Supplementary Materials

Neurocognitive Graphs of Schizophrenia and Major Depression Based on Cognitive Features

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#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 (HAM-D-17) \(^5\). In this study, only depressive patients with HAM-D scores \(\geq 18\) 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.
\begin{align*}
\text{Accuracy} &= \frac{TP + TN}{TP + FP + FN + TN} \quad (S1) \\
F1 \text{ score} &= \frac{2TP}{2TP + FP + FN} \quad (S2)
\end{align*}

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, \( \Pi \), could be derived from the inverse covariance matrix. Given \( \Sigma^{-1} \), the partial correlation matrix was calculated through the following equation \[10\]:

\[ \Pi_{ij} = \frac{\sum_i \sum_j \Sigma^{-1}_{ij}}{\sqrt{\sum_i \Sigma^{-1}_{ii} \sum_j \Sigma^{-1}_{jj}}} \quad (S3) \]

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 \( \text{DoubErr (double error)} \) and \( \text{WithErr (within error)} \) in \( \text{SWM} \), as well as between \( \text{VIQ} \) 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

<table>
<thead>
<tr>
<th></th>
<th>FES</th>
<th>MDD</th>
<th>HC</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 215)</td>
<td>(n = 125)</td>
<td>(n = 237)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>25.98 (6.69)</td>
<td>27.22 (7.62)</td>
<td>26.00 (7.63)</td>
<td>F = 1.40, P = 0.25</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>98/117</td>
<td>49/76</td>
<td>102/135</td>
<td>χ² = 1.31, P = 0.52</td>
</tr>
<tr>
<td>Education, mean (SD),</td>
<td>13.29 (3.06)</td>
<td>13.42 (3.26)</td>
<td>13.82 (3.08)</td>
<td>F = 1.75, P = 0.18</td>
</tr>
</tbody>
</table>
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

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Table S2. Neurocognitive tests and measurements

<table>
<thead>
<tr>
<th>Neurocognitive Tests</th>
<th>Measurements</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail Making Test (2)</td>
<td>Completed time</td>
<td>Processing speed</td>
</tr>
<tr>
<td>WAIS-RC (3)</td>
<td>Verbal and performance IQ, full scale IQ</td>
<td>General intelligence</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Neurocognitive Tests in CANTAB</th>
<th>Features in CANTAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail Making Test-TMT</td>
<td>Trail Making part A and part B-M</td>
</tr>
<tr>
<td>Big Circle/Little Circle-BLC</td>
<td>BLC_CRL (mean correct latency), BLC_PC (percent</td>
</tr>
</tbody>
</table>
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)
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


