomic status	3.07 (0.72)	3.16 (0.67)	$1.475_{(508)}$	0.141
Years of education	11.2 (3.37)	10.6 (3.47)	$2.000_{(508)}$	0.046*
CASH global ratings at intake (SD)				
Reality distortion	3.70 (1.40)	3.62 (1.38)	$0.666_{(508)}$	0.506
- Delusions	3.65 (1.46)	3.67 (1.40)	$0.192_{(508)}$	0.847
- Hallucinations	2.21 (1.77)	2.02 (1.87)	$1.134_{(508)}$	0.258
Disorganization	2.36 (1.62)	2.09 (1.58)	$1.892_{(508)}$	0.059
- Bizarre behaviour	1.98 (1.48)	1.83 (1.51)	$1.115_{(508)}$	0.265
- Formal thought disorders	1.74 (1.78)	1.44 (1.69)	$1.917_{(508)}$	0.056
- Attention	2.18 (1.74)	1.69 (1.65)	$3.305_{(508)}$	0.001*
- Inappropriate affect	0.83 (1.33)	0.71 (1.28)	$0.998_{(508)}$	0.319
Negative	1.25 (1.43)	1.30 (1.39)	$0.453_{(508)}$	0.651
- Affective flattening	0.94 (1.41)	1.07 (1.35)	$1.025_{(508)}$	0.306
- Alogia	1.09 (1.45)	1.03 (1.34)	$0.426_{(508)}$	0.670
- Abulia/apathy	1.25 (1.54)	1.40 (1.63)	$1.037_{(508)}$	0.300
- Anhedonia/ asociality	1.68 (1.76)	1.99 (1.89)	$1.884_{(508)}$	0.060
Catatonia	0.83 (1.28)	0.69 (1.20)	$1.326_{(508)}$	0.185
Mania	0.87 (1.48)	0.61 (1.34)	$2.133_{(508)}$	0.033*
Depression	1.21 (1.68)	1.17 (1.69)	$0.279_{(508)}$	0.780
DSM 5 diagnoses, n (%)				
Schizophrenia	72 (29.6)	89 (33.3)		
Schizophreniform disorder	40 (16.5)	39 (14.6)		
Brief psychotic disorder	41 (16.9)	40 (15.0)		
Delusional disorder	16 (6.6)	23 (8.6)		
Schizoaffective disorder	13 (5.3)	12 (4.5)		
Bipolar disorder/ mania	20 (8.2)	23 (8.6)		
Major depressive disorder	29 (11.9)	30 (11.2)		
Psychotic disorder not otherwise specified	12 (4.9)	11 (4.1)		
Sociodemographic and clinical characteristics at follow-up				
Age	48.5 (10.4)			
No. of psychiatric admissions	5.85 (6.24)			
GAF	64.0 (19.8)			
Social functioning – SOFAS total score (lifetime)	65.5 (18.75)			
Adherence to treatment (lifetime)	1.26 (1.41)			
Lifetime antipsychotic dose-years	55 (45.47)			
Illness course, n (%)				
Full remission	73 (30.0)			
Partial remission	149 (61.3)			
Chronic/continuous	59 (24.3)			

* p <0.05.

(Andreasen, 1987; Andreasen et al., 1992) (see supplementary material for a more detailed description). The three levels of analysis were structured as follows. The micro-level analysis consisted of an analysis of the 74 CASH symptoms; the meso-level comprised the 12 global ratings plus inappropriate affect; and the macro-level included six domains of psychopathology commonly found in most factor analyses: reality distortion, disorganization, negative, mania, depression (Allardyce et al., 2007; Demjaha et al., 2009; Heckers et al., 2013) and catatonia (Peralta and Cuesta, 2017).

Ratings were performed by experienced psychiatrists (LMI, EGA, SEGPEP group) who conducted face-to-face interviews with the subjects and collected information provided by treating physicians, clinical records, and significant others. The interviewers showed good interrater reliability (intraclass correlation coefficient > 0.80) on most CASH items. A lifetime diagnosis of a psychotic disorder according to the DSM-5 criteria (APA, 2013) was reached by consensus among the senior authors (V.P. and M.J.C.) using all available information.

Outcome measures: The clinical relevance of the network structure of the symptomatologic dimensions at the long-term follow-up was ascertained at macro level with the inclusion of four lifetime outcomes in the network analysis. The four outcome variables were estimated through lifetime assessment and they were: a final diagnosis of schizophrenia (DSM-5 criteria), psychosocial functioning, adherence to treatment and antipsychotic dose-years. Functional outcome was rated by means of the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992). SOFAS is a 100-point scale with clear descriptions of each 10-point interval. It focuses only on functioning and does not include symptom assessment. All the information collected by means of the CASH interview allowed for the lifetime assessment of adherence to treatment and it was measured on a 6-point Likert scale (where complete lack of adherence to treatment is scored as 5, and ready acceptance of treatment is scored as 0). To evaluate the lifetime exposure to antipsychotic drugs we used the Andreasen et al. (2010) formula. This formula is able to compute chlorpromazine dose equivalents for antipsychotic drugs and multiply these equivalents by the time an individual has been on a given dose to derive a cumulative value measured in dose-years.

The study was approved by the Ethics Committee of the Regional Health Service of Navarra (5–2017, 12/12/2017), and written informed consent was obtained from all study participants or their legal representatives.

2.2. Statistical analysis

We first performed a univariate analysis to compare the sociodemographic and clinical variables of the patients who were followed up and those who were not. There were no missing data in the sample used for this study. Since the data did not show a normal distribution, Spearman's correlation matrices were used to construct the networks.

2.3. Network estimation and analysis

The estimation of the network was based on L1 regularization using extended Bayesian information criterion (EBIC) model selection by means of the graphical least absolute shrinkage and selection operator (gLASSO). Three networks were created for each time point: one at the micro-level (with 74 symptoms), one at the meso-level (with 12 global ratings plus inappropriate affect), and one at the macro-level (with 6 domains). To cluster the nodes at the three levels, we performed an exploratory graph analysis (EGA) using *EGAnet* (Golino and Christensen, 2019), enabling the variables to be grouped empirically with the walktrap algorithm. This procedure was used to evaluate the data from both the T1 and T2 groups. Finally, we created a second macro network at T2, this time including 4 clinical relevant domains lifetime estimated, namely social functioning (SOFAS total score), adherence to treatment, lifetime antipsychotic dose-years and a final diagnosis of schizophrenia.

2.4. Centrality analysis

Centrality indices were also calculated to quantify the importance of each node in the network by estimating 2 indices: strength and expected influence (EI). A bridge centrality analysis was also performed to assess how well a node is connected to other clusters, allowing for a bridge variant of the 2 indices mentioned previously to be obtained.

2.5. Network comparison

Once formed, network structures were compared with each other to determine whether there were any differences between T1 and T2 at the three levels. To determine whether such differences existed, we used the network comparison test (NCT) (van Borkulo et al., 2017) (details in supplementary material).

2.6. Robustness analysis

Edge and centrality stability and the accuracy of the results were estimated via nonparametric and case dropping bootstrapping, respectively. To quantify the stability of the centrality estimates, we employed the correlation stability coefficient (CS coefficient, see supplementary material) (Epskamp et al., 2018).

All of the statistical analyses were carried out with R statistical software using the *qgraph* (Epskamp et al., 2012), *bootnet* (Epskamp et al., 2018) and *networktools* (Jones et al., 2019) R packages.

3. Results

There were some significant sociodemographic and clinical differences between patients who agreed to participate in the follow-up (T2) study and those who did not (Table 1). The subjects who agreed to participate in the follow-up were younger at intake ($t = 4.2$ $p < 0.001$), had more years of education ($t = 2$ $p = 0.046$), and scored higher on the attention ($t = 3.3$ $p = 0.001$) and mania ($t = 2.13$ $p = 0.033$) components of the CASH at intake.

3.1. Micro-level

Fig. 1a displays the network structure at the micro-level analysis of the 74 CASH symptoms of T1 patients. The symptom layout clusters them into 7 main psychopathological clusters: reality distortion, disorganization, diminished expressivity, avolition/anhedonia, catatonia, mania and depression. A visual inspection shows that relationships of individual symptoms within the same domain are stronger than those regarding other domains. The CASH symptom that was most unconnected to the network was delusions of jealousy.

The standardized centrality indices for each node included in the micro-level network (Supplementary Fig. 1) show that the three most relevant symptoms in terms of strength at T1 were depressive mood (dep), illogicality (ill) and inability to feel intimacy/closeness (int). In relation to the bridge centrality indices (Supplementary Fig. 4), which only consider relationships with symptoms from dimensions outside its own, the 3 symptoms with the highest strength in T1 were the inability to feel intimacy/closeness (int), stupor (stu) and poverty of speech (pov). The T1 micro network with the bridge nodes highlighted can be visualised in Supplementary Fig. 8a.

Fig. 1b shows the micro-network in T2. Symptoms were also grouped into 7 domains: reality distortion, diminished expressivity, avolition/anhedonia, mania, depression and two domains of disorganization, including variables of formal thought disorders and bizarre behaviour. The first of the disorganization domains also includes variables of attention and catatonia, and the second includes inappropriate affect. As at T1, the relationships within domains were stronger than those regarding other domains. The presence of negative edges was lower than at T1.

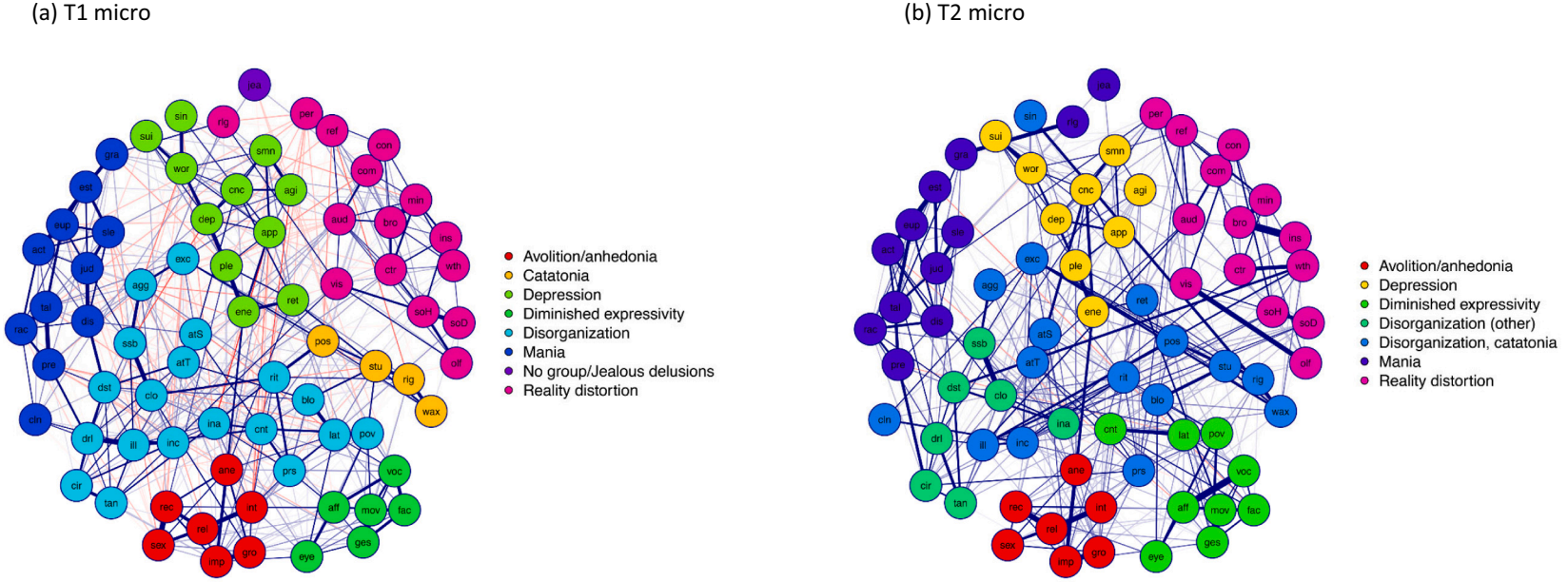

Fig. 1. Micro network structure in (a) T1 and (b) T2.
Symptoms abbreviations: per = Persecutory delusions, jea = Jealousy delusions, sin = Sin/guilt delusions, gra = Grandiose delusions, rlg = Religious delusions, soD = Somatic delusions, ref. = Reference delusions, ctr = Delusions of being controlled, min = Mind reading delusions, bro = Thought broadcasting, ins = Thought insertion, wth = Thought withdrawal, aud = Auditory hallucinations, com = Voices commenting, con = Voices conversing, soH = Somatic or tactile hallucinations, olf = Olfactory hallucinations, vis = Visual hallucinations, clo = Clothing/appearance, ssb = Inappropriate social/sexual behaviour, agg = Aggressive/agitated behaviour, rit = Ritualistic or stereotyped behaviour, drl = Derailment (loss of associations), tan = Tangentiality, inc = Incoherence, ill = Illogicality, cir = Circumstantiality, pre = Pressure of speech, dst = Distractible speech, cln = Clanging, ina = Inappropriate affect, atS = Social inattentiveness, atT = Inattentiveness during mental testing, stu = Stupor, rig = Rigidity, wax = Waxy flexibility, exc = Excitement, pos = Posturing and mannerisms, fac = Unchanging facial expression, mov = Decreased spontaneous movements, ges = Paucity of expressive gestures, eye = Poor eye contact, aff = Affective nonresponsivity, voc = Lack of vocal inflections, pov = Poverty of speech, cnt = Poverty of content of speech, blo = Thought blocking, lat = Increased latency of response, prs = Perseveration of speech, gro = Grooming and hygiene, imp = Impersistence at work or school, ane = Physical anergia, rec = Recreational interests/activities, sex = Sexual interest/activity, int = Inability to feel intimacy/closeness, rel = Relationships with friends/peers, eup = Euphoric mood, act = Increase in activity, tal = Talkativeness, rac = Racing thoughts, est. = Inflated self-esteem, sle = Decreased need for sleep, dis = Distractibility, jud = Poor judgment, dep = Depressive mood, app = Change in appetite or weight, smn = Insomnia or hypersomnia, agi = Psychomotor agitation, ret. = Psychomotor retardation, ple = Loss of interest or pleasure, ene = Loss of energy, wor = Feelings of worthlessness, cnc = Inability to think or concentrate, sui = Thoughts of death/suicide.

The three most important symptoms in terms of strength at T2 were distractible speech (dst), racing thoughts (rac) and talkativeness (tal). In relation to the bridge centrality indices, the 3 symptoms with the highest strength at T2 were perseveration of speech (prs), distractible speech (dst) and illogicality (ill) (Supplementary Fig. 4). A T2 micro network with emphasized bridge nodes can be observed in Supplementary Fig. 8b.

3.2. Meso-level

At T1, the 12 CASH global ratings plus inappropriate affect were grouped into four second-order psychopathological dimensions: the reality distortion domain, containing delusions and hallucinations; the negative domain, including anhedonia, abulia, alogia and affective flattening; the mixed domain of disorganization, containing formal thought disorders, bizarre behaviour, attention, inappropriate affect and catatonia and mania; and the depression domain, which exists between the negative and disorganization domains (Fig. 2a). Regarding centrality indices, in terms of strength, the three most important dimensions were abulia, alogia and affective flattening (Supplementary Fig. 2), and in terms of bridge strength, they were depression, alogia and inappropriate affect (Supplementary Fig. 5). A depiction of the bridge nodes in the T1 network is shown in Supplementary Fig. 9a.

In the T2 meso-network (Fig. 2b), we found 3 domains: reality distortion, disorganization and negative. The difference compared to T1 is that depression, catatonia and attention were in the negative domain. The three dimensions showing the greatest strength in the T2 meso-network were affective flattening, alogia and formal thought disorders (Supplementary Fig. 2), and regarding bridge strength, they were formal thought disorders, delusions and bizarre behaviour (Supplementary Fig. 5). A visual representation of the bridge nodes in the network is provided in Supplementary Fig. 9b.

3.3. Macro-level

The domains were grouped into a single general factor of psychopathology (Fig. 3a). The connections and interrelationships between variables appear to be equally divided between positive and negative relationships. Disorganization was the domain with the highest value in strength, followed by the negative domain (Supplementary Fig. 3).

At T2, the domains were grouped into a single factor (Fig. 3b). Disorganization was the domain with the highest value in strength, with the negative domain in second place (Supplementary Fig. 3). Since all of the domains were grouped into a single factor at T1 and T2, bridge centrality indices were not applicable.

3.4. T1-T2 network comparison test

Significant differences were found between the T1 and T2 network structures (micro M = 0.41, $p = 0.01$; *meso* M = 0.27 p = 0.01; macro M = 0.42, $p < 0.001$) but not in overall strength (micro S = 0.59, $p = 0.85$; meso S = 0.71, $p = 0.44$; macro S = 0.33, $p = 0.62$) at the three levels of analysis. Moreover, we identified several significant differences between edges and centrality measures of the two network structures (Supplementary Table 1).

A visual inspection shows that the micro-level network at T1 has more negative connections than does the network at T2, which has more positive and stronger connections. T1, analysed at the meso-level, reveals more negative connections. At T2, there were more positive and overall connections. At the macro-level, the previous pattern was repeated, with more negative connections found at T1.

3.5. Robustness analysis

Bootstrapping of the sample showed that the 95 % CIs were quite narrow at T1, indicating that the edge weight estimates were reliable and accurate. At T2, CIs were wider, showing less reliable and accurate network edge estimates (Supplementary Fig. 6). The case-dropping subset bootstrap procedure showed that the centrality values remained stable even after omitting large portions of the sample (Supplementary Fig. 7). The correlation stability coefficients (CS coefficients) of the micro-analysis of the T1 network were 0.75 for strength, EI and bridge homologues. The micro-analysis of the T2 network revealed that strength and EI had a CS of 0.28, and its bridge counterparts had a CS of 0.36. The meso-analysis of the T1 network showed that the centrality and bridge indices were >0.50. In the meso-analysis of the T2 network, all of the indices were >0.50 except bridge strength (CS = 0.36). Finally, the macro-analysis of T1 revealed that all of the indices range from 0.44 to 0.59, and in the macro-analysis of T2, all of the indices were >0.50.

3.6. Clinical relevance

The macro T2 network including the clinically relevant variables is displayed in Fig. 4. High scores in long-term negative and disorganization dimensions and higher lifetime dose-years of antipsychotic drugs

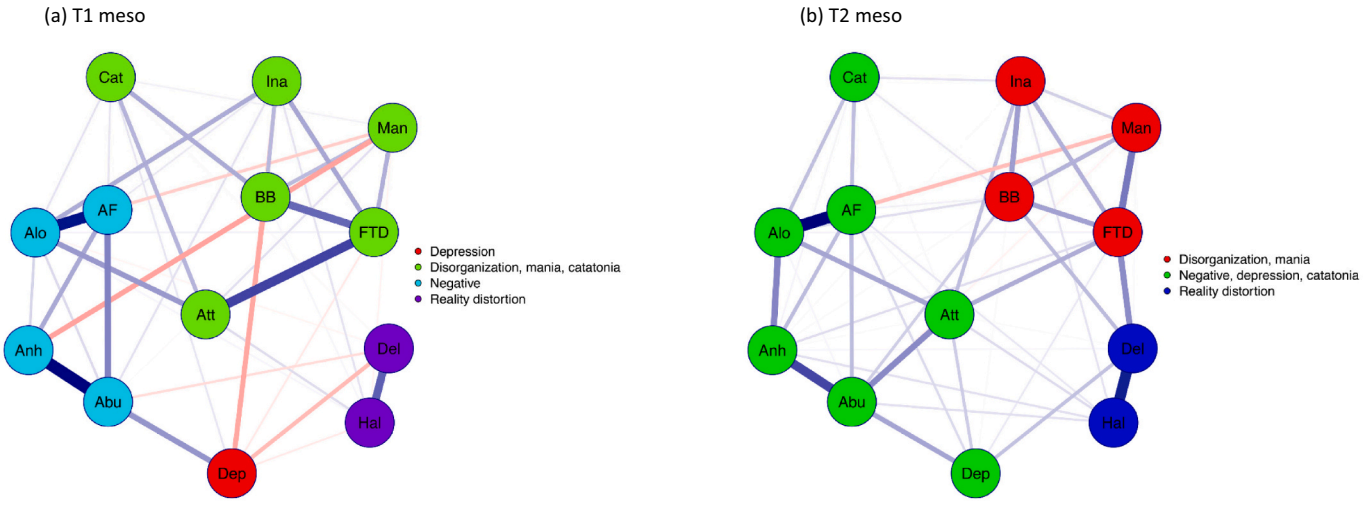

Fig. 2. Meso network structure in (a) T1 and (b) T2.
Abbreviations: mania (Man), depression (Dep), catatonia (Cat), delusions (Del), hallucinations (Hal), bizarre behaviour (BB), formal thought disorders (FTD), attention (Att), affective flattening (AF), alogia (Alo), abulia/apathy (Abu), anhedonia/asociality (Anh).

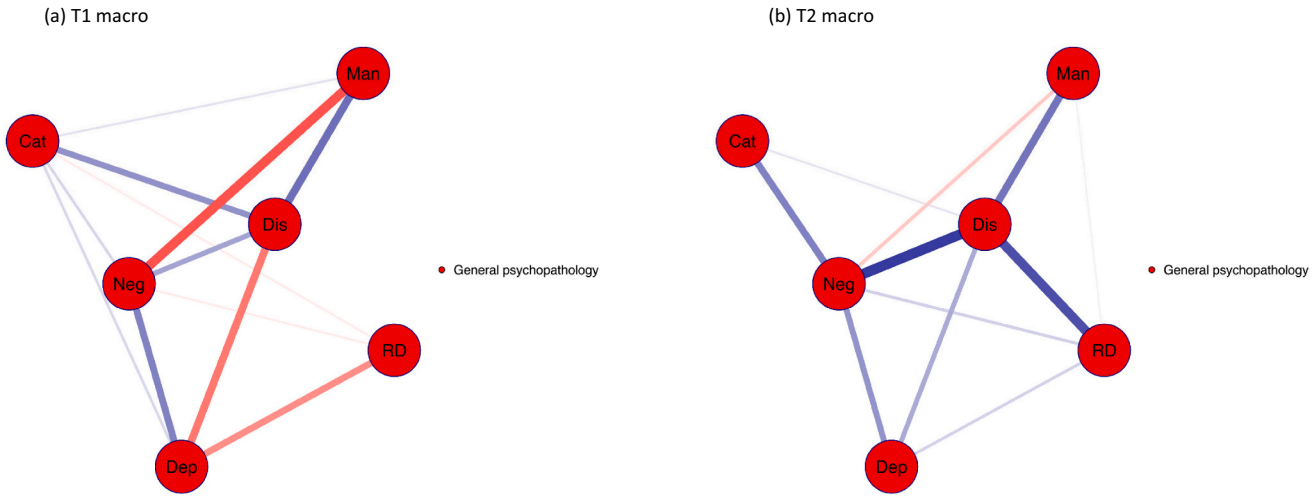

Fig. 3. Macro network structure in (a) T1 and (b) T2.
Abbreviations: mania (Man), depression (Dep), catatonia (Cat), reality distortion (RD), disorganization (Dis), negative (Neg).

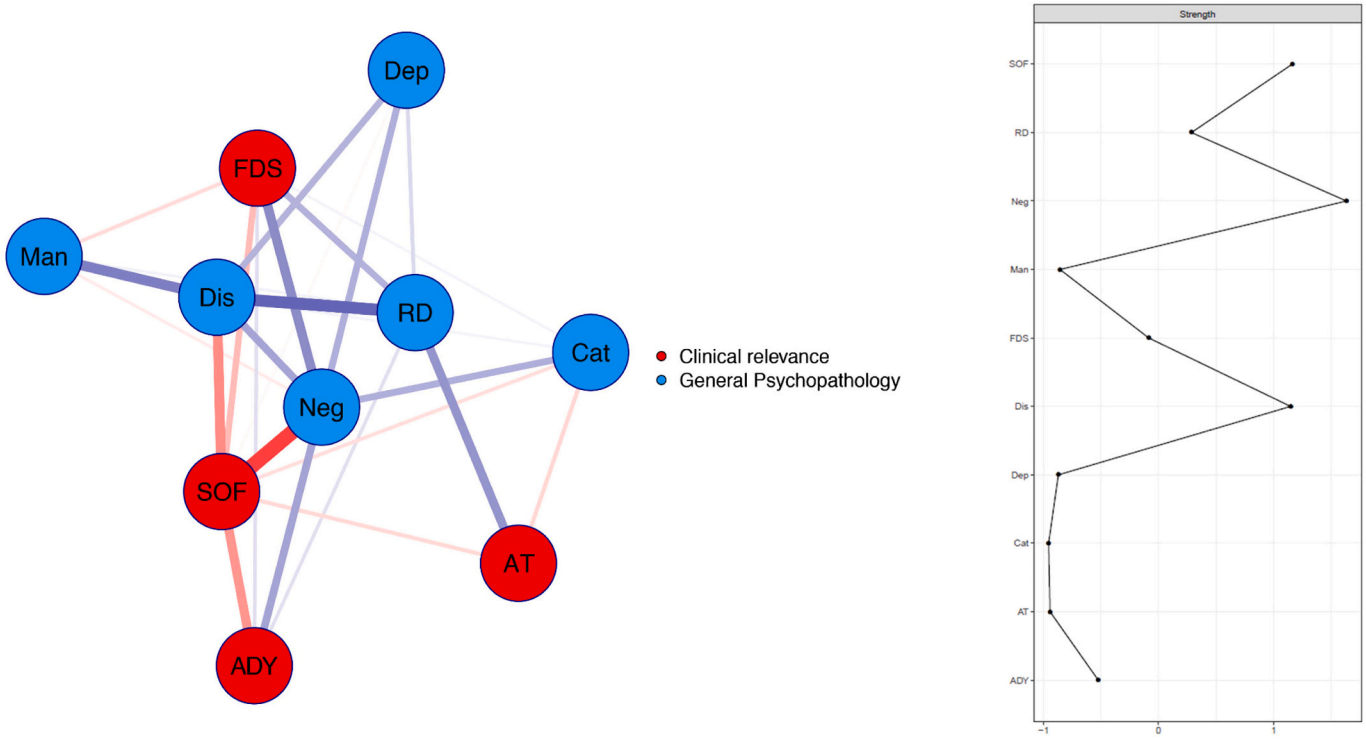

Fig. 4. Macro network structure with clinical variables in T2 (left) and its corresponding strength centrality index (right).
Abbreviations: mania (Man), depression (Dep), catatonia (Cat), reality distortion (RD), disorganization (Dis), negative (Neg), social functioning (SOFAS total score, SOF), lifetime antipsychotic dose-years (ADY), adherence to treatment (AT), final diagnosis of schizophrenia (FDS).

showed strong relationships with poor social functioning (SOFAS total score, SOF). Long-term reality distortion dimension were strongly and positively associated with poor lifetime adherence to treatment (AT). Besides, a final diagnosis of schizophrenia (FDS) was mainly related to negative and reality distortion dimension. And higher lifetime antipsychotic dose-years (ADY) showed strong associations with negative and depressive dimensions and with poor social functioning.

The information provided by the centrality indices showed that disorganization and negative symptoms had the highest strength in the network, together with social functioning.

4. Discussion

Our analysis of the interrelationships of symptoms and dimensions in first-episode psychosis and the long-term follow-up revealed three main findings. First, seven dimensions were found at the micro-level, three/four at the meso-level and one at the macro-level of analysis. Second, significant differences were found between baseline and follow-up time points in the three levels of network structure and in specific symptom connections and centrality measures but not in global strength. Third, the resulting macro psychopathological network at the long-term follow-up allowed for a better integration of our results for clinical practice. To our knowledge, this study is the first addressing the

longitudinal structure of psychopathological symptoms at 3 levels of analysis by means of network analysis in a first-episode psychosis sample.

4.1. Networks at the three level of analysis

4.1.1. Micro-level

The examination of the connections between nodes or symptoms allowed for the extraction of 7 psychopathological dimensions at baseline: reality distortion, disorganization, diminished expressivity, avolition/anhedonia, catatonia, mania and depression. The network obtained is compatible with the factors of the dimensional model of psychosis symptomatology accepted by the literature (Demjaha et al., 2009; Russo et al., 2014). Our results differed from those of van Rooijen et al. (2017), who reported 5 dimensions in their network analysis using the CASH interview. However, our results were based on EGA, which does not predefine dimensions and allows the variables to be grouped empirically, in line with a previous study using the same method (Peralta et al., 2020). The clustering found appears to be largely invariant, both in the first episode or cross-sectional phase, and therefore is replicated in both studies, as well as in the long-term follow-up, which is what the present study provides.

In our study, the clustering at T2 varied by 12 symptoms compared to that at T1 and included two overlapping domains of disorganization, one of them encompassing catatonia symptoms. Differences in disorganization dimensions between T1 and T2 may be explained by differences on illness stages (FEP versus long-term follow-up). Disorganized speech and behaviour are associated with greater clinical severity even in the beginning of psychosis (Harrow and Marengo, 1986; Metsänen et al., 2006; Oeztuerk et al., 2022; Roche et al., 2014). Therefore, it may be useful to target patients with more severe needs for adjunctive psychosocial treatments and rehabilitation interventions.

An outstanding finding of this study is that, in the T1 and T2 groups, in the micro-analysis, we identified the presence of two distinct dimensions associated with the negative factor of psychotic symptomatology. Previous evidence exists favouring factorial cross-sectional studies using different scales or assessment tools (Barch et al., 2013; Cuesta et al., 2021; Richter et al., 2019; Strauss et al., 2018). Our finding, in network analysis, was previously reported in two cross-sectional studies (Peralta et al., 2020; Strauss et al., 2019), but this study is the first time that it has been reported in a long-term stabilized follow-up sample, contributing to the validity of these subdimensions.

4.1.2. Meso-level

There were four psychopathological dimensions at T1: reality distortion, disorganization, negative and depression. These dimensions were reduced to three at T2: reality distortion, disorganization and negative (including depression). Our T1 and T2 networks are in agreement with studies reporting the hierarchical structure of psychopathological dimensions, by which dimensions are embedded into branches at different levels of arborification of a common trunk (Cuesta and Peralta, 2001; Kotov et al., 2020b). According to this structure, the dimensions of reality distortion and disorganization plus mania would be found in the thought disorder spectrum of the HiTOP model, while the negative dimension is found in the detachment spectrum.

Despite the particular differences in the groupings of certain variables at the micro- and meso-levels of assessment at T1 and T2, general clustering can be observed and remains intact across the two time periods. This global psychopathological invariance over time is in agreement with other studies (Kotov et al., 2016; Russo et al., 2014). In fact, a long-term follow-up study (Kotov et al., 2017) found that negative, disorganization and reality distortion symptomatology has a worsening course over time, whereas mania and depression are not aggravated.

A marker of disease severity is symptoms of disorganization (Harrow and Marengo, 1986; Metsänen et al., 2006; Roche et al., 2014). In T2, in stabilized patients, the influence of disorganization at the micro-level becomes more extensive, including the presence of two clusters in the network. At the T2 meso-level, the symptoms of disorganization and reality distortion are reinforced, specifically bizarre behaviour, formal thought disorders and delusions. This pattern is also manifest at the macro-level, underscoring the influence between disorganization and reality distortion over time.

4.1.3. Macro-level

The six common clusters of domains of psychopathology are integrated into a single general network of general psychopathology at the two time frames. This finding aligns with previous evidence suggesting that there is a single factor involved in a person's susceptibility to mental disorder, which is referred to as “p” by means of factor analytic techniques (Caspi et al., 2014; Caspi and Moffitt, 2018) or network analysis (Chavez-Baldini et al., 2021). This general factor also aligns with hierarchical models of psychopathology (Cuesta and Peralta, 2001; Kotov et al., 2020a; Peralta et al., 2021a), which in a previous study explained 61 % of the variance in symptoms (Peralta et al., 2021a).

4.2. Centrality differences

4.2.1. Micro-level

Between T1 and T2, significant differences were found at the level of strength and expected influence on negative symptoms and depression. There is a greater influence on acute episodes in physical anergia (ane), sexual interest/activity (sex), decreased need for sleep (sle) and depressive mood (dep). These results are in agreement with those of previous studies in which negative and depressive symptoms seemed to play an important role in maintaining symptoms across different disorders (Isvoranu et al., 2017; van Rooijen et al., 2017).

With regard to bridge centrality, a greater influence of negative symptoms at baseline was observed in the rest of the clusters of the network. However, at follow-up, disorganization symptoms had the greatest influence across clusters, as seen with visual inspection. This finding is in line with recent proposals that these symptoms form the core deficit of schizophrenia (Liddle, 2019), as well as the influence of these symptoms in long-term stabilized patients (Roche et al., 2014).

4.2.2. Meso-level

Negative symptoms, mainly alogia, have a greater influence at T1, while disorganization predominates at T2, mainly as formal thought disorders. This finding is in keeping with the reported pattern of low variation of negative symptomatology over long-term (Austin et al., 2015), although the course of negative symptoms in FEP patients seem to be heterogeneous (Chang et al., 2019). The significant difference in strength of delusions at T2, both overall and in bridge centrality, is noteworthy since it highlights the strong interrelation of delusions with formal thought disorders and bizarre behaviour, which was also found in a 2-year follow-up of FEP patients (Pelizza et al., 2021).

4.2.3. Macro-level

Reality distortion, negative and disorganization domains showed different patterns of predominance between baseline and follow-up. While reality distortion domains showed a general pattern of reduction over time, negative and disorganization dimensions showed less variation and suggested a more severe course at the follow-up (Austin et al., 2015; Roche et al., 2014).

4.3. Longitudinal psychopathological network comparison

In this study, NCT revealed that the difference in network structure is significant at the three assessment levels when comparing the networks at T1 and T2. Most studies have acknowledged that more densely connected networks tend to align with enhanced symptoms, so sparser networks represent a better prognosis (Borsboom, 2017). However, there have been studies suggesting the opposite might be true (Esfahlani

et al., 2017). In this study, the three levels of assessment showed different sparsity patterns without a differentiated density pattern, but with significant differences in the structure at all levels. Our results suggested the that it might not be only the density of a network that determines the prognosis, the structure of the network itself and its relationships between variables is also influencing. For instance, by visual inspection, it can be observed that the networks at T2 have stronger and more positive connections, whereas more negative connections can be seen in T1. This finding suggests that the strongest and most positive connections could be due to long-term state of patients with psychosis.

4.4. Clinical relevance

A final diagnosis of schizophrenia was strongly associated with negative dimension and poor functioning, and moderately with reality distortion dimension and mania dimension (inverse association) as it was expected. Indeed, course and poor outcome was used to determine diagnosis (APA, 2013; Strauss et al., 2018).

In this line, poor psychosocial functioning was also expected to be strongly related to negative dimension but interestingly it was strongly related to high antipsychotic dose-years. This association can be interpreted bi-directionally, either those patients with more severe illness are usually prescribed higher doses along their illness trajectory (Malandain et al., 2022) or a reverse possibility. In fact, antipsychotic drugs might increase the negative dimension over the long-term of FEP patients by increasing secondary negative symptoms (Fervaha et al., 2014; Peralta et al., 2000), and a lesser exposure to antipsychotics might be associated with a more favourable long-term outcome in some FEP patients (Wunderink et al., 2013). In this regard, higher cumulative doses of antipsychotic drugs seem to be a facilitator factor of depressive dimension in the outcome of FEP patients (Basu et al., 2020) and it was moderately associated with mode severe reality distortion dimension (Correll and Schooler, 2020).

The strong association between lifetime poor lifetime adherence and delusions in our long-term psychopathological network at macro level is in agreement with numerous studies addressing medication adherence in psychosis patients. In fact, medication adherence is a complex phenomenon that is influenced not only for symptomatic dimensions but also by individual factors, illness characteristics, type of drugs and the environment (Cuesta and Peralta, 1994; Czobor et al., 2015; Kirchner et al., 2022; Mohamed et al., 2009; Semahegn et al., 2018). Furthermore, discontinuation of antipsychotic medication has repeatedly associated with poor clinical outcomes in many domains, such as psychotic relapse and hospitalizations (Hui et al., 2013; Winton-Brown et al., 2017), functional deterioration (Malla et al., 2002; Suvisaari et al., 2018), and resistance to treatment (Emsley et al., 2012). Taken together, there is strong evidence supporting that a good cooperation with antipsychotic drugs allows for a better outcome at short- and long-term in FEP patients (Kim et al., 2020).

5. Conclusions

In conclusion, a fine-grained analysis of psychosis symptoms at micro level allowed for the identification of seven groups that showed relative clustering invariance with the presence of two domains of disorganization as the most notorious difference over time. Moreover, a relative stability in the global strength of the interconnections was also shown even though the network structure varied significantly in the long-term follow-up. Dynamic changes of clusters at *meso* level also showed a low variation over the follow-up. The severity of disorganization at the follow-up was associated with a more severe course of the psychosis, while negative and depression seem to have a relevant role in maintaining the symptoms. Finally, the macro-level allowed integrating all dimensions into a general factor of psychopathology, and in identifying their associations with lifetime outcomes, such as negative with poor functioning, disorganization with high antipsychotic dosage, and delusions with poor adherence to treatment.

5.1. Limitations

Our study is composed of two assessments conducted at different times in the patients' clinical courses. The assessments were also performed at two different stages in the patients' clinical courses: an acute stage designated T1 and a long-term stabilized stage termed T2. Owing to the different times at which the studies were conducted and because of the clinical stage differences of the participants, it is not feasible to establish dynamic/causal relationships of the psychopathological dimensions that were noted. New studies should be undertook from a longitudinal approach by resorting cross-sectional data to a longitudinal network, such it was recently performed in a study on prediction of change trajectories in borderline personality disorder (von Klipstein et al., 2021). Alternatively, directed acyclic graphs can be used to assess the directionality of interrelationships if several measures are available (Moffa et al., 2021).

Another limitation of the study is that the *n* values of T1 and T2 were quite different, with the sample size at T2 being reduced compared to that at T1. In this regard, we should be cautious about the network findings at T2, especially on the micro level, given the number of variables and the sample, where the stability correlation coefficients were reduced with respect to T1. Four variables showed significant differences between T1 and T2 participants. Patients who continue the follow-up were younger, with more years of education, and higher scores in attention and mania at study's intake. However, there were not significant differences in DSM 5 diagnoses but these differences might have introduced some bias in the collection of data.

One of the intrinsic limitations of the network approach, which has been widely debated in the literature, is that it is unable to demonstrate the reproducibility of the networks (Borsboom et al., 2017; Borsboom et al., 2018; Forbes et al., 2017). This study partly supports the stability of the network approach. We found that it is possible to replicate the network of a past study (Peralta et al., 2020) using the same symptoms in a different sample, but such replication is only found in acute phase patients. This fact emphasizes the caution that must be taken when generalizing results in network analysis since the network structure of one group with specific clinical characteristics might not be equivalent to the network structure of other groups.

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CRediT authorship contribution statement

Dr. Cuesta and Dr. Peralta and designed the study and wrote the protocol. Dr. Moreno-Izco, Dr. D. Peralta, Dr. Janda and Dr. García de Jalón performed the clinical assessments. Dr. Sánchez-Torres and Gil-Berrozpe performed the cognitive assessments and aided with patient recruitment and data collection. Dr. Cuesta and Gil-Berrozpe performed the literature search and data processing. Dr. Sánchez-Torres and Gil-Berrozpe performed the statistical analysis, and Dr. Cuesta and Gil-Berrozpe wrote the first draft of the manuscript. All authors contributed to, revised and approved the final manuscript.

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Declaration of competing interest

None.

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