Supplementary Materials

Neurocognitive Graphs of Schizophrenia and Major Depression Based on Cognitive Features

Sugai Liang#, Roberto Vega#, Xiangzhen Kong, Wei Deng, Qiang Wang, Xiaohong Ma, Mingli Li, Xun Hu, Andrew J. Greenshaw, Russell Greiner, Tao Li

#These authors contributed equally to this work.

Materials and Methods

Participants

All participants were interviewed by a trained psychiatrist (DW, WQ and ML) using the Structured Clinical Interview for DSM-IV: SCID-NP for controls [1] and SCID-P for patients [2]. Individuals with any history of head trauma, neurological disorders or severe medical conditions that might alter cognitive function or intellectual ability were excluded. This study also excluded those who had organic brain syndrome, learning disability, substance use disorder or psychoses secondary to medical illness. Potential healthy controls who reported mental disorders in one or more first-degree relatives were also excluded. In order to clarify the diagnosis, participants diagnosed with schizophreniform psychosis or first-episode depression were subject to prospective longitudinal observation over a period of 6 months or longer. In the current study, all patients met the DSM-IV criteria for schizophrenia or major depression disorder (MDD) [3].

In this study, 16 out of 215 patients with first-episode schizophrenia (FES) had been minimally treated with antipsychotics such as risperidone or olanzapine at low dosage (ranging from 25 to 75 mg of chlorpromazine daily dose equivalents) for less than 3 days. The remaining schizophrenic patients were treatment-naïve. Ninety-three out of 125 MDD patients were first-episode. The other 32 MDD patients relapsed but they had not taken antidepressants at least during the previous three months when they were recruited into this study.

Clinical assessment

Clinical symptoms of schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS) [4]. The severity of depressive symptoms was evaluated with the Hamilton Rating Scale for Depression (HAMD-17) [5]. In this study, only depressive patients with HAM-D scores ≥18 were included in the MDD group.

Neuropsychological assessments

For the short form of WAIS [6, 7], the Verbal IQ (VIQ) of scaled scores sum was calculated as follows: 2 (Information + Similarities) + Arithmetic + Digit Span; Performance IQ (PIQ) sum was obtained by 2 (Picture Completion + Block Design) + Digit Symbol. Full Scale IQ estimates were based on FSIQ = VIQ + PIQ. The estimated sums of scaled scores derived from these formulae were then converted to IQ scores using the standard procedure and age-corrected conversion tables in the WAIS-RC manual [8].

Perceptual sensitivity was assessed through the principles of Signal Detection Theory (SDT) in DMS and RVP [9]. In the case of DMS A' (A prime) indicates the subject's sensitivity to errors, regardless of error tendency; the DMS B" (B double prime) indicates the strength of trace required to elicit an error. In the case of RVP, A' (A prime) is the signal detection measure of sensitivity to the target, regardless of response tendency; B" (B double prime) is the signal detection measure of the strength of trace required to elicit a response.

The Trail Making Test (TMT) is a test of complex visual scanning with a motor component which can evaluate the flexibility in shifting the course of an ongoing activity. Final scores are measured as the time taken to complete each part of the task. In the TMA, the participant drew the lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. In the TMB-M, the participant should draw the lines alternately between numbers and Chinese letters. The duration for completion of this test was measured.

Performance metrics

The performance of the classification was assessed using accuracy and F1 score.

$$Accuracy = \frac{TP + TN}{TP + FP + FN + TN} \quad \text{(S1)}$$

$$F1\ score = \frac{2TP}{2TP + FP + FN} \quad \text{(S2)}$$

TP is the number of true positives, TN is the number of true negatives, FN is the number of false negatives and FP is the number of false positives. The average of the performance metrics were reported in the main text.

Partial correlation model

The partial correlation matrix, Π, could be derived from the inverse covariance matrix. Given Σ^{-1}, the partial correlation matrix was calculated through the following equation [10].

$$\Pi_{ij} = \frac{\sum_{ij}^{-1}}{\sqrt{\sum_{ii}^{-1}\sum_{jj}^{-1}}} \quad \text{(S3)}$$

Similar to linear correlation, the interval of partial correlation coefficients is [-1, 1].

Results

Descriptive statistics

Descriptive statistics were computed for basic demographic and clinical variables (Table S1). Gender distribution was analyzed using the Chi-square test; continuous variables (age and education level) were compared with one-way analysis of variance (ANOVA). This part was analyzed on R (https://www.r-project.org/).

Table S2 showed that in this study, patients with schizophrenia, patients with MDD, and healthy controls did not differ significantly based on gender, age or education level.

The top 3 positive and negative connections in neurocognitive graphs of FES and HC

The top 3 positive connections in the graphs were reported as follows: Both neurocognitive graphs of FES and HC showed strong positive connections between *DoubErr (double error)* and *WithErr (within error) in SWM*, as well as between *VIQ* and

FSIQ. The strong positive connection was also evident between *RVP_TFA (total false alarms)* and *RVP_PFA (probability of false alarms)* in the graph of FES, as well as between *IED_CSE (completed stage errors)* and *IED_CST (completed stage trials)* for HC.

The top 3 negative connections in the graphs were reported as follows: Both graphs showed close negative bonds between *IED_ATE (adjusted total errors)* and *StagesC (stages completed in IED)*. Close negative bonds in the graph of FES were also featured between *PC0D (percent correct in 0 ms delay)* and *PC4D (percent correct in 4000 ms delay) in DMS*, as well as between *VIQ* and *PIQ*. Those of HC were revealed between *PC0D* and *PC12D (percent correct in 12000 ms delay) in DMS*, as well as between *PreED_E (errors in pre-extra dimensions)* and *EDS_E (errors in extra dimensions) in IED*. Fig. 3 displays the neurocognitive graphs of FES and HC.

The top 3 positive and negative connections in neurocognitive graphs of FES and MDD

The top 3 positive connections were reported as follows: Both neurocognitive graphs of FES and MDD had connections between *IED_CSE* and *IED_CST*, as well as between *DoubErr* and *WithErr in SWM*. Strong positive connections were evident between *VIQ* and *FSIQ* in the graph of FES and between *RVP_TFA* and *RVP_PFA* in the graph of MDD.

The top 3 negative connections were as follows: Both neurocognitive graphs of FES and MDD showed close bonds between *IED_ATE* and *StagesC*, and between *PC0D* and *PC4D in DMS*. Close negative bonds were also evident between *VIQ* and *PIQ* in the graph of FES, and between *PreED_E* and *EDS_E in IED* in the graph of MDD. Fig. 3 displays the neurocognitive graphs of FES and MDD.

The top 3 positive and negative connections in neurocognitive graphs of MDD and HC

The top 3 positive connections in the graphs were reported as follows: Both graphs featured connections between *DoubErr* and *WithErr in SWM*, and between *IED_CSE* and *IED_CST*. A strong positive connection was also evident between *ILM (immediate*

logical memory) and *DLM (delayed logical memory) in WMS* in the graph of MDD, and between *VIQ* and *FSIQ* in the graph of HC.

The top 3 negative connections were reported as follows: Both neurocognitive graphs of MDD and HC revealed close negative bonds between *IED_ATE* and *StagesC*, as well as between *RVP_TM (total misses)* and *RVP_PH (probability of hits)*. A close negative bond were evident between *PreED_E* and *EDS_E* in the graph of MDD, as well as between *RVP_TM* and *RVP_TH (total hit)* in the graph of HC. Fig. 4 displays the neurocognitive graphs of MDD and HC.

Table S1. Demographic and clinical characteristics of participants

	FES (*n* = 215)	**MDD (*n* = 125)**	**HC (*n* = 237)**	**Statistic**
Age, mean (SD), years	25.98 (6.69)	27. 22 (7.62)	26.00 (7.63)	$F = 1.40$, $P = 0.25$
Gender, M/F	98/117	49/76	102/135	$\chi^2 = 1.31$, $P = 0.52$
Education, mean (SD),	13.29 (3.06)	13.42 (3.26)	13.82 (3.08)	$F = 1.75$, $P = 0.18$

years				
Duration, mean (SD), months	13.82 (20.55)	19.15 (26.20)	-	t = -1.64, P = 0.10
PANSS, mean (SD)	86.70 (19.610)	-		-
HAMD, mean (SD)	-	21.57 (5. 57)	-	-

PANSS, Positive and Negative Syndrome Scale; HAMD, Hamilton Depression Scale

Table S2. Neurocognitive tests and measurements

Neurocognitive Tests (Number of Features)	**Measurements**	**Evaluation**
Trail Making Test (2)	Completed time	Processing speed
WAIS-RC (3)	Verbal and performance IQ, full scale IQ	General intelligence

WMS-RC (2)	Immediate and delayed logical memory	Logical memory
CANTAB		
Big Circle / Little Circle (2)	Reaction time, accuracy	Visuomotor and processing speed
Delayed Matching to Sample (10)	Reaction time, accuracy, SDT measures	Visual memory
Intra/extra Dimensional Set Shift (7)	Errors, Number of blocks completed	Shifting and flexibility
Pattern Recognition Memory (4)	Reaction time, accuracy	Visual memory
Rapid Visual Information Processing (9)	Reaction time, accuracy, SDT measures	Sustained attention and inhibition
Stockings of Cambridge (4)	Reaction time, mean minimum moves	Planning
Spatial Working Memory (8)	Errors, strategy, reaction time	Working memory

Reaction time is in milliseconds (ms). SDT, Signal Detection Theory.

Table S3. Neurocognitive tests and features in CANTAB

Neurocognitive Tests in CANTAB	Features in CANTAB
Trail Making Test-TMT	Trail Making part A and part B-M
Big Circle/Little Circle-BLC	BLC_CRL (mean correct latency), BLC_PC (percent

	correct)
Delayed Matching to Sample-DMS	DMS_AP (DMS_A'), DMS_BDP (DMS_B"); DMS_Ld (mean correct latency in all delay), DMS_Ls (mean correct latency in simultaneous); DMS_PC (percent correct), DMS_PCd (percent correct in all delays), DMS_PCs (percent correct in all simultaneous), PC0D (percent correct in 0 ms delay), PC4D (percent correct in 4000 ms delay), PC12D (percent correct in 12000 ms delay)
Intra/extra Dimensional Set Shift-IED	PreDE_E (pre-extra dimensional errors), ESD_E (Extra dimensional errors), IED_ATE (adjusted total errors), IED_CSE (completed stage errors); IED_ATT (adjusted total trials), StagesC (stages completed), IED_CST (completed stage trials)
Pattern Recognition Memory-PRM	PRM_Li (mean correct latency in immediate), PRM_Ld (mean correct latency in delay); PRM_PCi (percent correct in immediate trails), PRM_PCd (percent correct in delay trials)
Rapid Visual Information Processing-RVP	RVP_AP (RVP _A'), RVP _BDP (RVP _B"); RVP_TH (total hits), RVP_TM (total miss), RVP_TFA (total false alarms), RVP_TCR (total correct rejections), RVP_PH (probability of hit), RVP_PFA (probability of false alarm); RVP_ML (mean latency)
Stockings of Cambridge-SOC	SOC_MIT (mean initial thinking time), SOC_MST (mean subsequent thinking time); SOC_PSM (problems solved in minimum moves), SOC_MM (mean minimum moves in 2, 3, 4 and 5 trials)

Spatial Working Memory-SWM	SWM_MFR (mean time to first response), SWM_MLR (mean time to first response), SWM_MTP (mean token-search preparation time); BetwErr (between errors), WithErr (within errors), DoubErr (double errors), TotalErr (total errors); Strategy

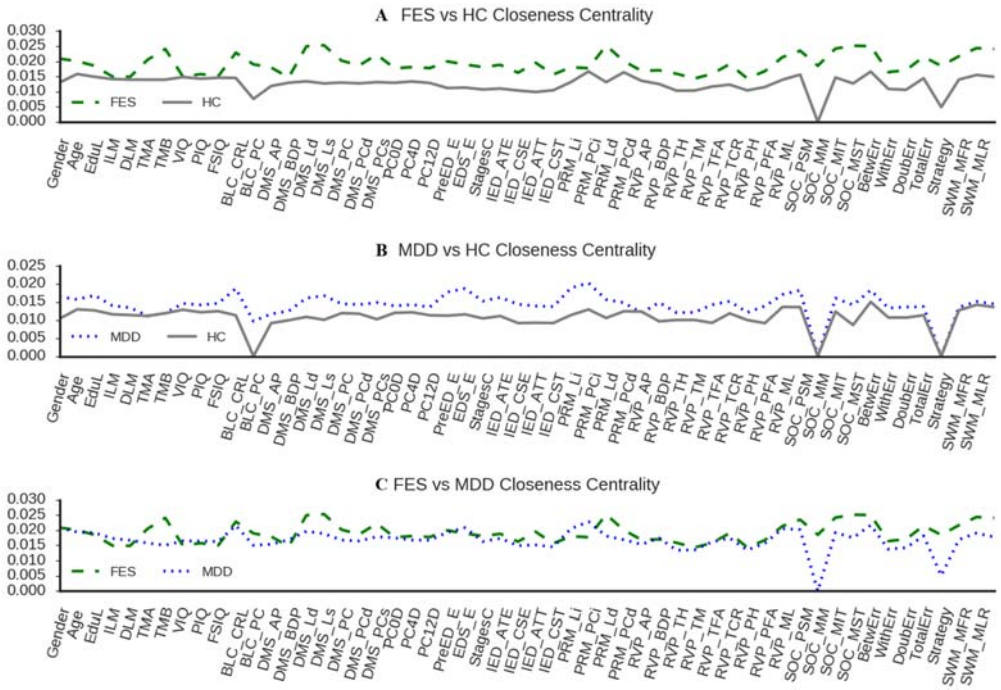

Fig. S1 Node closeness centrality in one-versus-one scenarios. (A) Node closeness centrality for schizophrenia and HC; (B) node closeness centrality for MDD and HC; (C) node closeness centrality for schizophrenia and MDD. Green dash line, node closeness centrality of FES. Gray solid line, node closeness centrality of HC. Blue dotted line, node closeness centrality of MDD.

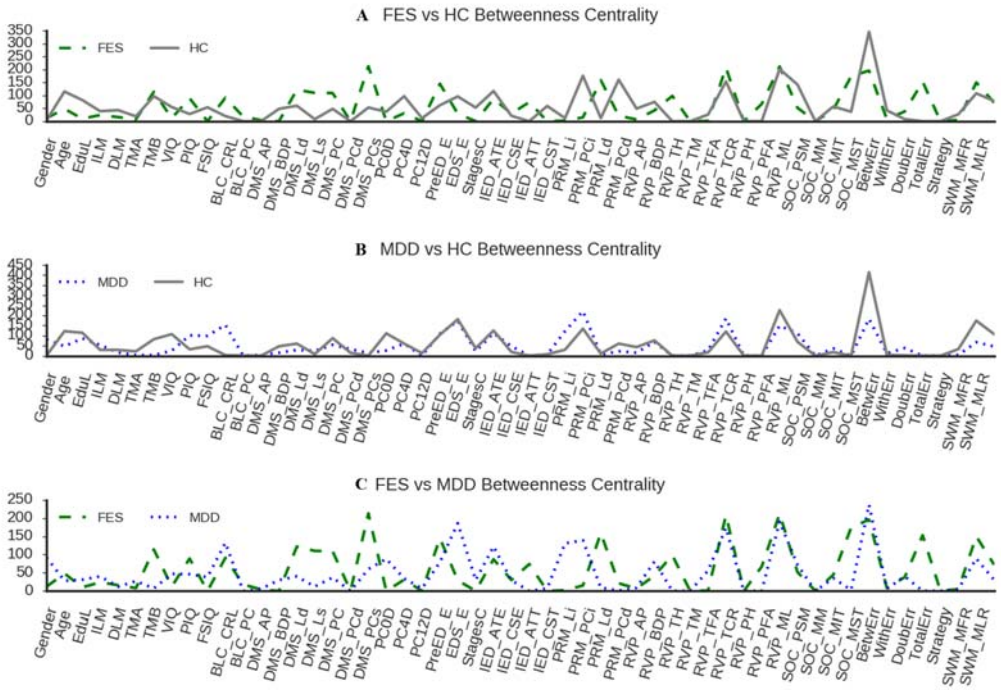

Fig. S2 Node betweenness centrality in one-versus-one scenarios. (A) Node betweenness centrality for schizophrenia and HC; (B) node betweenness centrality for MDD and HC; (C) node betweenness centrality for schizophrenia and MDD. Green dash line, node betweenness centrality of FES. Gray solid line, node betweenness centrality of HC. Blue dotted line, node betweenness centrality of MDD.

References

[1] First M, Spitzer R, Williams J, Gibbon M. Structured clinical interview for DSM-IV-non-patient edition (SCID-NP, version 1.0). American Psychiatric, Washington, DC 1995.

[2] First M, Spitzer R, Williams J, Gibbons M. Structured clinical interview for DSM-IV-Patient version. New York: Biometrics Research Department, New York State Psychiatric Institute 1995.

[3] First MB. Diagnostic and statistical manual of mental disorders. DSM IV-4th edition. APA. p 1994: 97-327.
[4] Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987, 13: 261.
[5] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960, 23: 56-62.
[6] Ward LC. Prediction of verbal, performance, and full scale IQs from seven subtests of the wais-r. Journal of Clinical Psychology 1990, 46: 436-440.
[7] Ryan JJ, Weilage ME, Spaulding WD. Accuracy of the seven subtest WAIS-R short form in chronic schizophrenia. Schizophrenia Research 1999, 39: 79-83.
[8] Gong Y. Manual of modified wechsler adult intelligence scale (WAIS-RC). Changsha, China: Hunan Med College 1982: 45-48.
[9] Yang X, Ma X, Huang B, Sun G, Zhao L, Lin D*, et al.* Gray matter volume abnormalities were associated with sustained attention in unmedicated major depression. Compr Psychiatry 2015, 63: 71-79.
[10] Whittaker J. Graphical models in applied multivariate statistics. Wiley, 1990.