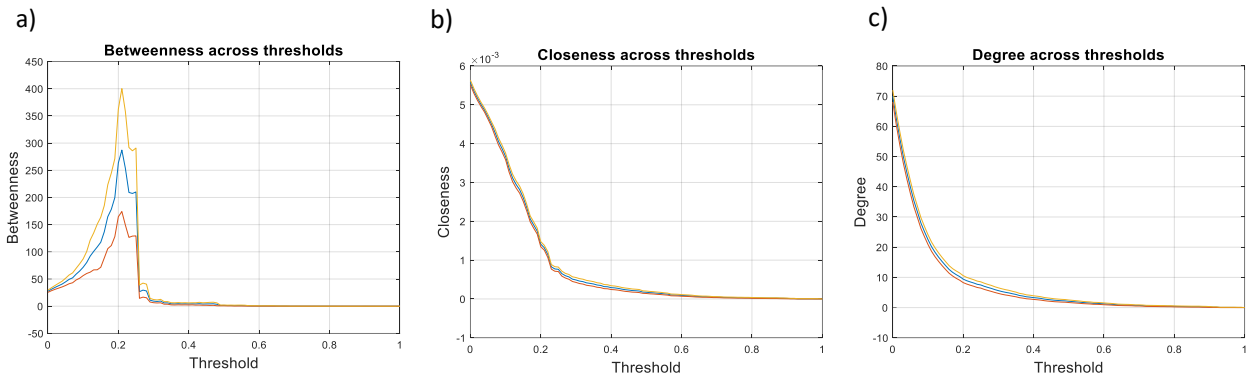
Supplementary Material

Table of Contents

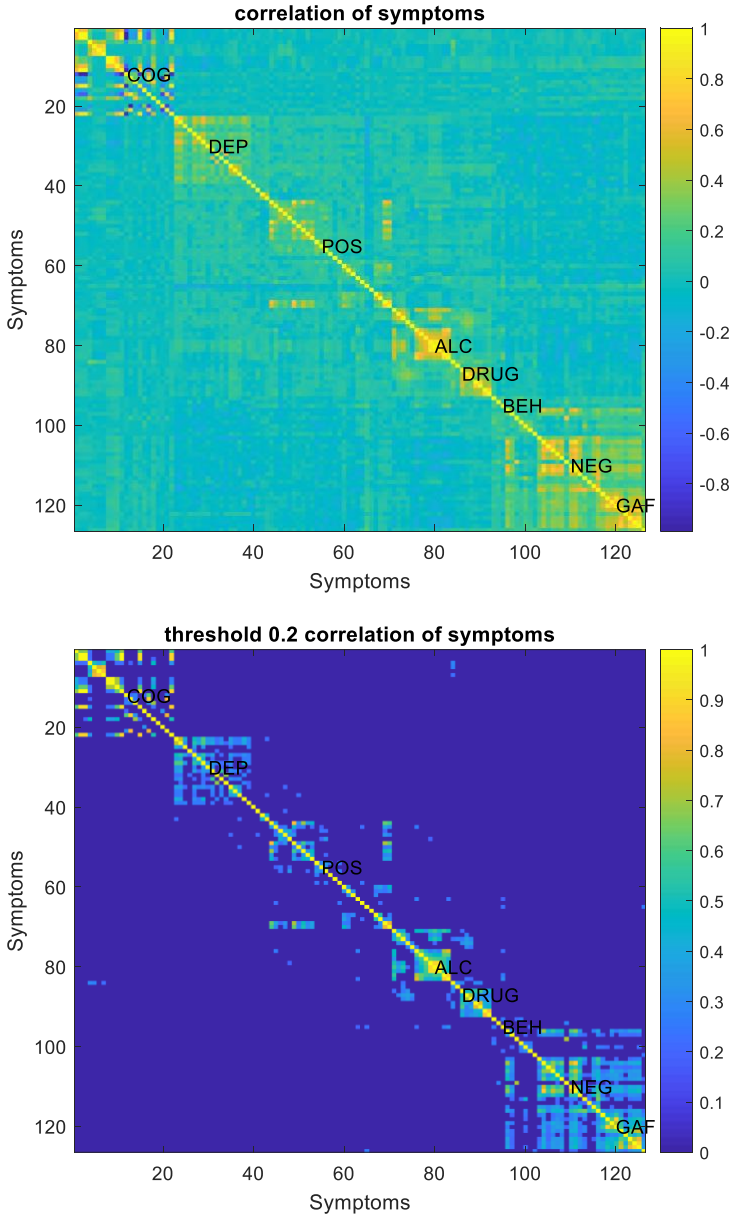
DWI processing

DWI processed data were taken from a prior study, methods for which are described in detail elsewhere (ref). In brief, DWIs were pre-processed with FMRIB Software Library (FSL, version 5.11) [32]. This involved i) visual inspection for artifacts and removal of four scans due to poor image quality, ii) correction for motion and gradient-induced eddy currents [33, 34] ; and, iii) computation of fractional anisotropy (FA) volumes by fitting a single-diffusion tensor to the harmonized DWIs.

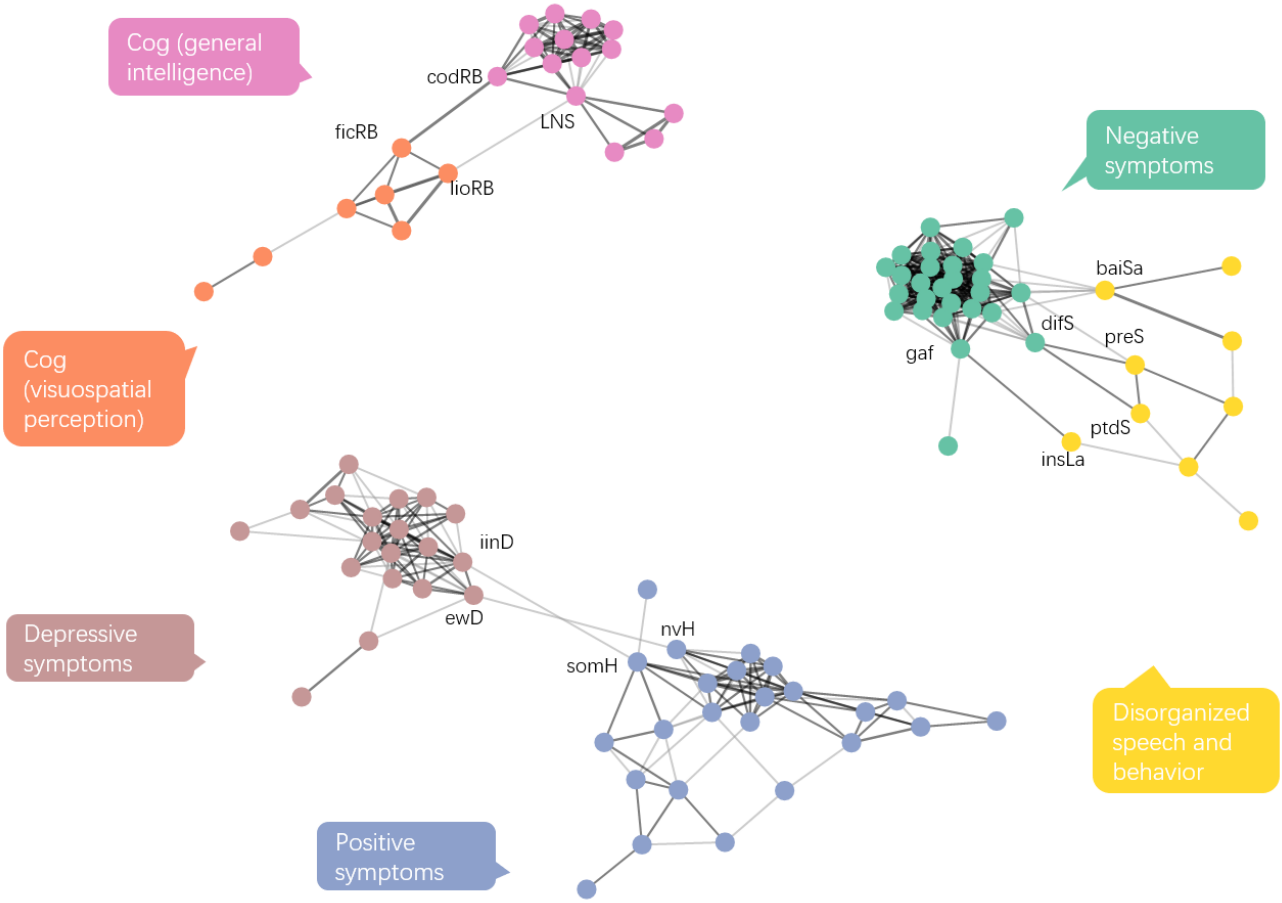
ENIGMA-DTI protocols (http://enigma.ini.usc.edu/protocols/dti-protocols/) were used to extract average FA estimates from voxels on a white matter skeleton [35]. First, ANTs (http://stnava.github.io/ANTs/) was used to nonlinearly register FA maps to the common ENIGMA-DTI target, derived from 400 adult brains [35]. Second, individually registered brains were projected onto the ENIGMA-DTI white matter skeleton with FSL's tract-based spatial statistics (*TBSS*) [36], which was employed to alleviate any residual misalignment error. Resulting skeletonized FA maps were used to extract values from a subset of white matter regions comprising the JHU white matter atlas (48 regions). To define each region of interest (ROI), FA was averaged over skeleton-voxels traversing a given atlas region. Statistical inference was performed on the resulting skeletonized ROIs.



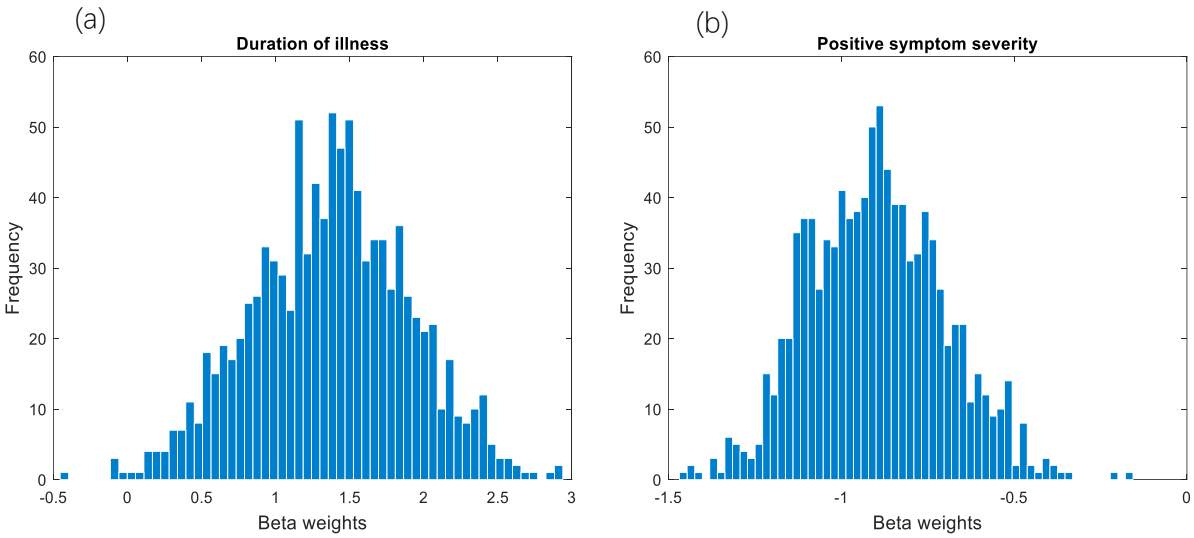
Supplementary Figure 1. Centrality measures across thresholds. The impact of network thresholding on centrality estimates, including degree, closeness and betweenness. Increasing the correlation threshold (vertical axis) resulted in lower degree (a) and closeness (b). Whereas, betweenness peaked at a threshold around r=.2 and declined thereafter. The lines represent the mean (blue) and standard deviation (yellow) across all symptom items.



Supplementary Figure 2. Correlation matrix (network) of symptoms in schizophrenia. A total of 126 symptoms from all subjects were used to construct symptom correlation matrices. Each cell in the matrix quantifies the relationship between a pair of symptoms. The network was contructed using (a) the raw correlation coefficients, which were (b) thresholded to remove weak/spurious connections (0.2 is the threshold where all the symptoms in the network exhibit the highest betweenness). Symptom associations were characterized by both negative correlations (blue), and positive correlations (yellow). **Abbreviations.** COG: cognitive symptoms; GAF: General Assessment of Functioning Scale; NEG: Negative symptoms; BEH: behavior affect symptoms; ALC: alcohol drug abuse; POS: positive symptoms; DEP: depressive symptoms.



Supplementary Figure 3. Symptom comorbidity network without substance use items. Circles represent nodes (symptoms), and lines represent associations between symptom pairs, where thicker lines indicate stronger correlations. The network layout is force-directed, whereby distant variables are weakly correlated and adjacent variables are strongly correlated. Modularity analysis yielded 6 symptom modules: negative symptoms (green), positive symptoms (blue), depressive symptoms (brown), disorganized speech and behavior (yellow), cognition - intelligence (violet) and cognition - visuospatial perception (orange). Refer to Supplementary Table 1 for specific item names. As shown, omitting substance use items removed between-module connections representing substance use items in the original network, while preserving local (within module) network structure. These results confirm the centrality of substance use items in a schizophrenia symptom network and demonstrates network stability between symptom networks computed with and without substance use/abuse items.



Supplementary Figure 4. Beta weight frequency across repetitions of the 10-fold cross validation analyses. Histograms present beta weight frequency across 1000 repetitions of the 10-fold cross validation analyses evaluating associations between the number of connected components with duration of illness (a) and with positive symptom severity (b). Results from the 10-fold cross validation suggest that the association between duration of illness and the number of connected components is significant in 42.4% out of 1000 repetitions, whereas the association between psychosis severity and number of connected components is significant in 96.8% out of 1000 repititions.

Supplementary Table 1.1 Symptom items included in network construction

Scale	Symptom/s assessed
Diagnostic Interview for psychosis (DIP)	Social functioning and disability, psychosis (positive and negative symptoms), patterns of service utilization and patient-perceived need for services, as well as drug use (emphasis on alcohol use and tolerance).
Wechsler Abbreviated Scale of Intelligence (WASI)	Verbal, nonverbal, and general cognitive functioning.
WTAR (Wechsler Test of Adult Reading)	Premorbid IQ and memory performance.
COWAT (Controlled Oral Word Association Test)	Verbal fluency.
LNS (Letter Number Sequencing)	Verbal working memory
RBANS (Repeatable Battery for Assessment of Neuropsychological Status)	Cognitive performance across 5 domains: memory (immediate and delayed), visuospatial function, language (semantic Fluency) and attention.
SANS (Scale for Assessment of Negative Symptoms)	Five aspects of negative symptoms: alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attentional impairment.
GAF (Global Assessment Functioning)	The degree to which an individual's symptoms affect their day-to-day life.

Supplementary Table 1.2 Symptom abbreviations corresponding to Figure 2 (main text)

Items Included	Modules	Abbreviation	Symptom scales
USA standard IQ score*	9	usWT	WTAR (Wechsler Test of Adult Reading)
Vocab	9	vocWA	WASI (Wechsler Abbreviated Scale of Intelligence)
Matrix reasoning	9	mrWA	WASI (Wechsler Abbreviated Scale of Intelligence)
IQ score	9	iqWA	WASI (Wechsler Abbreviated Scale of Intelligence)
LNS	9	LNS	LNS (Letter Number Sequencing)
Naming words starting with F	9	wsfCO	COWAT (Controlled Oral Word Association Test)
Naming words starting with A	9	wsaCO	COWAT (Controlled Oral Word Association Test)
Naming words starting with S	9	wssCO	COWAT (Controlled Oral Word Association Test)
List total (list learning + list recall)	9	lisRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Story memory	8	stoRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Figure copy	8	ficRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Line orientation	8	lioRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Picture	9	picRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Semantic fluency	8	sefRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Digit	8	digRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Coding	9	codRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
List recognition	8	lirRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Story recall	8	strRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Figure recall	9	firRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Dysphoria	11	dysD	DIP depression (Diagnostic Interview for Psychosis)
Pleasure loss	11	ploD	DIP depression (Diagnostic Interview for Psychosis)
Suicidal thoughts	11	suiD	DIP depression (Diagnostic Interview for Psychosis)
Diurnal activities	11	diuD	DIP depression (Diagnostic Interview for Psychosis)
Poor concentration	11	pcoD	DIP depression (Diagnostic Interview for Psychosis)
Activity levels	11	sacD	DIP depression (Diagnostic Interview for Psychosis)
Energy levels	11	loeD	DIP depression (Diagnostic Interview for Psychosis)
Libido	11	libD	DIP depression (Diagnostic Interview for Psychosis)
Poor appetite	11	paD	DIP depression (Diagnostic Interview for Psychosis)
Increased appetite	11	inaD	DIP depression (Diagnostic Interview for Psychosis)
Weight loss	11	wloD	DIP depression (Diagnostic Interview for Psychosis)
Weight gain	11	wgaD	DIP depression (Diagnostic Interview for Psychosis)
Insomnia (early in the night)	11	iinD	DIP depression (Diagnostic Interview for Psychosis)
Insomnia (middle of the night)	11	minD	DIP depression (Diagnostic Interview for Psychosis)
Early waking	11	ewD	DIP depression (Diagnostic Interview for Psychosis)
Excessive sleep	11	esD	DIP depression (Diagnostic Interview for Psychosis)
Excessive self-guilt	11	esgD	DIP depression (Diagnostic Interview for Psychosis)
Nihilistic	10	denD	DIP depression (Diagnostic Interview for Psychosis)
Elevated mood	11	elMa	DIP mania (Diagnostic Interview for Psychosis)
Irritable mood	11	irMa	DIP mania (Diagnostic Interview for Psychosis)
Auditory	10	auH	DIP hallucination (Diagnostic Interview for Psychosis)
Visual	10	viH	DIP hallucination (Diagnostic Interview for Psychosis)
Olfactory	10	olfH	DIP hallucination (Diagnostic Interview for Psychosis)
Somatic	10	somH	DIP hallucination (Diagnostic Interview for Psychosis)
Sexual	10	she	DIP hallucination (Diagnostic Interview for Psychosis)
All modalities	10	amH	DIP hallucination (Diagnostic Interview for Psychosis)
Nonverbal	10	nvH	DIP hallucination (Diagnostic Interview for Psychosis)
Abusive	10	abH	DIP hallucination (Diagnostic Interview for Psychosis)
Commentary	10	comH	DIP hallucination (Diagnostic Interview for Psychosis)
Third person	10	tpH	DIP hallucination (Diagnostic Interview for Psychosis)
Insertion	10	insT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Broadcasting	10	broT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Withdrawal	10	wiT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Echolalia	10	echT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)

Passivity	10	paDe	DIP delusion (Diagnostic Interview for Psychosis)
Persecutory	10	pscDe	DIP delusion (Diagnostic Interview for Psychosis)
Influence	10	infDe	DIP delusion (Diagnostic Interview for Psychosis)
Perception	10	perDe	DIP delusion (Diagnostic Interview for Psychosis)
Grandiose	1	graDe	DIP delusion (Diagnostic Interview for Psychosis)
Bizarre	10	bizDe	DIP delusion (Diagnostic Interview for Psychosis)
Lack of insight	3	insLa	DIP insight (Diagnostic Interview for Psychosis)
Organized delusions	10	orgPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Widespread delusions	10	wsPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
one week (Delusions and concurrent hallucinations period)	10	owPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Jealous delusions	10	jePs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Alcohol – ever used	1	aleAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Frequency of alcohol use	1	freAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Heavier frequency (6 or more drinks /time)	1	hfAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Difficulty reducing alcohol use	1	cdAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Guilt associated with alcohol use	1	gltAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Criticism associated with alcohol use	1	criAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Morning alcohol consumption	1	mrAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Risk taking to acquire alcohol	1	rtAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Craving	1	craAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Capacity to control alcohol intake	1	ctcAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Tolerance	1	tlrAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Withdrawal problems	1	wpAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Social legal problems	1	slpAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Drugs ever used	1	dreDr	DIP drug (Diagnostic Interview for Psychosis)
Tobacco ever used	1	tbeDr	DIP drug (Diagnostic Interview for Psychosis)
Drug abuse	1	abDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime alcohol use	1	ltaDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to alcohol use	1	ppaDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime cannabis use	1	ltcDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to cannabis use	1	ppcDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime use of other drugs	1	ltoDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to other drugs	1	ppoDr	DIP drug (Diagnostic Interview for Psychosis)
Agitated	2	agiBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Catatonia	2	cttBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Bizarre	1	bizBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Restricted	3	reBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Blunted	3	bluBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Inappropriate	2	inaBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Speech pressure	2	preS	DIP speech (Diagnostic Interview for Psychosis)
Speech difficulties	3	difS	DIP speech (Diagnostic Interview for Psychosis)
Speech - positive thought disorder	2	ptdS	DIP speech (Diagnostic Interview for Psychosis)
Speech incoherence	3	ichS	DIP speech (Diagnostic Interview for Psychosis)
Speech – negative thought disorder	3	ntdS	DIP speech (Diagnostic Interview for Psychosis)
Blunted affect – facial expression	3	bafSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – spontaneous movement	3	basSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – gestures	3	bagSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – eye contact	3	baeSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – responsivity	3	banSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – inappropriate	2	baiSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – vocal inflections	3	bavSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – overall	3	baSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – speech poverty	3	alpSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – speech content	3	alcSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – blocking	3	albSa	SANS (Scale for Assessment of Negative Symptoms)

Alogia – latency response	3	allSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – overall	3	aloSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – grooming	3	avgSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – persistence	3	aviSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – physical anergia	3	avpSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – overall	3	avoSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – recreational	3	asrSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – sexual/activity	3	assSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – intimacy	3	asiSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – relationships	3	areSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – overall	3	asoSa	SANS (Scale for Assessment of Negative Symptoms)
Global functioning score	3	Gaf	GAF (Global Assessment Functioning)
Items Included	Modules	Abbreviation	Symptom scales
USA standard IQ score*	9	usWT	WTAR (Wechsler Test of Adult Reading)
Premorbid IQ Score	9	sWT	WTAR (Wechsler Test of Adult Reading)
UK Standard IQ score	9	stWT	WTAR (Wechsler Test of Adult Reading)
Vocab	9	vocWA	WASI (Wechsler Abbreviated Scale of Intelligence)
Matrix reasoning	9	mrWA	WASI (Wechsler Abbreviated Scale of Intelligence)
IQ score	9	iqWA	WASI (Wechsler Abbreviated Scale of Intelligence)
LNS	9	LNS	LNS (Letter Number Sequencing)
Naming words starting with F	9	wsfCO	COWAT (Controlled Oral Word Association Test)
Naming words starting with A	9	wsaCO	COWAT (Controlled Oral Word Association Test)
Naming words starting with S	9	wssCO	COWAT (Controlled Oral Word Association Test)
List total (list learning + list recall)	9	lisRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Story memory	8	stoRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Figure copy	8	ficRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Line orientation	8	lioRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Picture	9	picRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Semantic fluency	8	sefRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Digit	8	digRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Coding	9	codRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
List recognition	8	lirRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Story recall	8	strRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Figure recall	9	firRB	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Dysphoria	11	dysD	DIP depression (Diagnostic Interview for Psychosis)
Pleasure loss	11	ploD	DIP depression (Diagnostic Interview for Psychosis)
Suicidal thoughts	11	suiD	DIP depression (Diagnostic Interview for Psychosis)
Diurnal activities	11	diuD	DIP depression (Diagnostic Interview for Psychosis)
Poor concentration	11	pcoD	DIP depression (Diagnostic Interview for Psychosis)
Activity levels	11	sacD	DIP depression (Diagnostic Interview for Psychosis)
Energy levels	11	loeD	DIP depression (Diagnostic Interview for Psychosis)
Libido	11	libD	DIP depression (Diagnostic Interview for Psychosis)
Poor appetite	11	paD	DIP depression (Diagnostic Interview for Psychosis)
Increased appetite	11	inaD	DIP depression (Diagnostic Interview for Psychosis)
Weight loss	11	wloD	DIP depression (Diagnostic Interview for Psychosis)
Weight gain	11	wgaD	DIP depression (Diagnostic Interview for Psychosis)
Insomnia (early in the night)	11	iinD	DIP depression (Diagnostic Interview for Psychosis)
Insomnia (middle of the night)	11	minD	DIP depression (Diagnostic Interview for Psychosis)
Early waking	11	ewD	DIP depression (Diagnostic Interview for Psychosis)
Excessive sleep	11	esD	DIP depression (Diagnostic Interview for Psychosis)
Excessive self-guilt	11	esgD	DIP depression (Diagnostic Interview for Psychosis)
Nihilistic	10	denD	DIP depression (Diagnostic Interview for Psychosis)
Elevated mood	11	elMa	DIP mania (Diagnostic Interview for Psychosis)
Irritable mood	11	irMa	DIP mania (Diagnostic Interview for Psychosis)
Auditory	10	auH	DIP hallucination (Diagnostic Interview for Psychosis)
Visual	10	viH	DIP hallucination (Diagnostic Interview for Psychosis)

Olfactory	10	olfH	DIP hallucination (Diagnostic Interview for Psychosis)
Somatic	10	somH	DIP hallucination (Diagnostic Interview for Psychosis)
Sexual	10	she	DIP hallucination (Diagnostic Interview for Psychosis)
All modalities	10	amH	DIP hallucination (Diagnostic Interview for Psychosis)
Nonverbal	10	nvH	DIP hallucination (Diagnostic Interview for Psychosis)
Abusive	10	abH	DIP hallucination (Diagnostic Interview for Psychosis)
Commentary	10	comH	DIP hallucination (Diagnostic Interview for Psychosis)
Third person	10	tpH	DIP hallucination (Diagnostic Interview for Psychosis)
Insertion	10	insT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Broadcasting	10	broT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Withdrawal	10	wiT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Echolalia	10	echT	DIP Subjective thought disorder (Diagnostic Interview for Psychosis)
Passivity	10	paDe	DIP delusion (Diagnostic Interview for Psychosis)
Persecutory	10	pscDe	DIP delusion (Diagnostic Interview for Psychosis)
Influence	10	infDe	DIP delusion (Diagnostic Interview for Psychosis)
Perception	10	perDe	DIP delusion (Diagnostic Interview for Psychosis)
Grandiose	1	graDe	DIP delusion (Diagnostic Interview for Psychosis)
Bizarre	10	bizDe	DIP delusion (Diagnostic Interview for Psychosis)
Lack of insight	3	insLa	DIP insight (Diagnostic Interview for Psychosis)
Organized delusions	10	orgPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Widespread delusions	10	wsPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
one week (Delusions and concurrent hallucinations period)	10	owPs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Jealous delusions	10	jePs	DIP psychotic symptoms (Diagnostic Interview for Psychosis)
Alcohol – ever used	1	aleAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Frequency of alcohol use	1	freAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Heavier frequency (6 or more drinks /time)	1	hfAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Difficulty reducing alcohol use	1	cdAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Guilt associated with alcohol use	1	gltAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Criticism associated with alcohol use	1	criAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Morning alcohol consumption	1	mrAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Risk taking to acquire alcohol	1	rtAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Craving	1	craAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Capacity to control alcohol intake	1	ctcAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Tolerance	1	tlrAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Withdrawal problems	1	wpAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Social legal problems	1	slpAlc	DIP alcohol (Diagnostic Interview for Psychosis)
Drugs ever used	1	dreDr	DIP drug (Diagnostic Interview for Psychosis)
Tobacco ever used	1	tbeDr	DIP drug (Diagnostic Interview for Psychosis)
Drug abuse	1	abDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime alcohol use	1	ltaDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to alcohol use	1	ppaDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime cannabis use	1	ltcDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to cannabis use	1	ppcDr	DIP drug (Diagnostic Interview for Psychosis)
Lifetime use of other drugs	1	ltoDr	DIP drug (Diagnostic Interview for Psychosis)
Psychopathology linked to other drugs	1	ppoDr	DIP drug (Diagnostic Interview for Psychosis)
Agitated	2	agiBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Catatonia	2	cttBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Bizarre	1	bizBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Restricted	3	reBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Blunted	3	bluBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Inappropriate	2	inaBe	DIP behavior affect (Diagnostic Interview for Psychosis)
Speech pressure	2	preS	DIP speech (Diagnostic Interview for Psychosis)
Speech difficulties	3	difS	DIP speech (Diagnostic Interview for Psychosis)
Speech - positive thought disorder	2	ptdS	DIP speech (Diagnostic Interview for Psychosis)
Speech incoherence	3	ichS	DIP speech (Diagnostic Interview for Psychosis)

Speech – negative thought disorder	3	ntdS	DIP speech (Diagnostic Interview for Psychosis)
Blunted affect – facial expression	3	bafSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – spontaneous movement	3	basSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – gestures	3	bagSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – eye contact	3	baeSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – responsivity	3	banSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – inappropriate	2	baiSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – vocal inflections	3	bavSa	SANS (Scale for Assessment of Negative Symptoms)
Blunted affect – overall	3	baSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – speech poverty	3	alpSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – speech content	3	alcSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – blocking	3	albSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – latency response	3	allSa	SANS (Scale for Assessment of Negative Symptoms)
Alogia – overall	3	aloSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – grooming	3	avgSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – persistence	3	aviSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – physical anergia	3	avpSa	SANS (Scale for Assessment of Negative Symptoms)
Avolition – overall	3	avoSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – recreational	3	asrSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – sexual/activity	3	assSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – intimacy	3	asiSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – relationships	3	areSa	SANS (Scale for Assessment of Negative Symptoms)
Asociality – overall	3	asoSa	SANS (Scale for Assessment of Negative Symptoms)
Global functioning score	3	Gaf	GAF (Global Assessment Functioning)

*Module: 1. Substance abuse; 2. Disorganized speech and behavior; 3. Negative symptoms; 8. Cognitive symptoms (visuospatial perception); 9. Cognitive symptoms (general intelligence); 10. Positive symptoms; 11. Depressive symptoms.

*DIP drug scales including amphetamine, cannabis, cocaine, ecstasy, heroin, inhalants solvents, LSD, tranquilizer were removed in data processing due to high missing data rate.

Items removed due to low correlation coefficients and form modules disconnected to the network

Items	Modules	Symptom scales
List recall	4	RBANS (Repeatable Battery for Assessment of Neuropsychological Status)
Delusions of poverty	5	DIP depression (Diagnostic Interview for Psychosis)
Primary	6	DIP delusions (Diagnostic Interview for Psychosis)
Antipsychotics – insight	7	DIP insight (Diagnostic Interview for Psychosis)

Supplementary Table 2. Similarity in betweenness centrality across sites

r	Sydney (n=123)	Melbourne (n=148)	Brisbane (n=168)	Perth (n=163)	Newcastle (n=47)
Sydney	1.000	0. 1434	0.2765*	0.2364*	0.1750*
Melbourne		1.000	0.2321*	0.1182	0.1109
Brisbane			1.000	0.1621	0.2058*
Perth				1.000	0.1444
Newcastle					1.000

Values represent correlation coefficients and * denotes significance (p<0.05)

Supplementary Table 3. Similarity in closeness centrality across sites

r	Sydney (n=123)	Melbourne (n=148)	Brisbane (n=168)	Perth (n=163)	Newcastle (n=47)
Sydney	1.000	0.6933*	0.6343 *	0.5177*	0.3091*
Melbourne		1.000	0.6786*	0.4837*	0.4002*
Brisbane			1.000	0.5967*	0.4073*
Perth				1.000	0.3544*
Newcastle					1.000

Values represent correlation coefficients and * denotes significance (p<0.05)

Supplementary Table 4. Similarity in degree centrality across sites

	Sydney (n=123)	Melbourne (n=148)	Brisbane (n=168)	Perth (n=163)	Newcastle (n=47)
Sydney	1.000	0.6855*	0.6937*	0.5947*	0.3815*
Melbourne		1.000	0.6977*	0.5463*	0.4643*
Brisbane			1.000	0.6458*	0.4001*
Perth				1.000	0.4060*
Newcastle					1.000

Values represent correlation coefficients and * denotes significance (p<0.05)

Supplementary Table 5. Similarity in centrality measures across males and females

	betweenness	closeness	degree
Male (n=433) Female (n=209)	0.088	0.665*	0.730*

Values represent correlation coefficients and * denotes significance (p<0.05)

Supplementary Table 6. Similarity between the LASSO network and Pearson network.

Similarity	betweenness	closeness	degree
gamma=0.3	0.046	0.265*	0.444*

Values represent correlation coefficients and * denotes significance (p<0.05)

Supplementary Table 7. Cohen's d effect size for each between-group comparison

	Duration of illness			Positive Symptom Severity		
# of components	**t-value**	**p-value**	**Cohen's d**	**t-value**	**p-value**	**Cohen's d**
1 and 2	-1.4371	0.1512	0.1440	3.8173	1.4861e-04	0.3825
2 and 3	-1.3642	0.1745	0.2895	1.4670	0.1445	0.3113
1 and 3	-2.3311	0.0201	0.4608	3.4391	6.3093e-04	0.6798

Supplementary Table 8. GLM results across different thresholds to define ranked symptoms as 'severe'

	Classified as severe symptoms (%)		
GLM analyses	Top 10% *t*	Top 15% *t*	Top 20% *t*
Impact of clustering on positive symptom severity	-5.306*	-5.467*	-5.827*
Impact of clustering on illness duration	3.036*	2.688*	2.080*

Values represent correlation coefficients and * denotes significance ($p<0.05$)

Exploring the potential confound of study site.

Supplementary analyses were performed to further ameliorate potential site effects and to establish the reliability of our findings. First, a leave-one-site-out cross-validation was conducted by partitioning the symptom data by study site. In each fold, a single site was left out and a symptom comorbidity network was mapped using subjects from the remaining sites. The left-out subjects from one site were then projected onto the network to determine their number of active modules. This was repeated for each site. At the end of this leave-out-one-site cross-validation procedure, we were left with an out-of-sample estimate of the number of active modules for each subject. The GLM results reproduced the main findings: a significant linear increase in the number of connected components as a function of illness duration ($t=2.818$, $\beta=1.309$, $p=0.005$), as well as a significant decrease in the number of connected components with positive symptom severity ($t=-5.297$, $\beta=-0.868$, $p<0.001$). Similarly, results from repeating the canonical correlation analysis (CCA) in a leave-one-site-out cross-validation framework were consistent with findings from the main CCA. Specifically, the degree of symptom clustering was significantly and positively correlated to regional FA values ($r=0.65$, $p<0.001$, bootstrap=5000).

We further repeated our analyses after simply controlling for study site. Consistent with the main finings, GLM analyses yielded a significant linear increase in the number of connected components as a function of illness duration ($t=2.218$, $\beta=1.654$, $p=0.027$), as well as a significant linear decrease in the number of connected components with positive symptom severity ($t=-4.915$, $\beta=-1.268$, $p<0.001$), after controlling for study site and the number of active symptom modules. Results from repeating the CCA after controlling for study site were also consistent with the main findings, such that increased symptom clustering significantly covaried with decreased regional FA values ($r=0.59$, $p=0.049$, bootstrap=5000).