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Prospective Memory Influences Social Functioning in People With First-Episode Schizophrenia:
A Network Analysis and Longitudinal Study

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ABSTRACT

Background: Prospective memory (PM) impairment is associated with impaired social functioning, but evidence is limited to chronic schizophrenia samples and cross-sectional design. The aim of this study was to utilize network analysis to address the complex interplay between PM, psychopathology, and functional outcome.

Methods: This longitudinal study recruited 119 people with first-episode *DSM-IV* schizophrenia and followed up with them for 2 to 6 years. PM and working memory were assessed at baseline (in 2010–2015) using valid computerized tasks and the Letter-Number Span Test, respectively. Psychopathology and social functioning were assessed at endpoint (in 2016–2017) using the Positive and Negative Syndrome Scale (PANSS) and the Social and Occupational Functioning Assessment Scale (SOFAS), respectively. Network analysis examined the effect of baseline PM on SOFAS while accounting for the effects of psychopathology.

Results: The resultant network showed that social functioning, PANSS positive symptoms, and PANSS general symptoms clustered together, whereas time-based and event-based PM and working memory formed another cluster. Time-based PM linked event-based PM and working memory with social functioning. Time-based PM (expected influence [EI] = 0.69), event-based PM (EI = 0.65), and working memory (EI = 0.83) demonstrated high values of expected influence, but social functioning (variance explained = 0.685) and PANSS negative (variance explained = 0.657) and general (variance explained = 0.583) subscales demonstrated high values of predictability.

Conclusions: Time-based PM is the central node linking neurocognitive functions with social functioning. PM and working memory are "target" nodes for interventions bringing changes to the network, whereas social functioning and psychopathology are "malleable" nodes. PM and working memory are promising intervention targets for functional recovery in schizophrenia.

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Prospective memory (PM) is the ability to carry out an intended action in the future.[1] In prospective remembering, an individual must correctly encode a delayed intention, maintain it during a lapse of time, retrieve it when appropriate cues and specified time come, and execute the delayed intention.[1] Thus, PM involves retrospective memory and executive functions (such as working memory and task switching).[2] Two types of PM are widely recognized: time-based PM, which involves carrying out the intended action at a specified time, and event-based PM, which involves carrying out the intended action when a specified event occurs.[3] PM impairments are found in people with schizophrenia.[4,5] Previous studies found that individuals with schizophrenia and impaired PM exhibited a high degree of disabilities in their daily functioning.[6–8] Other studies also reported that PM impairments in schizophrenia could be translated into problems in managing medication[9,10] and contribute to relapse and functional deteriorations.

Although empirical evidence[6–10] generally supports that PM impairment is associated with functional and clinical outcomes in people with schizophrenia, several important issues remain unresolved in the literature. First, previous studies using cross-sectional design[6–8,10] were less able to link PM to clinical and social functioning outcomes. Moreover, since previous PM studies recruited people with chronic schizophrenia,[6–10] their findings may not be generalizable to people with early-stage schizophrenia. Importantly, psychopathology is known to influence neurocognitive performance in people with schizophrenia,[11] yet previous findings failed to account for the effects of psychopathology-neurocognition interaction on social functioning.[6,7] Supplementary Table 1 compares the previous studies that investigated the relationship between PM and functional outcomes.[6–8,10,44]

Network analysis[12] is a useful method to study the interplay between various factors, such as psychopathology and neurocognitive and social functions.[13] This data-driven approach is able to construct networks that consist of nodes (variables) connected to each other by edges and is a useful tool for visualizing and interpreting relational data.[14,15] Traditional models regarded symptoms as

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Clinical Points

- Schizophrenia is associated with poor functional outcomes, and cognitive functions influence social functioning.
- Prospective memory (PM) is the ability to remember to carry out an intended action in the future and is important for everyday functioning in people with schizophrenia.
- PM and working memory are important intervention targets for improving social functioning in people with schizophrenia.

manifestations of a common latent factor (or disease process) and suggested that the interplay between symptoms can be explained by the common influence of such a latent factor.[15] In contrast, the network approach posits that the causes of symptoms are multifactorial. In the dynamic interplay between different nodes of the network, variables such as psychopathology and neurobiological and social constructs could directly influence each other and are assumed to have autonomous causal power.[15] In constructing the network structure, partial correlations of each 2 variables are estimated, with other variables being controlled for. Thus, the correlation between 2 nodes reflects their direct relationship. In network analysis, the index of expected influence (EI) is the sum of edge weights of a given node.[16] Nodes with more edge weights suggest they are more closely connected within the network and thus are more important and "impactful" than other nodes. Predictability, another useful index, estimates the variance of a given node, which is determined by neighbor nodes.[17] A higher predictability index suggests that a given node will more easily be subjected to change and is more dependent on the network.[17]

This novel approach has been used in psychopathology and personality research. For instance, Fonseca-Pedrero et al[18] recently demonstrated a network linking schizotypal symptoms in a large healthy sample, confirming the dimensional model previously found in subclinical samples. Based on network analysis, a theoretical model for understanding psychosis has been proposed.[15] For instance, closely linked nodes (such as anxiety and paranoid symptoms) may implicate a relatively direct causal relation (eg, anxiety may activate paranoid symptoms), whereas loosely connected nodes (such as hallucination and depressed mood) implicate relatively indirect causal relation (eg, hallucination may directly activate anxiety and in turn indirectly activate depressed mood).

Applying network analysis to psychosis research on functional outcomes, a recent large-scale study conducted by Galderisi et al[13] has employed network analysis to elucidate the relationship between neurocognitive functions, psychopathology, and social functioning in people with schizophrenia. The results showed that neurocognitive functions (ie, working memory, attention, and visuospatial and verbal learning) are connected with everyday functioning through the bridging link of functional capacity. However, Galderisi and colleagues' study[13] was cross-sectional and used a sample with a long duration of illness of schizophrenia (mean = 16.4 years). This group of authors conducted another longitudinal network analysis study[19] that reassessed the same cohort after 4 years and found that the network structure at baseline was longitudinally stable. Another recent network analysis study[20] examined the interactions between neurocognitive functions, psychopathology, and social functioning in people with first-episode psychosis and found that the disorganization subscale of the Positive and Negative Syndrome Scale (PANSS)[21] bridged the link between neurocognitive functions and social functioning. Hasson-Ohayon et al (2018)[11] investigated the relationship between neurocognitive, social cognitive, and metacognitive variables as well as psychopathology in people with schizophrenia, using network analysis. They found that the "cognitive symptoms" subscale[22] of the PANSS appeared the most central in the network, followed by metacognitive variables. Taken together, these recent findings support the notion that psychopathology-neurocognition interaction could influence functional outcomes in people with schizophrenia.[11,13,19,20] Table 1 compares the strengths and weaknesses of these previous network analysis studies. To our knowledge, no study has been conducted to examine the impact of PM on functional outcomes using longitudinal design and network analysis.

This study therefore sought to examine the relationship between PM, psychopathology, and social functioning using network analysis. To address the limitations (see Table 1 and Supplementary Table 1) of previous studies,[6–8,10,11,13,19] we recruited people with first-episode schizophrenia for detailed PM assessments and followed up with them for 2 to 6 years. We hypothesized that baseline PM impairments would be connected to functional outcomes beyond 2 years, even after the effects of psychopathology have been accounted for. In view of previous evidence suggesting that time-based, instead of event-based, PM impairment is more longitudinally stable,[23,24] we also hypothesized that time-based PM at the baseline would be strongly connected to functional outcomes beyond 2 years of follow-up in people with first-episode schizophrenia, after accounting for the effects of psychopathology.

METHODS

Participants

One hundred nineteen individuals with first-episode schizophrenia were recruited conveniently from an early psychosis intervention clinic at Castle Peak Hospital (CPH), Hong Kong. Our participants formed part of a larger cohort recruited in a research project at CPH, which specifically examined the endophenotypic properties and translational potentials of cognitive markers, including PM.[25] In our sample, *DSM-IV*[26] diagnosis of schizophrenia was ascertained using the best-estimate approach, supplemented with medical records and structural interviews by qualified psychiatrists. The inclusion criteria included (1) aged 15–60 years, (2) ethnic Chinese, and (3) able to communicate in written and oral Chinese. The exclusion criteria included

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Table 1. Previous Network Analysis Studies Investigating the Interplay Between Neurocognitions, Psychopathology, and Functional Outcomes in Schizophrenia Patients

Study	Sample (N)	Study design	Neurocognitive nodes	Social functioning nodes	Clinical symptoms nodes	Other variables	Summary of results	Strengths	Weaknesses
Galderisi et al (2018)[13]	742 SCZ patients	27 variables, cross-sectional design	Neurocognitions (by MCCB): verbal learning, visuospatial memory, attention, problem solving, working memory, processing speed Social cognitions: FEIT, MCCB, MSCEIT, TASIT	UPSA-B (for functional capacity), SLOF (for real-life functioning)	PANSS, BNSS, CDSS	Internalized stigma, resilience, social support, engagement of MHS	The most central node is functional capacity (the level of functioning that a person can potentially achieve) Nodes of neurocognition and social cognition were densely interconnected and linked to real-life functioning Social cognition is not directly connected to real-life functioning	Large sample size A large number of nodes Multiple measures for functioning Included negative symptoms	PM was not included Cross-sectional in design
Hasson-Ohayon et al (2018)[11]	81 SCZ patients	Cross-sectional design	Neurocognitions (by MATRICS): processing speed, attention, working memory, verbal learning, visual learning, reasoning Social cognitions: picture-sequencing task (mentalizing ability), BLERT (emotion recognition), Hinting Test (ToM), Social Attributions Test Metacognition: MAS	None	PANSS	NA	Metacognition has high strength of centrality in the network	Included metacognition	PM was not included Cross-sectional in design Lack of social functioning measures
Chang et al (2019)[20]	323 SCZ spectrum	16 variables, cross-sectional design	Digit span, digit symbol, logical memory, visual reproduction, verbal fluency, WCST	RFS (role function), PAS (premorbid function), QoL	PANSS, SANS, CDSS	NA	Amotivation node has highest centrality SF was most connected with amotivation in the network Among cognitive nodes, digit span has the highest centrality	Large sample size Multiple measures for functioning Included negative symptoms	PM was not included Cross-sectional in design
Galderisi et al (2020)[19]	618 SCZ patients	27 variables, longitudinal design, 4-year follow-up	Neurocognitions (by MCCB): verbal learning, visuospatial memory, attention, problem solving, working memory, processing speed Social cognitions: FEIT, MCCB, MSCEIT, TASIT	UPSA-B (functional capacity), SLOF (real-life functioning)	PANSS, BNSS, CDSS	Internalized stigma, resilience, social support, engagement of MHS	The network found at the baseline (see Galderisi et al, 2018[13]) remained stable at 4-year follow-up Social cognition was initially not connected to functional capacity but became connected at 4-year follow-up Neurocognition was initially not connected to functional capacity but became connected at 4-year follow-up	Large sample size A large number of nodes Multiple measures for functioning Included negative symptoms Follow-up	PM was not included

Abbreviations: BLERT = Bell-Lysaker Emotional Recognition Task, BNSS = Brief Negative Symptom Scale, CDSS = Calgary Depression Scale for Schizophrenia, FEIT = Facial Emotion Identification Test, MAS = Metacognition Assessment Scale, MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, MCCB = Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, MHS = Mental Health Service, MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test, NA = not applicable, PANSS = Positive and Negative Syndrome Scale, PAS = Premorbid Adjustment Scale, PM = prospective memory, QoL = quality of life, RFS = Role Functioning Scale, SANS = Schedule for the Assessment of Negative Symptoms, SLOF = Specific Level of Functioning Scale, TASIT = The Awareness of Social Inference Test, UPSA-B = University of California San Diego Performance-Based Skills, WCST = Modified Wisconsin Card Sorting Test.

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(1) any comorbid *DSM-IV* Axis I disorder, (2) estimated IQ less than 70, (3) severe hearing or visual impairment, (4) history of head injury or neurologic disorders, (5) history of receiving electroconvulsive therapy (ECT) in the past 6 months, and (6) history of alcohol or substance abuse in the last 1 year.

Procedures

All participants were assessed as outpatients using valid cognitive tests at the baseline in 2010–2015 and were reassessed as outpatients in 2016–2017 for completion of outcome measurements. The data on PM performance in our participants have been reported in our earlier papers,[23,24,27,28] but the data on social functioning collected at the endpoint have never been used or published before. The research questions and methods of analysis of this study also differed critically from our earlier published papers.[23,24,27,28] All of the assessments were administered by trained research assistants (4 staff were involved), in a quiet room located within the psychiatric clinic of CPH. The full set of assessments took around 1 hour. A single session was adequate to complete the baseline or endpoint assessments.

Ethical Consideration

This study was approved by the Clinical & Research Ethics Committee of the New Territories West Cluster of the Hospital Authority of Hong Kong (protocol numbers: NTWC/CREC/823/10 and NTWC/CREC/16063). All participants provided informed written consent.

PM and Working Memory Assessment at the Baseline

A well-validated laboratory paradigm[27,28] was used to assess participants' prospective remembering. This computerized paradigm was "dual-task" in design[29] and comprised 2 sessions, ie, the time- and event-based PM sessions, each lasting for about 6 minutes. In each session, participants were engaged continuously in an ongoing "lexicon decision" task, while they were required to complete the PM task whenever the specified time or the specified event occurred. In the time-based PM session, when the digital clock situated near the keyboard reached a full minute (eg, 12:00), participants had to press a specified button. In the event-based PM session, when they saw the appearance of an animal character (eg, monkey) embedded in the lexicon of the ongoing task, they had to press a specified button. To complete the PM task successfully, participants had to encode and maintain the delayed intention (ie, pressing a specified button when the clock reaches a full minute or when an animal character appears), switch from the ongoing lexicon decision task to the PM task (either by self-initiation or by detection of the PM cue of animal characters) at the appropriate time and event, and execute the delayed intention.[30] Each session comprised 5 trials of the PM task. The PM score was calculated based on the percentage of accuracy in the PM task, which ranged from 0 to 1. The higher the PM score, the better the PM performance.

The Letter-Number Span Test (LNT)[31] was used to assess participants' working memory performance. In the LNT, a series of letters and numbers was read out by the interviewers, and participants were required to recall first the numbers in ascending order and then the letters in alphabetical order. Higher scores on the LNT indicate better working memory performance. Working memory is believed to be related to PM and social functioning.[4,28,31]

Assessments of Psychopathology and Social Functioning at the Endpoint

At the end of follow-up, a set of scales was administered by trained psychiatrists to all participants, including the PANSS,[21] the Montgomery-Åsberg Depression Rating Scale (MADRS),[32] the Simpson-Angus Scale (SAS),[33] and the Barnes Akathisia Scale (BAS).[34] The PANSS contains 3 subscales, namely the positive, the negative, and the general symptom subscales. The PANSS has been found to have good validity in previous research[21] and also demonstrated acceptable α coefficients in the present sample (ie, the Cronbach α values for the positive, the negative, and the general symptom subscales = 0.434, 0.886, and 0.561, respectively). The MADRS is a commonly used scale for measuring depressive symptoms in people with schizophrenia. It has been found to have good psychometric properties in previous research[35] and demonstrated a Cronbach α of 0.422 in the present sample. The SAS and the BAS are commonly used scales for measuring parkinsonism features and akathisia, as results of extrapyramidal side effects. These measures were found to have satisfactory psychometric properties in previous studies[36,37] and also demonstrated satisfactory α coefficients in the present sample (SAS: Cronbach α = .761; BAS: Cronbach α = .887). The Social and Occupational Functioning Assessment Scale (SOFAS)[38] was used to measure the level of social and occupational functioning from the *DSM-IV-TR*. The SOFAS is a clinician-rated scale, with scores ranging from 0 to 100. Lower scores indicate lower social and occupational functioning. The SOFAS has been found to be reliable and valid in assessing social functioning of people with schizophrenia.[38]

Statistical Analysis

A total of 11 variables were included in our network analysis, as shown in Table 2. The baseline neurocognitive variables included time-based and event-based PM and LNT, whereas the outcome variables included the scores of the positive, negative, and general symptom subscales of the PANSS; the MADRS; the scores of the scales assessing extrapyramidal side effects (ie, the SAS and the BAS); the SOFAS; and the total number of psychiatric hospitalizations since psychosis onset. Shapiro-Wilks tests were performed for each of the 11 variables to examine its normality. Nonparametric transformation (using the shrunken empirical cumulative distribution function in the huge package in R) was performed to ensure that all variables entered into network analysis would be of normal distribution.[39]

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Table 2. Variables for Network Analysis

Node	Timepoint	Mean	SD	Shapiro-Wilk normality test	
				W	*P*
Time-based prospective memory	Baseline	0.682	0.367	0.789	<.001
Event-based prospective memory	Baseline	0.476	0.343	0.895	<.001
Working memory	Baseline	14.529	3.512	0.976	.03
Number of relapses	Endpoint	1.210	1.241	0.835	<.001
PANSS positive subscale	Endpoint	0.483	1.259	0.511	<.001
PANSS negative subscale	Endpoint	0.381	1.274	0.815	<.001
PANSS general subscale	Endpoint	1.466	1.920	0.823	<.001
MADRS	Endpoint	7.580	1.324	0.773	<.001
SAS	Endpoint	13.118	6.970	0.435	<.001
BAS	Endpoint	19.193	3.492	0.339	<.001
SOFAS	Endpoint	77.748	14.975	0.882	<.001

Abbreviations: BAS = Barnes Akathisia Scale, MADRS = Montgomery-Åsberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

We constructed the covariation network based on partial correlations between the 11 nodes.[12,14,15] In the covariation network, the correlation between each pair of nodes accounted for the influence of all the other nodes. Then, we applied the least absolute shrinkage and selection operator (LASSO) technique[12,14] to regularize the covariation network and assigned penalties to the partial correlations between variables to shrink small correlations to zero. After regularization, only a small number of correlations that were sufficiently strong would be retained in the network. The syntax used for network analysis can be found in Supplementary Material.

The resultant LASSO network showed a graphical representation of the 11 variables (as nodes) and their partial correlations (as edges). Thicker edges denoted stronger correlations, with blue edges representing positive correlations and red edges representing negative correlations. The LASSO network was displayed in a way that strongly connected nodes would appear at the center of the graph but weakly connected nodes would appear at the periphery. The proximity of nodes was determined by weighing the attractive and repulsive forces (as positive and negative correlations) on each node. In the LASSO network, nodes that were strongly connected would be placed in closer proximity.

To evaluate the importance of each node in the graphical LASSO network, we computed the index of expected influence (EI). The EI is the sum of edge weights of a given node and represents how impactful a node is in the network.[16] Therefore, nodes with high EI may be easy targets to alter the network. Moreover, we computed the predictability of each node in the LASSO network. Predictability is the degree to which a given node can be predicted by neighbor nodes in the network.[17] This index provides an interpretable absolute scale (eg, 40% of variance explained) as to how much a node could be determined by neighboring nodes in the network. Therefore, nodes with a high predictability are easier to change, whereas nodes with a low predictability are less dependent on the network.

Table 3. Demographic and Clinical Characteristics of the Participants (N = 119)

Characteristic	Timepoint	Value
Age, mean (SD), y	Baseline	29.034 (6.152)
Sex, male, n (%)	Baseline	62 (52.1)
Length of education, mean (SD), y	Baseline	16.534 (2.953)
Estimated IQ, mean (SD)[a]	Baseline	100.65 (16.76)
Living environment, home vs supervised hostel, n	Endpoint	112 vs 7
Socioeconomic status, n (%)	Endpoint	
Full-time open employment		99 (83.2)
Part-time open employment		9 (7.6)
Supported employment		3 (2.5)
Student		4 (3.4)
Unemployed		5 (4.2)
Duration of untreated psychosis, mean (SD), mo	Baseline	7.555 (13.213)
Duration from baseline to outcome assessments, mean (SD), mo	Endpoint	53.261 (11.109)
History of hospitalization between service entry and endpoint, n (%)[b]	Endpoint	77 (64.7)
Number of psychiatric admission(s) (n = 77), mean (SD)[b]	Endpoint	1.468 (0.718)
Antipsychotic medication at baseline, CPZ equivalence (mg/d), mean (SD)	Baseline	267.783 (199.512)
Antipsychotic medication at endpoint, CPZ equivalence (mg/d), mean (SD)	Endpoint	499.943 (292.448)

[a]Participants' IQ was estimated using the arithmetic, similarities, and digit-span subscales of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Gong, 1992).
[b]Counted during the period from service entry to the endpoint.
Abbreviation: CPZ = chlorpromazine.

To evaluate the robustness of the network, we computed the stability of each edge shown in the LASSO network, using bootstrapping. The 95% confidence interval (CI) of each edge weight was estimated accordingly. We also estimated the correlation stability coefficient of the network in terms of EI.

Data management and descriptive analyses were conducted using Stata, version 13.1 (StataCorp). We used R, version 3.3.3 (R Foundation for Statistical Computing) to perform the network analysis; specifically, the package qgraph was used to obtain the network and centrality indices.

RESULTS

Sample Characteristics

Table 3 shows the demographic and clinical characteristics of our participants. In brief, our participants were all ethnic Chinese residing in Hong Kong. Our participants with schizophrenia had a mean age of 29.03 years (SD = 6.15), and the majority of them were living at home with family (83.2%) at the endpoint. They had a mean estimated IQ of 100.7 (SD = 16.8). All participants received early psychosis intervention services. None dropped out at the endpoint, and the mean duration of follow-up was 53.23 months (SD = 11.11 months). Among our sample, 77 participants had a history of psychiatric admission(s) at the endpoint. Among these participants (n = 77), the mean number of psychiatric admission(s) during the follow-up was 1.47 (SD = 0.72). Notably, 33.6% of our participants had only 1 episode of schizophrenia, and the remaining participants had 2 (35.3%),

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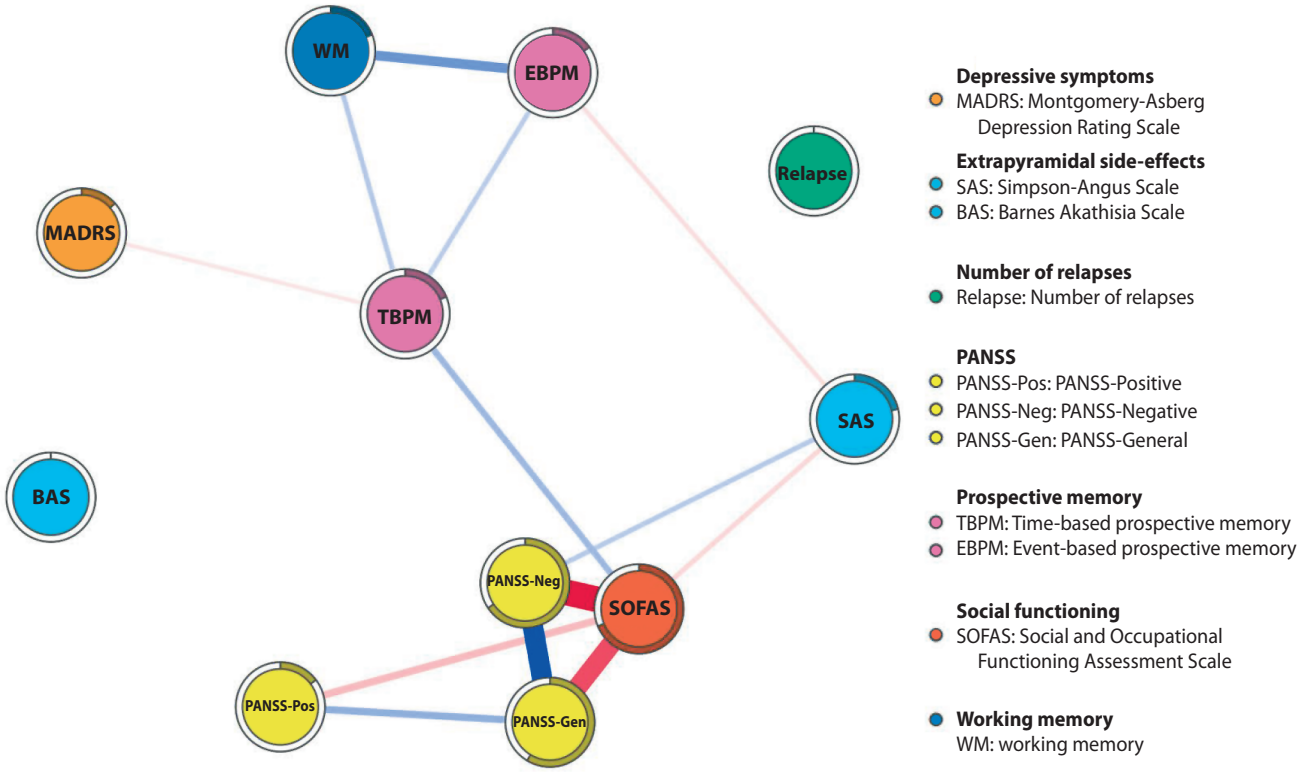
Figure 1. Graphical LASSO Network of 11 Variables[a]



[a]Blue lines are positive associations, whereas red lines are negative. Thickness and saturation of lines depict the strength of associations. The filled part of the circle around each node depicts predictability, ie, the variance of the nodes explained by all its neighbors (0.685 for SOFAS, 0.657 for PANSS-Neg, 0.583 for PANSS-Gen, 0.213 for SAS, 0.194 for WM, 0.188 for TBPM, 0.158 for EBPM, 0.147 for PANSS-Pos, 0.128 for MADRS, < 0.001 for BAS and relapse).

3 (16.0%), 4 (9.2%), 5 (3.4%), or 6 (2.5%) psychotic episodes during the follow-up period. All participants were at clinical stabilization at the endpoint, and the majority of them had full-time open employment (82.4%). Table 3 shows the mean of the 11 variables (nodes) in our sample. The results showed that these variables were nonparametric (*P* values < .05) and were transformed before entering network analysis.

Network Structure

The graphical LASSO network shows the nodes and the regularized edges (Figure 1). In general, the network suggested that negative symptoms and general symptoms as measured by the PANSS at the endpoint were strongly connected with the outcome of social functioning. The higher the severity of these symptoms, the lower the social functioning. Depressive symptoms as measured by the MADRS were not connected with the PANSS symptom subscales. On the other hand, time-based and event-based PM and working memory at baseline were interconnected as a cluster in the network, and the edges between these 3 nodes showed positive correlations. Compared with time-based PM, event-based PM was more strongly connected with working memory. Regarding the nodes representing extrapyramidal side effects at the endpoint, akathisia as measured by the BARS did not show sufficient connection with other nodes in the network, whereas parkinsonism signs as measured by the SAS were connected with negative symptoms and social functioning at the endpoint. The higher the severity of parkinsonism signs, the lower the social functioning. Lastly, the node of the number of relapses in people with schizophrenia was not sufficiently strong to be connected with other nodes in the LASSO network.

The node of time-based PM at the baseline played an important role in our network and bridged the clusters of nodes representing neurocognitive functions at the baseline with the clusters of nodes representing the outcomes of social functioning and clinical symptoms at the endpoint. Time-based PM at the baseline was connected with depressive symptoms at the endpoint. Event-based PM at the baseline was not connected with the outcome of social functioning in our network, but it formed a significant cluster with other neurocognitive functions. Interestingly, event-based PM at the baseline was connected with parkinsonism signs at the endpoint.

Results of Centrality Indexes

Figure 2 shows the EI of each node. Time-based (EI = 0.69) and event-based (EI = 0.65) PM and working memory (EI = 0.83) at the baseline showed the highest expected influence and were therefore the most influential nodes in the network. As shown in Figure 1, our results suggested that the SOFAS (variance explained = 68.5%), the PANSS

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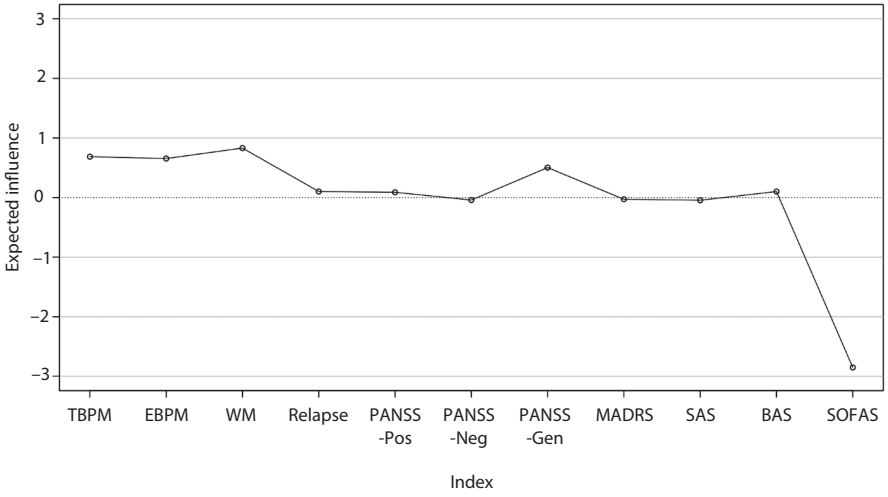
Figure 2. Expected Influence of the 9 Nodes in the Network Depicted in Figure 1[a]



[a]Expected influence is the sum of edge weights of a given node and represents how impactful a node is in the network. The expected influence for each node is as follows: 0.686 for TBPM, 0.655 for EBPM, 0.830 for WM, 0.102 for relapse, 0.089 for PANSS-Pos, −0.042 for PANSS-Neg, 0.503 for PANSS-Gen, −0.029 for MADRS, −0.045 for SAS, 0.102 for BAS, −2.850 for SOFAS.
Abbreviations: BAS = Barnes Akathisia Scale, EBPM = event-based PM, MADRS = Montgomery-Åsberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, PANSS-Gen = PANSS general psychopathology subscale, PANSS-Neg = PANSS negative symptoms subscale, PANSS-Pos = PANSS positive symptoms subscale, PM = prospective memory, SAS = Simpson-Angus Scale, SOFAS = Social and Occupational Functioning Assessment Scale, TBPM = time-based PM, WM = working memory.

negative symptom subscale (variance explained = 65.7%), and the PANSS general psychopathology subscale (variance explained = 58.3%) were strongly dependent on the effects of other nodes in the network.

Network Stability and Accuracy

The sample mean and bootstrapped mean of the edge weights (R) with the 95% CI in the network are shown in Supplementary Figure 1. The results of the stability analysis of the overall network are shown in Supplementary Figure 2.

DISCUSSION

To our knowledge, this study is one of the first few to use network analysis to investigate the complex interplay between PM, working memory, psychopathology, and social functioning in first-episode schizophrenia. Moreover, we adopted a longitudinal design that assessed neurocognitive functions at the baseline but psychopathology and social functioning at the endpoint. In general, our findings of network analysis are consistent with our hypotheses, supporting the notion that PM, in particular the time-based type, is an influential factor for social functioning outcome. Specifically, PM at the baseline could influence first-episode schizophrenia individuals' social functioning beyond 2 years after service entry, in the naturalistic early psychosis intervention clinic. PM together with working memory apparently constitute suitable intervention targets for improving longitudinal clinical and functional outcomes in people with first-episode schizophrenia, because social functioning and clinical symptoms are "malleable" variables (nodes) in the resultant network, easily influenced by the effects of other factors (nodes).

Inspecting the network structure reveals that time-based PM appears to be the bridging node connecting neurocognitive functions (eg, event-based PM and working memory) and social functioning. This is consistent with Galderisi and colleagues' network analysis studies,[13,19] which found that functional capacity served as the central node bridging the different clusters of nodes of neurocognitive functions, psychopathology, and resilience. The generated network as such remained largely stable after 4 years of naturalistic observation, but social cognitive and neurocognitive factors initially not connected to functional capacity became connected to this functional outcome variable 4 years later.[19] Moreover, our network structure in this study found that social functioning was positively connected with time-based PM, which implied that better time-based PM ability is associated with better social functioning. However, no connections were found between event-based PM and social functioning, which is consistent with our hypothesis that time-based PM is more influential than event-based PM to social functioning. The literature of PM in schizophrenia did not find time-based PM more important than event-based PM in correlating with functioning of schizophrenia individuals. In fact, several studies[6,8] reported that event-based PM instead of time-based PM was correlated with social functioning. However, these previous findings are mainly applicable to samples with chronic schizophrenia, and it is possible that

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the interplay between PM and social functioning would change with time. Moreover, these studies[6,8] utilized PM paradigms different from ours, and the time-based and event-based PM task sessions were not as comparable as ours. Different PM paradigms may have different levels of task difficulty. It is possible that our time-based PM task is psychometrically more sensitive than our event-based PM task in detecting neurocognitive impairments. On the other hand, several previous studies using the PM paradigm identical to ours generally found time-based PM impairments being more severe[28] and longitudinally stable along the course of illness,[23,24] compared with event-based PM. Similar to the current one, these previous studies also recruited first-episode schizophrenia samples.[23,24,28] It is likely that event-based PM impairments, which are relatively mild and improve naturalistically, might not influence social functioning at the endpoint as much as time-based PM does. In the network, the node of working memory was found to be closely connected to PM, in particular the event-based type. This finding concurs with the theoretical and empirical relationship between PM and working memory. According to the Preparatory Attention and Memory (PAM) theory[40] and the PM decision-making theory,[41] proper functioning of PM is believed to depend on working memory as well as other cognitive functions. Empirical evidence also consistently supports the association between PM and working memory in people with schizophrenia.[4,28]

In addition, we found that the node of social functioning was inversely connected with the 3 nodes of the PANSS, indicating that higher severity of psychopathology, in particular negative symptoms and general symptoms, would be associated with poorer social functioning. Previous findings support that negative and general psychopathology constitute key determinants of social functioning outcome.[42] The isolated node of the BAS in our network may be partly explained by the fact that all first-episode schizophrenia participants except 6 had already received second-generation antipsychotic medications at the baseline, which may have resulted in low risk of akathisia side effects.

Inspecting the centrality indexes, our findings suggested that time-based PM, event-based PM, and working memory showed the highest EIs among all nodes in the network. These results indicate that these 3 cognitive functions have more connections within the network than other variables and therefore appear to be more "impactful" to the network. As such, they are suitable targets for interventions aiming at bringing changes to this network. It is noteworthy that social functioning at the endpoint showed the highest predictability. Thus, the variance of social functioning at the endpoint would be better accounted for by the influences of other nodes in the network. Our findings support the notion that social functioning is malleable in the network. In view of our relatively small sample size, only a few edges (see Supplementary Figure 1) in the network showed an edge weight with a 95% CI above zero. Nevertheless, the overall stability of the network remained satisfactory, with an EI of 0.672, which lies above the recommended threshold of 0.5.[14] Taken together, our findings corroborate the hypothesis that PM at the baseline could influence the outcome of social functioning beyond 2 years after psychosis onset. Consistent to our hypothesis, time-based PM appears to be a more influential factor than event-based PM to the outcome of social functioning.

In this study, PM and working memory were measured at the baseline, whereas all other variables were assessed at the endpoint. Therefore, our network reflected cross-sectional clusters of psychopathology, extrapyramidal side effects, and social functioning variables, whereas the cluster of neurocognitive variables bore the additional effects of time. There are 2 plausible interpretations to our findings. First, this design feature may have artificially diminished the role of neurocognition in the network analysis, by introducing the variance associated with time to neurocognitive variables. This is not unimportant, because the degree to which variables are correlated with all others in network could lead to conclusions regarding the centrality of each variable as a potential target of intervention. Second, the links evident between time-based PM and social functioning after follow-up may reflect the same covariance evident at the baseline (though it may have been diminished by the effects of time). Unless longitudinal changes in psychopathology and social functioning are measured, there is no way to clarify to what extent time-based PM at the baseline could serve as a selective link to the subsequent outcome of social functioning (which is a major aim of this study). Future studies should adopt a more rigorous longitudinal design to capture all of these measures at the baseline to verify our speculation. In addition, future network analysis in this area should include resilience and environmental factors, because these variables could also affect social functioning and interact with psychopathology and neurocognition.[15]

This study has several limitations. First, we did not recruit a healthy control group, and the network we found in clinical populations could not be compared with that of healthy individuals. Second, the follow-up duration varied among different participants, though they all were reassessed at time of clinical stabilization. This limitation must be balanced against the fact that we included the factor of the number of relapses during the follow-up period, and this particular node was found to have very little connections with other nodes in the network. Third, we studied only a limited number of neurocognitive functions at the baseline. Future study should include other neurocognitive variables such as executive functions, attention, and other memory types, to fully examine the psychopathology-neurocognition connection with social functioning.[11,13,19,20] The network structure may change when other neurocognitive variables are included in the network analysis. Fourth, we did not measure the longitudinal change of the relationship between PM and social functioning. Future longitudinal network analysis should address this issue thoroughly. Last,

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our measure of social functioning was relatively crude, and other variables previously shown to mediate the effects of PM on clinical outcomes, such as medication adherence and ability to manage medications, were not included.[9,10] Likewise, attitudinal factors, such as internalized stigma, may influence social functioning in schizophrenia but were not included in this study.[43]

To conclude, this network analysis extends the previous findings of the relationship between PM and social functioning. PM at the baseline could influence schizophrenia individuals' social functioning beyond 2 years after psychosis onset. PM, together with working memory, appear to be suitable treatment targets for improving the outcome of psychopathology and social functioning.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

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Supplementary Material

Article Title: Prospective Memory Influences Social Functioning in People With First-Episode Schizophrenia: A Network Analysis and Longitudinal Study

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List of Supplementary Material for the article

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Supplementary Materials

Supplementary Table 1. Previous studies investigating the relationship between prospective memory (PM) and functional outcomes in schizophrenia patients

Study	Sample	Study design	PM measure	Functional outcome Measures	Other outcome measures	Clinical symptoms	Other cognitive measures	Summary of results	Limitations
Twamley et al. (2008) [8]	72 SCZ patients	• Single group • Cross-sectional • Regression analysis	The Memory for Intentions Screening Test (MIST)	UCSD Performance-Based Skills Assessment-Brief Version	None	PANSS, HAM-D	IQ, LNT, visual memory, WCST, digit span, Trail making, continuous performance test	Better PM was predictive of higher functional capacity	(1) Only 58 of 72 SCZ patients had completed social functioning measurement (2) Small sample size (3) Medication adherence was not measured (4) Cross-sectional design cannot infer causal relationships
Au et al. (2014) [6]	44 SCZ patients	• Single group • Cross-sectional • Correlational analysis • Regression analysis	The Cambridge Prospective Memory Test (CAMPROMPT)	The Functional Needs Assessment (FNA)	None	PANSS	RM, IQ	PM was correlated with community living skills but not self-care. PM predicted community living skills after controlling for IQ and delayed recall	(1) Small sample size (2) Medication adherence was not measured (3) Cross-sectional design cannot infer causal relationships
Raskin et al. (2014) [10]	41 SCZ patients, 25 controls	• Case-control • Cross-sectional • Comparative statistics • Correlational analysis • Regression analysis	The MIST	None	Medication adherence, as measured by the MMAA	PANSS	Trail making test, verbal learning	SCZ patients had poorer PM than controls, PM predicted medication management ability after controlling for verbal learning	(1) Small sample size (2) cross-sectional design cannot infer causal relationships (3) Lack of social functioning measures

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								and executive functions	
Xiang et al. (2010) [44]	110 SCZ patients	• Single group • Cross-sectional • Correlational analysis • Regression analysis	A computerized PM paradigm	FNA	None	BPRS	IQ, Design Fluency Test, Tower of London, WCST, RM	PM was not correlated with social functioning	(1) PM was not the key cognitive variables to be measured (2) Limited measures of SF
Burton et al. (2019) [7]	58 SCZ, 37 BD, 58 MDD	• Case-control • Cross-sectional • Correlational analysis • Regression analysis	The MIST	(1) UCSD Performance-Based Skills Assessment-Brief Version. (2) work outcomes	None	None	None	PM predicted functional capacity and work duration in the entire sample	(1) Subjects with different diagnosis were recruited (2) Did not measure other cognitive functions (3) Did not measure clinical symptoms

Note: BD = Bipolar disorder, BPRS = Brief Psychiatric Rating Scale, IQ = intelligence, MDD = major depression, MMAA = Medication Management Ability Assessment, PANSS = Positive and Negative Syndrome Scale, PM = prospective memory, RM = retrospective memory, SCZ = schizophrenia, SF = social functioning, WCST = Wisconsin Card Sorting Test.

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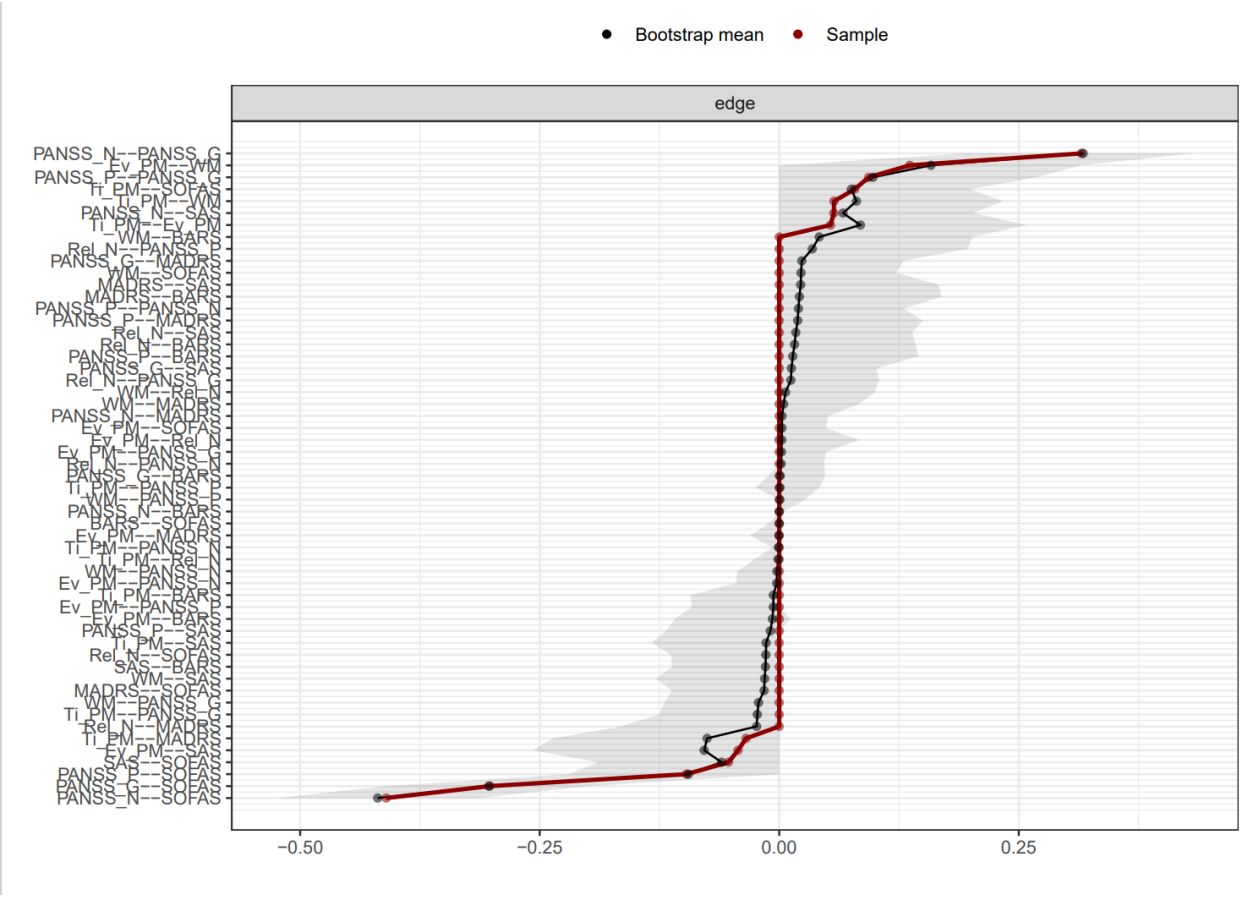
Supplementary Figure 1.



Supplementary Figure 1. The sample mean and bootstrapped mean of the edge weights (R) with the 95% CI in the network depicted in Figure 1.

The black dots indicate the sample mean, whereas the red black dots indicate the bootstrapping mean, for each of the edge weight. The shadowed area shows the range of R falling within the 95% CI. Edge having a R with 95% CI above and below zero indicates better stability.

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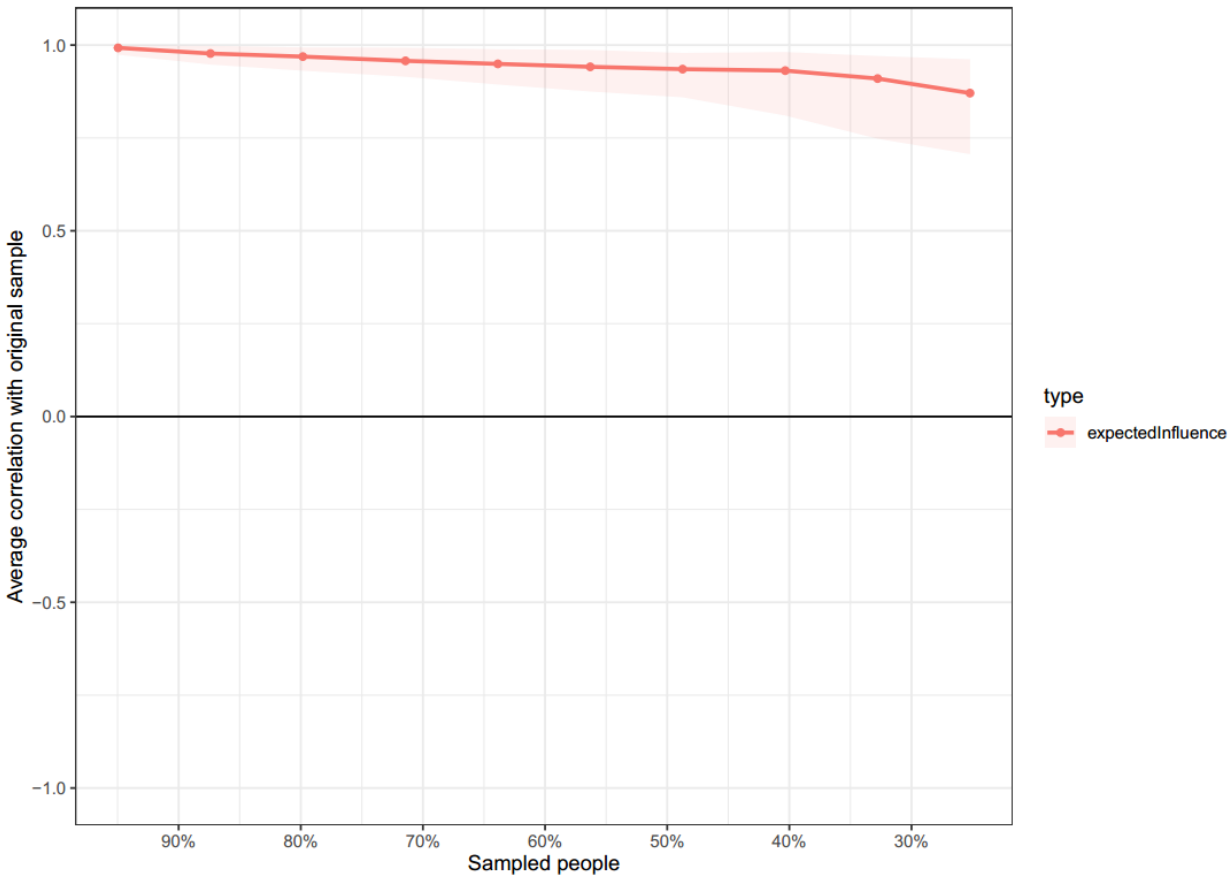
Supplementary Figure 2.



Supplementary Figure 2. Stability of the network

The y-axis represents the correlation between the EI of all the nodes in the original network and the EI of all the nodes in the network constructed using bootstrapping method of a proportion of the original sample. The x-axis represents the percentage of sampled population in descending order. The red dots indicate the correlation coefficients between the EIs of the two networks. Shadowed areas represent 95% CI of the correlation coefficients.

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The Syntax for Network Analysis

########library basic toolbox######

```
library("qgraph")
library("gdata")
library("readxl")
library('mgm')

library(mnormt)
library(nortest)

Data_HK_T1 <-
as.data.frame(read_excel("C:\\networkTry\\HK\\Cognition_Symptoms_SF_cog_symp_SF_T1.xlsx",sheet=1,na = "."))
head(Data_HK_T1)

library(mvnormtest)
mshapiro.test(t(Data_HK_T1[1:11]))

#########normalization##############
library(huge)
Data_HK_T1_trans <- huge.npn(Data_HK_T1, npn.func = "shrinkage", verbose = TRUE)
mshapiro.test(t(Data_HK_T1_trans[1:11]))

Names <- scan("C:\\networkTry\\HK\\Nodename2.txt",what = "character", sep = "\n")

Groups1 <- c(rep("PM",2),rep("WM",1),rep("Number of relapse",1),rep("PANSS",3),
rep("MADRS",1),rep("SAS",1),rep("Barthes",1),rep("Social functioning",1))
```

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```
#######Predictivity calculation########

set.seed(1)

fit_obj <- mgm(data = Data_HK_T1_trans, type = rep('g', 11), level = rep(1, 11), lambdaSel =
'CV',

          ruleReg = 'OR')

pred_obj <- predict(object = fit_obj,

                data = Data_HK_T1_trans,

                errorCon = 'R2')

pred_obj$error #####show value


smallNetwork <- estimateNetwork(Data_HK_T1_trans, default="EBICglasso", tuning=0.25)

graph_small <- plot(smallNetwork, layout = "spring", pie=pred_obj$error[,2], cut=0, vsize=7,

                filename="HK_Network_Final_Trans", width=6, height=5, repulsion=1.1,

                border.color='#555555', label.color="#555555", labels = colnames(Data_HK_T1),
nodeNames=Names, groups=Groups1, legend.cex = 0.35, filetype="pdf", theme='colorblind')

smallNetwork$graph


####expected influence########

smallNetwork$graph

EI_s <- scale(colSums(smallNetwork$graph))

EI_s


plot(EI_s, ylab="Expected Influence", xlim=c(1,11), ylim=c(-3,3),xaxt='n')

abline(h=0,col="black", lty = 3)

abline(h=c(-3,-2,-1,1,2,3), col="#d6d6d6")
```

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```
axis(1, at=c(1,2,3,4,5,6,7,8,9,10,11),labels=c("Ti_PM","Ev_PM","WM","Rel_N",
"PANSS_P","PANSS_N","PANSS_G","MADRS","SAS","BARS","SOFAS") )

lines(EI_s, type="l", col="#555555")


#################stability analysis############################


#################node stability#################################

boot1<-bootnet(smallNetwork, nBoots=1000, type="case",nCores=1)

plot(boot1,labels = FALSE) #edge-weight stability

corStability(boot1)

### Centrality stability coefficient (value)

corStability (boot1, statistic="expectedInfluence")##0.75



#################edge stability#################################

boot2 <- bootnet(smallNetwork, nBoots = 1000, nCores = 1)

plot(boot2, order = "sample")



######Normality checking for single variable############

shapiro.test(t(Data_HK_T1[1]))

shapiro.test(t(Data_HK_T1[2]))

shapiro.test(t(Data_HK_T1[3]))

shapiro.test(t(Data_HK_T1[4]))

shapiro.test(t(Data_HK_T1[5]))

shapiro.test(t(Data_HK_T1[6]))

shapiro.test(t(Data_HK_T1[7]))
```

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```
shapiro.test(t(Data_HK_T1[8]))

shapiro.test(t(Data_HK_T1[9]))

shapiro.test(t(Data_HK_T1[10]))

shapiro.test(t(Data_HK_T1[11]))
```

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