Impacts of risk thresholds and age on clinical high risk for psychosis: a comparative network analysis

Clinical high risk and network analysis

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Abstract

One of the main goals for supporting people with a psychotic disorder is early detection and intervention, and the detection of Clinical High Risk (CHR) is a major challenge in this respect. This study sought to compare core symptoms of CHR for psychosis networks based on two CHR self-assessment tools, across different risk thresholds and age groups. This cross-sectional online investigation analyzed 936 individuals for CHR, in France and the UK, with the Prodromal Questionnaire-16 (PQ-16) and the Perceptual and Cognitive Aberrations (PCA). Twelve different symptom networks were constructed, assessing relationships, compactness, centrality, predictability, and comparisons between them, based on different thresholds and age groups. In the above-threshold PQ-16 network, the most central symptom was "Voices or whispers"; in the PCA network, the most central symptom was "Non-relevant thoughts distract or bother". They presented low overall predictability. No significant difference was found between them. This study makes three key contributions. First, this cross-network analyses highlight the relative importance of some central symptoms. Secondly, comparisons between networks demonstrate the unity of the CHR construct across scales, thresholds, and ages, affirming its phenotypic homogeneity, an essential issue for patient care pathways. Thirdly, the low average network predictability suggests the existence of unconsidered symptoms within these CHR networks. These results shed light on the organization of CHR symptoms using routine clinical questionnaires, offering insights for preventive targets in a logic of precision semiology.

Keywords: Symptom; Ultra-high-risk; Diagnosis; Comparison; Network analysis.

Introduction

One of the main goals for supporting people with a psychotic disorder is early detection and intervention. The prodromal psychosis symptoms are brought together under the term Clinical High Risk (CHR) for psychosis [1]. About 20-30% of individuals with a CHR transit to an above-threshold psychiatric disorder [2]. The CHR includes early basic symptoms (i.e., subjective sensory, cognitive, affective, and/or motor symptoms) and Ultra-High Risk (UHR) criteria (i.e., attenuated psychotic symptoms and/or brief and limited intermittent psychotic symptoms and/or genetic predispositions with risk of impaired global functioning). Assessment of these clinical components can be done by various standardized semi-structured instruments, such as the Structured Interview for Prodromal Syndrome (SIPS) [3–5], the Comprehensive Assessment of At-Risk Mental Status (CAARMS) [6], the Bonn Scale for the Assessment of Basic Symptoms Manual (BSABS) [7] or the Schizophrenia Propensity Instrument (SPI) [8]. To facilitate routine screening for CHR, short self-assessment screening questionnaires have been more recently developed, such as the Prodromal Questionnaire-16 (PQ-16) [9–13] or the Perceptual and Cognitive Aberrations (PCA) [14].

One of the major challenges that remains in understanding CHR phenotypes is to better explain the mutual interactions between symptoms [15–17]. For instance, in individuals with CHR, it is clinically relevant to consider that the sensation of thoughts racing through the head can lead to a lack of control of ideas or thoughts, which in turn can lead to a subjective feeling of disrupted and fragmented streams of thoughts, possibly leading to the thought of external forces controlling or forcing these thoughts. Vicious cycles of mutually reinforcing symptoms can thus be considered in the understanding of the motor, affective, sensory or cognitive CHR dimensions.

In a rapidly expanding literature, the potential contribution of symptom network analysis for chronic psychosis (e.g., [18–20]), first episode psychosis [21] and CHR [15–17, 22–25] has recently been demonstrated. Symptom network analysis is a computational technique that enables both the visualization of topological relationships between symptoms and identifies the strength of their relationships, referring to their “importance” to each other. Exploring and comparing the differential CHR networks based on differential psychometric measures can thus help to understand the different relationships and hierarchy between CHR symptoms. In the field of psychosis, symptom network analysis has helped to map transdiagnostic processes between psychosis and non-psychotic disorders [23], supported the understanding of CHR with comorbid disorders [16], led to the identification of novel

prevention targets (e.g., deconsolidation of symptom binding) [26], or helped to recognize the most central CHR symptoms [27, 28]. However, to our knowledge, none of these studies used scales, central to clinical practice, such as short self-assessment screening questionnaires (e.g., PQ-16 and PCA). In addition, the comparison of networks between distinct subgroups of CHR has never been carried out. These comparisons between networks will allow to better understand threshold of help-seeking. Thus, the objective of this study is to compare the symptom networks of CHR based on the PQ-16 and the PCA. We aim to highlight the differences in symptom relationships and centrality based on different risk thresholds and age.

Method

Recruitment and Participants

The Tone-P Study is a cross-sectional online study to investigate early auditory processing in non-help seekers screened for CHR. The Tone-P study is funded by Gorilla.sc. The study was approved by the ethical committees of the University Grenoble Alpes, France, Durham University, United Kingdom (UK) and Southampton University, United Kingdom (UK). Participants were recruited via Amazon's Mechanical Turk (MTurk) and via French and UK universities' undergraduate mailing lists. Participants were aged from 18 to 35 years, without any current or history of psychotic disorder, and residing in France or the UK. Informed consent for the study was provided online, followed by a socio-demographic assessment and by two screening questionnaires: the 16-item PQ-16 and the 9-item PCA scale.

Questionnaires

The PQ-16 is a validated self-assessment screening questionnaire for adult CHR, composed of 16 items. It was developed on the basis of the Prodromal Questionnaire (PQ), a 92-item self-report measure [29], itself based on the Schizotypal Personality Questionnaire [30]. Tested in a general non-help-seeking population, the initial validation study revealed a three-factor structure (perceptual abnormalities/hallucinations, unusual thoughts and negative symptoms). The scale was translated and validated in French in both adult and adolescent populations [31, 32]. The PQ-16 questions the degree of perceived distress, rated on a 4-point Likert scale (as "none", "mild", "moderate" or "severe"). The total score was the result of the sum of the scores obtained for each of the 16 items. For this scale, selection criteria for CHR were at least 6 or more endorsed items (and not a score of 6 or more – e.g., if an individual

scores 2 items at 3/3, it will not be considered as CHR) [11]. Also for the PQ-16, we used in parallel a cut-off score at 3 or more, based on the results of [31], described in **Supplementary Materials**.

The PCA is a validated self-assessment screening questionnaire for adult CHR, composed of 9 items. The scale was translated and validated in French in an adolescent population [32]. The PCA questions the degree of perceived distress, rated as "none", "mild", "moderate" or "severe" (4-point Likert scale). The total score was the result of the sum of the scores obtained for each of the 9 items. Selection criteria for CHR based on the PCA referred to a score at 3 or more [12].

Prevalence

Regarding participants, we provided mean, median and standard deviation for age, and number and percentages of each country, of males and females and of occupation, by providing the significant differences between the values of these variables. We also calculated whether there was a difference in age (t-test), sex (Chi^2) or occupation (Chi^2) according to the French and UK groups.

General analyzes

We provided the mean, median and standard deviation of the total score of the entire PQ-16 and PCA datasets, as well as the number and percentage of subjects exceeding the PQ-16 cut-offs and the PCA cut-off. Regarding prevalence based on the PQ-16 and the PCA, we provided the number and the percentage of endorsed items (i.e., the non-zero values of each item, considering the presence or absence of an item), and the mean and standard deviation of each item (i.e., considering the score of each item on the 4-point Likert scale).

Network analyses

PQ-16 and PCA networks

We constructed 12 networks: seven for the PQ-16 dataset, including above and below-threshold CHR networks and age-based networks, and five for the PCA (see **Supplementary Material 1** for details). We analyzed relationships and centrality measures for CHR symptoms, comparing the six PQ-16 networks in pairs. Following established network analysis guidelines [33], our study encompassed four key steps: network estimations, centrality measures, network comparisons, and network robustness, all performed for both the PQ-16 and PCA.

Network estimations

A gaussian graphical model was conducted to assess ordinal data. For the PQ-16, we rely on the 2-factor model retrieved by Howie et al. in the visualization of the network: "Avolition and excessive social anxiety" and "Perceptual abnormalities and unusual thought content" dimensions [34]. In order to obtain an overview of the sparsity/compactness of the network, we calculated for each network the Average Strength of the Network (ASN) based on the node centrality measures.

Centrality measures

We computed the centrality measures of each of the networks, representing symptoms that are highly connected to other symptoms [35]. Strength-type centrality is the most clinically relevant measure, computing the degree to which a node is connected with all the other nodes of a network [36]. Strength centrality measure is presented as a z-value (z), i.e., a standard score indicating how many standard deviations a data point is from the mean. Due to the clinical relevance of the highest centrality measures, we only note and discuss the three highest centrality measures for the most important networks, namely the above-threshold CHR networks.

Predictability

Predictability, computed for all the networks, refers to how well a given node in the network can be predicted by the directly neighboring nodes. Low predictability attests to probable unmeasured influences in the network (aka in one scale).

Network comparisons

Networks were compared in pairs based on the PQ-16 and on the PCA. Two kinds of significance indices were calculated: the global comparison in terms of connections ("edge weights analysis"), and the global comparison in terms of centrality ("global strength analysis") [37].

Network robustness

To verify the adequation of the number of subjects to perform such a network analysis, we analyzed the robustness of the network with a bootstrap analysis (N = 2,000 iterations).

All analyses and graphical visualizations were performed with R software (4.3.1). **Supplementary Material 1** gives technical details on the network approach, necessary for reproducibility and relative to the experimental section.

Results

Prevalence

Nine hundred forty-eight (948) participants were included in the study and, after processing missing data, 936 were analyzed. The mean age was 21.5 years, with a median of 20.0 and a standard deviation of 5.1. Three hundred sixty-seven (367) were included in France (39.2%) and 569 in the UK (60.8%) [Chi2 = 43.59, $p < 0.001$]. Two-hundred sixty-three (263) were male (28.1%) and 673 female (71.9%) [Chi2 = 179.59, $p < 0.001$]. Seven-hundred sixty-four (764) were students (81.6%), 119 were employed (12.7%) and 53 unemployed (5.6%) [Chi2 = 989.21, $p < 0.001$]. Between the French and UK groups, there was a significant difference for age ($t = 15.82$, $p < 0.001$ [4.74 – 6.09]), but not for sex (Chi2 ~ 0, p ~ 1) or occupation (Chi2 = 6, $p = 0.20$).

General analyses

Regarding the total scores of the entire PQ-16 dataset, we found a mean of 4.0 symptoms in the PQ-16 dataset and a mean of 2.5 symptoms in the PCA dataset (**Table 1**). One-hundred and fifty individuals (16.0%) were above the PQ-16 cut-off at 6 endorsed items, and 311 (33.2%) were above the PCA cut-off.

Table 1. Prevalence of the CHR symptoms (N = 936). Means and standard deviations of each CHR symptom; number and percentage of endorsed items (i.e., non-zero values of each CHR symptom).

PQ-16			PCA		
CHR symptoms of the PQ-16 (N=16)	**Means and standard deviations of CHR symptoms on the PQ-16 4-point Likert scale**	**Number and percentage of endorsed items at the PQ-16**	**CHR symptoms of the PCA (N=9)**	**Means and standard deviations of CHR symptoms on the PCA 4-point Likert scale**	**Number and percentage of endorsed items at the PCA**

Uninterested	0.49 [0.75]	325 [34.7]	Cannot understand spoken or written words	0.21 [0.54]	144 [15.4]
Déjà vu	0.23 [0.55]	165 [17.6]	Cannot remember familiar words	0.31 [0.65]	210 [22.4]
Smell or taste	0.09 [0.37]	66 [7.1]	Too many thoughts race through the head	0.33 [0.68]	209 [22.3]
Unusual sounds	0.21 [0.54]	150 [16.0]	Directing attention onto two different things	0.3 [0.64]	200 [21.4]
Real or imaginary	0.30 [0.65]	190 [20.3]	Non-relevant thoughts distract or bother	0.37 [0.69]	251 [26.8]
Changing face	0.10 [0.44]	55 [5.9]	Stream of thoughts is getting disrupted	0.32 [0.62]	224 [23.9]
Anxiety to meet	0.80 [0.95]	462 [49.4]	Experiences or conversations go through the mind again and again	0.53 [0.81]	331 [35.4]
Seen things	0.07 [0.33]	47 [5.0]	Cannot fit snatches of conversation together in a meaningful way	0.11 [0.39]	74 [7.9]
Strong thoughts	0.25 [0.63]	151 [16.1]	Things sometimes seem fragmented	0.07 [0.3]	49 [5.2]
Special meanings	0.07 [0.33]	45 [4.8]			
Non-control of ideas or thoughts	0.47 [0.80]	294 [31.4]			
Distracted by distant sounds	0.18 [0.50]	125 [13.4]			
Voices or whispers	0.08 [0.35]	50 [5.3]			
Others have it in for me	0.34 [0.72]	209 [22.3]			

Person or force around	0.15 [0.49]	91 [9.7]			
Changes in body parts	0.18 [0.53]	123 [13.1]			
	Overall mean/number and standard deviation of the means/numbers				
	0.25 [0.19]	161 [116]		0.28 [0.13]	188 [82]

CHR: Clinical-High-Risk. PQ-16: Prodromal Questionnaire-16. PCA: Perceptual and Cognitive Aberrations.

Network analysis

For the PQ-16 and PCA CHR networks, we present here: i) centrality measures (*z*), predictability (means and standard deviations), and network comparisons (p-value). Since the full results are presented in **Figure 1** for the PQ-16 and in **Figure 2** for the PCA, as well as in **Table 2** for the predictability measures, we describe below only the results of the CHR network above the conventional threshold (6 or more endorsed items for the PQ-16 and the sum of the scores for the PCA), i.e., patients with a CHR status.

Network centrality

For the above-threshold PQ-16 network, the three most central symptoms in terms of strength are: “Voices or whispers” (1.28), “Seen things” (1.09) and “Changing face” (0.91). All the seven PQ-16 networks, their strength-type centrality measures and their ASN are presented in **Figure 1** and **Figure S1** (**Supplementary Material**).

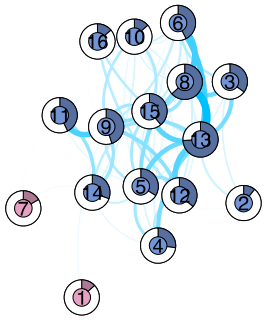
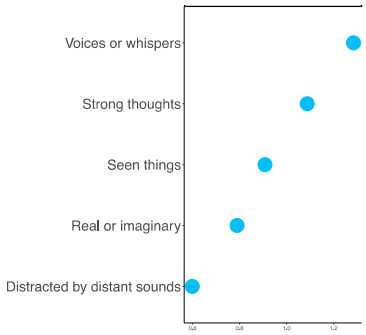
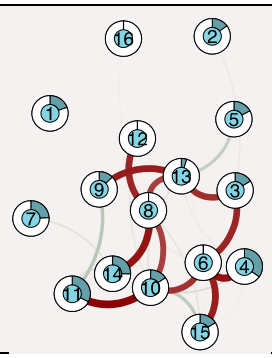
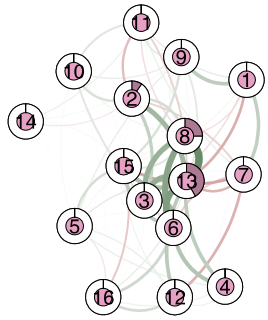
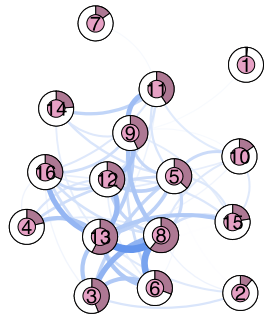
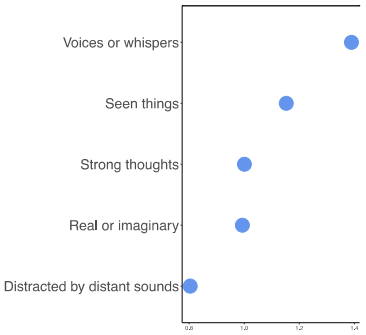
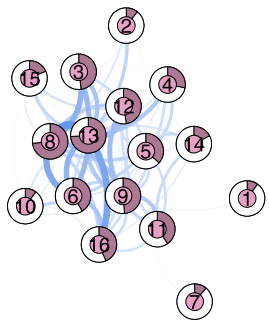
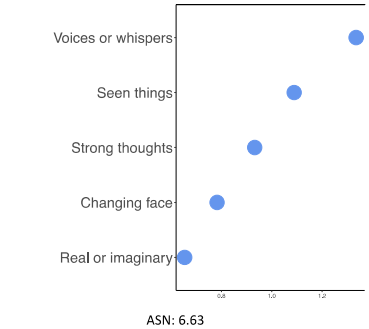
		PQ-16 Networks	Strength-type centrality measures
PQ-16 network on all the dataset (N = 936) (Blue: positive correlations; red: negative correlations)			 ASN: 6.38
According to the threshold at 6 or more (Green: positive correlations; red: negative correlations)	**Below-threshold-6 CHR network (N = 786)**		 ASN: 3.67
	Above-threshold-6 CHR network (N = 150)		 ASN: 2.06
According to the age (Blue: positive correlations; red: negative correlations)	**CHR network of young individuals (N = 474)**		 ASN: 4.34
	CHR network of old individuals (N = 332)		 ASN: 6.63

Fig. 1. PQ-16 CHR networks and their strength-type centrality measures (N = 936). Positive correlations are in blue or green, while negative correlations are in red. The thickness of the edges represents the level of correlation between two symptoms. Only the 5 most central nodes were represented for each network. The slightly nuanced background color for the below-threshold-6 CHR network highlights this network which interestingly only has negative relationships. The results for the cut-off at 3 are given in **Supplementary Material 2**. The symptoms are: (1) “Uninterested”, (2) “Déjà vu”, (3) “Smell or taste”, (4) “Unusual sounds”, (5) “Real or imaginary”, (6) “Changing face”, (7) “Anxiety to meet”, (8) "Seen things”, (9) “Strong thoughts”, (10) “Special meanings”, (11) “Non-control of ideas or thoughts”, (12) “Distracted by distant sounds”, (13) “Voices or whispers”, (14) “Others have it in for me”, (15) “Person or force around”, (16) “Changes in body parts”. Predictability of a node is depicted as a pie chart in the rings around nodes (the area in the outer ring of nodes represents the percentage of variance of the node that is explained by its directly neighboring nodes). For the general network, a 2-factor model is used to visualize dimensions [34], with the two nodes of the “Avolition and excessive social anxiety” dimension colored in pink and the other nodes of the “Perceptual abnormalities and unusual thought content” dimension colored in blue. Strength-type centrality measures are ordered by strength (i.e., the highest values of strength are located furthest to the right of the plot and the lowest values furthest to the left). Z-scores are used to plot standardized coefficients. ASN: Average Strength of the Network; CHR: Clinical-High-Risk; PQ-16: Prodromal Questionnaire-16.

For the above-threshold PCA network, the three most central symptoms in terms of strength are: “Non-relevant thoughts distract or bother” (1.93), “Stream of thoughts is getting disrupted” (0.55) and “Things sometimes seem fragmented” (0.25). The five PCA networks, their strength-type centrality measures and their ASN, are presented in **Figure 2**. Each of the PCA networks contains 9 nodes and 36 connections.

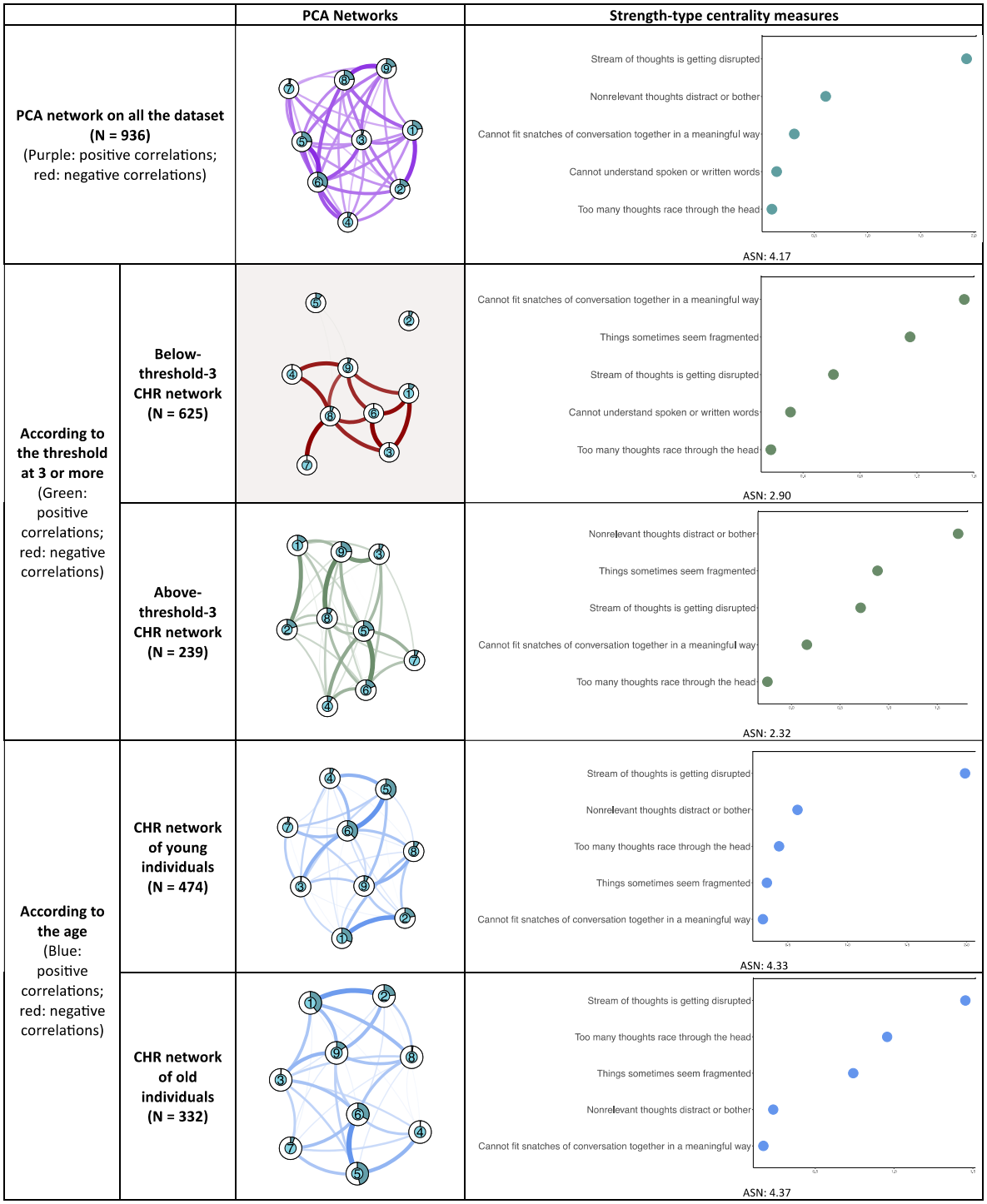


Fig. 2. PCA CHR networks and their strength-type centrality measures (N = 936). Positive correlations are in purple, blue or green, while negative correlations are in red. The thickness of the edges represents the level of correlation between two symptoms. The orange nodes correspond to the PCA symptoms. Only the 5 most central nodes were represented for each network. The slightly nuanced background color for the below-threshold-3 CHR network highlights this network which interestingly only has negative relationships. The symptoms are: (1) “Cannot understand spoken or written words”, (2) "Cannot remember familiar words”, (3)

"Too many thoughts race through the head", (4) "Directing attention onto two different things", (5) "Non-relevant thoughts distract or bother", (6) "Stream of thoughts is getting disrupted", (7) "Experiences or conversations go through the mind again and again", (8) "Cannot fit snatches of conversation together in a meaningful way", (9) "Things sometimes seem fragmented". Predictability of a node is depicted as a pie chart in the rings around nodes (the area in the outer ring of nodes represents the percentage of variance of the node that is explained by its directly neighboring nodes). Strength-type centrality measures are ordered by strength (i.e., the highest values of strength are located furthest to the right of the plot and the lowest values furthest to the left). Z-scores are used to plot standardized coefficients. ASN: Average Strength of the Network; CHR: Clinical-High-Risk; PCA: Perceptual and Cognitive Aberrations.

Predictability

Regarding predictability (i.e., when a node is predicted by all the nodes directly connected to it), the means and standard deviations are given in **Table 2** for the seven PQ-16 networks and the five PCA networks.

Table 2. Means and standard deviations of the predictability of the nodes of the seven PQ-16 CHR networks and of the five PCA CHR networks. CHR: Clinical-High-Risk. PQ-16: Prodromal Questionnaire-16; PCA: Perceptual and Cognitive Aberrations. The results for the cut-off at 3 are given in **Supplementary Material 2**.

PQ-16 CHR networks		
Types of PQ-16 networks		**Mean [Standard Deviation] of predictability of the PQ-16 symptoms**
All dataset (N = 936)		0.34 [0.18]
According to the thresholds	Below-threshold-6 PQ-16 network (N = 786)	0.06 [0.09]
	Above-threshold-6 PQ-16 network (N = 150)	0.13 [0.14]
According to age	PQ-16 network of young individuals (N = 474)	0.25 [0.15]
	PQ-16 network of old individuals (N = 332)	0.34 [0.21]
PCA CHR networks		

Types of PCA networks		Mean [Standard Deviation] of predictability of the PCA symptoms
All dataset (N = 936)		0.17 [0.10]
According to the threshold	Below-threshold PCA network (N = 625)	0.04 [0.05]
	Above-threshold PCA network (N = 239)	0.16 [0.10]
According to age	PCA network of young individuals (N = 474)	0.18 [0.15]
	PCA network of old individuals (N = 332)	0.19 0.18]

Network comparisons

Two kinds of results of the two-by-two comparison of the networks are computed, relative to the comparison between the symptom connections ("edge weights analysis"), and to the comparison between centrality measures ("global strength analysis"). These comparisons are provided in **Table 3**. No significant difference at 0.05 was found for the overall comparison between the connections between two networks compared two-by-two, for the PQ-16 as for the PCA.

Regarding the overall comparison between the strength-type centrality measure, a significant difference is retrieved only for the comparison between the below-threshold and above-threshold PCA networks (p-value < 0.001).

Table 3. Network comparisons regarding edge weights analysis and global strength analysis between the networks according to the thresholds of the PQ-16 and the PCA, and the age. "Strength-" refers to the global strength for each of the networks. The results for the cut-off at 3 are given in **Supplementary Material 2**.

	Comparisons between the CHR networks	Comparisons relative to the edge weights	Comparisons relative to the global strengths
PQ-16	**According to the threshold (at 6)**	Mean value = 0.157 p-value ~ 1	Strength-below-6 = 0.262 Strength-above-6 = 0.155 Strength value = 0.107 p-value = 0.91
	According to the age	Mean value = 0.101 p-value ~ 1	Strength-Young = 5.910 Strength-Old = 6.159 Strength value = 0.248 p-value = 0.51

PCA	**According to the threshold**	Mean value = 0.311 p-value = 0.21	Strength-below-3 ~ 0 Strength-above-3 = 2.790 Strength value = 2.790 **p-value < 0.001***
	According to the age	Mean value = 0.073 p-value ~ 1	Strength-Young = 3.639 Strength-Old = 3.671 Strength value = 0.032 p-value = 0.87

* p-value < 0.05 indicates a significant difference.

Network robustness

With the bootstrap analysis, the PQ-16 and the PCA CHR networks are stable with the case-dropping subset, with a CS-coefficient superior to 0.25 for all the networks.

Discussion

Three major contributions of this study could be raised. In an original way, these different cross-network analyzes allow to highlight the importance of each symptom in relation to each other. Furthermore, for the first time to our knowledge, the low mean network predictability suggests the existence of unconsidered symptoms in these CHR networks. Finally, considering CHR as a statistical construct (i.e., as a psychometrically validated conceptual entity), comparisons between networks show, also for the first time at our knowledge, the unity of this CHR construct across scales, thresholds and ages – a particularly appreciable and essential phenotypic homogeneity in the construction of care pathways for patients with a CHR. We discuss these different contributions in the remainder of the discussion.

First, in above-threshold CHR participants, symptom network centrality analysis highlighted that “Voices or whispers”, “Seen things” and “Changing face” emerged as central symptoms in the PQ-16 network. In the PCA network and in above-threshold CHR participants, “Non-relevant thoughts distract or bother”, “Stream of thoughts is getting disrupted”, and “Things sometimes seem fragmented” held central importance. Identifying the central symptoms that structure the network of patients with a CHR status could be essential for clinicians, in a logic of precision and personalized psychiatry focused on semiology [38–40]. For instance, by specifically targeting these most central symptoms, clinicians could obtain greater diagnostic accuracy [41]. Thus, while remaining particularly cautious about the translational aspect of such statistical models to clinical practice [42], these central symptoms

could help guide clinicians more precisely and quickly in clinical practice and could be important elements in the development of possible short versions of CHR scales.

Secondly, the particularly low mean predictability of the different networks (0.34 for the PQ-16 network and 0.17 for the PCA network) provides insightful highlights for CHR in clinical practice. This result is consistent with the low average appearance of each symptom for a given patient (0.25 on average per symptom for the PQ-16; 0.28 for the PCA), indicating the wide diversity of symptoms expressed by each individual and underscoring the need for network studies like this one. With such a predictability result, we testify to the probable existence of other symptoms not considered in CHR (when measured with such routine scales). This study does not enable to identify these missing factors but illustrates the need to henceforth conduct studies considering symptoms, biological elements or environmental factors sought beyond the symptoms measured in routine scales. The mean predictability is two to three times less important in the below-threshold networks compared to the above-threshold networks. A low mean predictability in these below-threshold networks supports the hypothesis of a (weakly connected) network that depends on a large number of other external factors, indicating the absence of a disorder (defined as a strongly connected network – see below). This empirical result reinforces the existence of a boundary between normal and pathological for the CHR construct.

Thirdly, in the symptom network theory, a condition such as CHR can be understood as a frozen network of mutual interrelationships between strongly connected symptoms [43]. Accordingly, the relationships between symptoms were mostly negative for the below-threshold networks (in red and with nuanced background color in **Figures 1** et **2**), testifying of a network whose nodes do not influence each other. This empirical result is in agreement with the symptom network theory: when there are no strong relationships between nodes, it means that disorders do not emerge because the network is not “frozen”, indicating that the symptoms are less likely to persist and reinforce one another – preventing the development of a stable, pathological state. Conversely, the symptoms of the three above-threshold networks were mainly positively related (in green in **Figures 1** et **2**). Moreover, the above-threshold networks were more compact, as illustrated by the ASN. Since all networks correspond to the CHR, as expected, the network comparisons showed no difference in the global structure of the networks (in terms of edge weights as well as global strength). However, this observation could be qualified by the differences in symptom centrality observed between the PCA and the PQ-16 questionnaires. Such differences could result from either statistical uncertainty (i.e., statistical noise related to sampling bias or measurement error) or real differences in how these scales

measure prodromal symptoms (i.e., capturing slightly different aspects of prodromal symptoms, such as certain positive, negative, cognitive, or affective symptoms). If the differences in centrality are not due to statistical noise, this could have significant implications for both therapeutic interventions and the definition of CHR: therapists might need to adapt their approaches based on the scale used to evaluate symptoms in ultra-high-risk patients; the CHR category itself could be questioned, suggesting that it may include fuzzy boundaries, consistent with a large body of theoretical psychiatric literature on this topic [44–46]. All these original results support the relevance of a CHR construct as a homogeneous phenotype, distinct, on the nosographic level, from other psychiatric entities or any other non-CHR condition. Interestingly, regarding the strength-type centrality comparison, only a significant difference was found between the below-threshold and above-threshold PCA networks. Such a difference in terms of centrality in the PCA suggests that the most central symptoms identified in the above-threshold PCA network could be even more important to identify in clinical practice.

Finally, regarding network comparisons based on age, while the networks of young and old individuals are relatively similar in terms of edge weights, strengths or compactness, predictability was more important in the network of older individuals in the PQ-16 network. This result supports the clinical relevance of these symptoms as diagnostic and therapeutic targets. This also reinforces the evidence that older CHR patients tend to present with specific and typical symptoms of CHR – consistent with the increased likelihood of CHR transitioning into a psychiatric disorder over time [47]. These results are thus consistent with a number of other studies [27, 47–52, 52–56], showing especially the existence of relationships between the presence of CHR symptoms and brain maturation processes [57, 58].

This study has a number of limitations. Firstly, CHR was ultimately not confirmed by the SIPS or the CAARMS. However, this apparent limitation should be qualified by considering the good predictive value of these screening questionnaires when used online [12]. Furthermore, the objective of our study is not to qualify and/or validate patients who have or do not have CHR, but to explore the symptoms of this construct. Secondly, our multicentric sample is made up of a majority of females (71.9%), considering that sex has been demonstrated to be significantly associated with CHR symptoms (the prevalence of CHR being mostly found in female) [53]. Regarding age, our sample did not include individuals under the age of 18. Finally, like any statistical and computational method, network analyzes have inherent limitations. Especially, the centrality results should be clinically interpreted with

caution – symptom networks highlight the mutual interaction between symptoms at a population level, but not at an individual level [42].

The development of diagnostic and therapeutic markers of the heterogeneous construct of CHR requires a detailed analysis at the level of symptoms. In this original network analysis, we offer insights into mutual importance and most central CHR symptoms, thus promising to refine the identification of preventive and specific targets for precision semiology.

Statements and Declarations

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Conflict of Interest.

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care.

Declaration of Interest Statement

None.

CRediT authorship contribution statement

Christophe Gauld: Writing, Original draft preparation, Conceptualization, Methodology, Editing; Pierre Fourneret: Conceptualization, Validation, Reviewing; Ben Alderson-Day: Reviewing, Resources and data, Validation; Emma Palmer-Cooper: Acquisition of data, Reviewing, Methodology, Validation; Clément Dondé: Methodology, Conceptualization, Editing, Supervision, Reviewing, Validation.

Abbreviations

ASN: Average Strength of the Network

Bonn Scale for the Assessment of Basic Symptoms

CAARMS: Comprehensive Assessment of At-Risk Mental Status

CHR: Clinical High Risk

eBIC: extended Bayesian Information Criterion

MGM: Mixed Graphical Models

NCT: NetworkComparisonTest

PQ-16: Prodromal Questionnaire-16

PCA: Perceptual and Cognitive Aberrations

SPI: Schizophrenia Propensity Instrument

UHR: Ultra-High Risk

UK: United Kingdom

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610

Figure Legends

Fig. 1. PQ-16 CHR networks and their strength-type centrality measures (N = 936). Positive correlations are in blue or green, while negative correlations are in red. The thickness of the edges represents the level of correlation between two symptoms. Only the 5 most central nodes were represented for each network. The slightly nuanced background color for the below-threshold-6 CHR network highlights this network which interestingly only has negative relationships. The results for the cut-off at 3 are given in **Supplementary Material 2**. The symptoms are: (1) “Uninterested”, (2) “Déjà vu”, (3) “Smell or taste”, (4) “Unusual sounds”, (5) “Real or imaginary”, (6) “Changing face”, (7) “Anxiety to meet”, (8) "Seen things”, (9) “Strong thoughts”, (10) “Special meanings”, (11) “Non-control of ideas or thoughts”, (12) “Distracted by distant sounds”, (13) “Voices or whispers”, (14) “Others have it in for me”, (15) “Person or force around”, (16) “Changes in body parts”. Predictability of a node is depicted as a pie chart in the rings around nodes (the area in the outer ring of nodes represents the percentage of variance of the node that is explained by its directly neighboring nodes). For the general network, a 2-factor model is used to visualize dimensions [34], with the two nodes of the “Avolition and excessive social anxiety” dimension colored in pink and the other nodes of the “Perceptual abnormalities and unusual thought content” dimension colored in blue. Strength-type centrality measures are ordered by strength (i.e., the highest values of strength are located furthest to the right of the plot and the lowest values furthest to the left). Z-scores are used to plot standardized coefficients. ASN: Average Strength of the Network; CHR: Clinical-High-Risk; PQ-16: Prodromal Questionnaire-16.

Fig. 2. PCA CHR networks and their strength-type centrality measures (N = 936). Positive correlations are in purple, blue or green, while negative correlations are in red. The thickness of the edges represents the level of correlation between two symptoms. The orange nodes correspond to the PCA symptoms. Only the 5 most central nodes were represented for each network. The slightly nuanced background color for the below-threshold-3 CHR network highlights this network which interestingly only has negative relationships. The symptoms are: (1) “Cannot understand spoken or written words”, (2) "Cannot remember familiar words”, (3) “Too many thoughts race through the head”, (4) “Directing attention onto two different things”, (5) “Non-relevant thoughts distract or bother”, (6) “Stream of thoughts is getting disrupted”, (7) “Experiences or conversations go through the mind again and again”, (8) “Cannot fit snatches of conversation together in a meaningful way”, (9) “Things sometimes seem

fragmented". Predictability of a node is depicted as a pie chart in the rings around nodes (the area in the outer ring of nodes represents the percentage of variance of the node that is explained by its directly neighboring nodes). Strength-type centrality measures are ordered by strength (i.e., the highest values of strength are located furthest to the right of the plot and the lowest values furthest to the left). Z-scores are used to plot standardized coefficients. ASN: Average Strength of the Network; CHR: Clinical-High-Risk; PCA: Perceptual and Cognitive Aberrations.