Supplementary Information

Network hub centrality and working memory performance in schizophrenia

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SUPPLEMENTARY METHODS

Clinical and cognitive outcomes

In order to assess the relationship between key clinical variables and cognitive outcomes, we tested whether clinical measures such as positive symptom severity, antipsychotic medication dose and duration of illness were correlated with working memory performance. Positive symptom severity was assessed via Positive and Negative Syndrome Scale (PANSS)\(^1\). Antipsychotic medication dose information was available for 23 of the 29 patients included in the current analysis. Chlorpromazine equivalent (CPZE) dose was calculated based on previously validated conversion formulas\(^2\). Duration of illness was considered from the onset of psychotic symptoms to the time of the experiment. Pearson’s correlation coefficients were calculated to assess the correlations between these variables and working memory performance (both average retrieval accuracy and reaction time). The resulting \(p\) values were Bonferroni corrected for the six comparisons (3 clinical variables and 2 cognitive outcomes) in this analysis.

Degree-based predictive modeling

In this analysis, we used leave-one-out cross-validation (LOOCV) in our entire sample (\(N=58\)) to i) select primary degree features associated with behavior in the training set (\(N=57\)), ii) build a summary statistic using these features (i.e., degree score), iii) test the model in the subject that is left out, iv) and evaluate the significance of the prediction using permutation testing. At each iteration of the cross-validation, we removed one subject’s data (test set) from the rest of the dataset (training set). We then selected the most relevant features in the training set using a significance threshold (\(p<0.1\)) for the correlation between nodal degree and behavior (WM accuracy or reaction time). The selected features were separated into positive and negative sets depending on the sign of the correlation with the behavioral outcome. Next, a summary degree statistic was computed (for each subject in the training set) by summing up the degree values of the nodes in the feature sets. Thus, a separate summary value was obtained for the positive and negative set. We then produced a combined summary score obtained by subtracting the negative set summary score from the positive set score, which utilizes and takes advantage of both feature sets\(^3\). This metric represented a summary “degree score”. The relationship between degree score and the behavioral variable was modeled using linear least squares regression:

\[
BV' = a \cdot DS + b
\]

Where \(BV\) stands for behavioral variable (WM accuracy or reaction time) and \(DS\) degree score. The models were built for positive and negative sets, as well as the combined set. Finally, the degree score was calculated in the test subject for all three sets, and the behavioral variable was estimated using their respective model. We repeated these steps until each of the 58 participants was used as a test subject. Then, the correlation between the predicted and the observed values of the behavioral variable determined the predictive power of these models. The significance of this correlation was tested via permutation testing. To obtain an empirical null distribution of the correlation, we applied the cross-validated procedure described above using the same degree data and randomly shuffled behavioral scores and repeated this step 1,000 times. Finally, the \(p\)-value was calculated as the proportion of permuted correlations that are greater than or equal to the true prediction correlation.
SUPPLEMENTARY RESULTS

Relationship between clinical and cognitive outcomes

Our analysis of correlation between the main clinical and cognitive outcomes in our study revealed no significant relationship between these sets of variables. The correlations between working memory accuracy and the three clinical variables were not significant: $r=-0.17$, $p=0.37$ (PANSS positive), $r=0.15$, $p=0.48$ (CPZE), and $r=-0.18$, $p=0.36$ (illness duration). Similarly, the correlation between average reaction time and the clinical variables did not reach significance ($r=0.24$, $p=0.21$ for PANSS positive, $r=-0.08$, $p=0.72$ for CPZE, and $r=0.08$, $p=0.70$ for illness duration).
**Task.** Sternberg Item Recognition Paradigm (SIRP) was used as the working memory task. Each block started with the encoding epoch where participants memorized 1, 3, 5, or 7 consonants. After a brief delay period, single probe letters were presented in succession (14 probes per block). The participants were instructed to press ‘1’ on the keypad if the letter was not in the memorized set (foil) and press ‘2’ if the letter was in the memory set (target). Participants completed 8 blocks (2 per WM load) consisting of 112 trials during a single fMRI run.
**Analysis pipeline.** Resting state functional connectivity was computed among 333 Gordon parcels covering the cerebral cortex for each participant. Subject-level connectivity graphs were defined at varying thresholds (from 2% to 10% edge density in 1% increments) to obtain a robust composite degree value at each node.
**Group difference.** Effect size (Cohen’s d) of group differences in nodal degree is shown on the surface maps. Warm colors indicate nodes with greater degree value in controls, cool colors indicate nodes with greater degree value in patients. Right anterior insula and right postcentral gyrus showed the strongest effects for lower nodal degree in schizophrenia, whereas left intraparietal sulcus showed the largest effect for higher nodal degree in patients.
**Relationship between nodal degree and behavior across all subjects.** Pearson’s correlation between weighted degree and each of the WM performance measures is shown on the surface maps. Parahippocampal gyrus and medial default mode network regions showed an inverse relationship between weighted degree and WM performance (i.e., higher degree was associated with poorer performance). Conversely, regions of the ventral attention network showed a positive correlation between nodal degree and WM accuracy.
Relationship between nodal degree and behavior in each group. Pearson’s correlation between nodal degree and WM performance measures is shown on the surface maps for controls (top) and schizophrenia patients (bottom). Both groups showed positive correlations between accuracy and nodal degree in superior temporal regions. The degree in default mode regions seemed to correlate more strongly with accuracy in controls, whereas it showed a stronger association with reaction time in patients.
Relationship between nodal degree and behavior in schizophrenia. Scatterplots illustrate the relationships between WM performance and degree in six of the fourteen nodes that showed a significant correlation with performance in patients. See Figure 3 in the main article for the other nodes. The data points and the best fit lines are plotted in blue for controls and in red for patients. The nodes are marked on the surface maps in the middle panel. Warm colors represent a positive correlation and cool colors reflect a negative correlation with the behavioral measure. Abbreviations: A: anterior, FEF: frontal eye field, FG: fusiform gyrus, IPS: intraparietal sulcus, P: posterior, PHG: parahippocampal gyrus, SMA: supplementary motor area, STS: superior temporal sulcus.
SUPPLEMENTARY TABLES

**Table S1.** Gordon parcels showing nominally significant group differences in nodal degree between schizophrenia patients and healthy controls.

| Region | X   | Y   | Z   | Network | p-value (uncorr.) | Cohen’s d |
|--------|-----|-----|-----|---------|------------------|-----------|
| IPS    | -34 | -61 | 42  | FPN     | 0.0004           | -0.977    |
| alns   | 27  | 20  | -15 | VAN     | 0.0006           | 0.998     |
| PoCG   | 50  | -7  | 36  | SML     | 0.0110           | 0.679     |
| IOFC   | -23 | 61  | -7  | UA      | 0.0148           | -0.653    |
| IOFC   | -40 | 50  | -5  | FPN     | 0.0148           | -0.657    |
| alns   | 34  | 23  | 4   | CON     | 0.0152           | 0.670     |
| SPL    | -29 | -45 | 62  | SM      | 0.0168           | -0.644    |
| dmPFC  | 14  | 47  | 42  | DMN     | 0.0184           | 0.638     |
| Precuneus | 10 | -57 | 58  | DAN     | 0.0186           | -0.637    |
| ROp    | -60 | -4  | 9   | CON     | 0.0483           | 0.541     |
| AG     | -39 | -74 | 38  | DMN     | 0.0480           | -0.528    |
| STS    | 46  | -37 | 3   | VAN     | 0.0488           | -0.523    |

Negative Cohen’s d values indicate higher degree in patients.

Abbreviations: AG: angular gyrus, alns: anterior insula, dmPFC: dorsomedial prefrontal cortex, IPS: intraparietal sulcus, IOFC: lateral orbitofrontal cortex, PoCG: postcentral gyrus, ROp: Rolandic Operculum, SPL: superior parietal lobule.

Networks: CON: cingulo-opercular network, DAN: dorsal attention network, DMN: default mode network, FPN: frontoparietal network, SM: somatomotor network, SML: somatomotor lateral, UA: unassigned, VAN: ventral attention network, VN: visual network.
Table S2. Correlations between behavioral outcomes and within- and between-network nodal degree in schizophrenia patients.

| Region   | Network | Coordinates | WN correlation | BN correlation | pcorr  | pcorr  |
|----------|---------|-------------|----------------|----------------|--------|--------|
|          |         | x   y   z   | WN  | WN   |         |         |
|          |         |     |     |         |         |        |
| WM ACCURACY |        |     |     |         |         |        |
| Precuneus | CON    | -17 | -36 | 43     | -0.483 | 0.008  | -0.573 | 0.001 |
| PHG      | UA      | 32  | -9  | -36    | -0.254 | **0.183** | -0.697 | 2.63E-05 |
| STS      | VAN     | 46  | -37 | 3      | 0.497  | 0.006  | 0.473  | 0.010 |
| STS      | VAN     | 47  | -22 | -9     | 0.379  | 0.042  | 0.465  | 0.011 |
| STS      | VAN     | 61  | -39 | 2      | 0.382  | 0.041  | 0.418  | 0.024 |
| REACTION TIME |       |     |     |         |         |        |
| dIPFC    | DMN     | -42 | 16  | 48     | 0.443  | 0.016  | 0.520  | 0.004 |
| FEF      | DAN     | -45 | 3   | 32     | 0.305  | **0.107** | 0.573  | 0.001 |
| IPL      | DMN     | -47 | -58 | 31     | 0.532  | 0.003  | 0.334  | **0.076** |
| SMA      | SM      | 5   | -17 | 52     | -0.536 | 0.003  | -0.386 | 0.038 |
| FG       | VN      | -34 | -44 | -22    | -0.379 | 0.042  | -0.459 | 0.012 |
| IPS      | DAN     | -43 | -45 | 43     | 0.238  | **0.213** | 0.624  | 0.0003 |
| STS      | VAN     | 58  | -45 | 9      | -0.297 | **0.118** | -0.594 | 0.0007 |
| SMA      | FPN     | -6  | 29  | 44     | 0.375  | 0.045  | 0.441  | 0.017 |
| SMG      | CON     | 58  | -40 | 35     | 0.311  | **0.101** | 0.492  | 0.007 |

**Abbreviations:** BN: between-network, dIPFC: dorsolateral prefrontal cortex, FEF: frontal eye field, FG: fusiform gyrus, IPL: inferior parietal lobule, IPS: intraparietal sulcus, PHG: parahippocampal gyrus, SMA: supplementary motor area, SMG: supramarginal gyrus, STS: superior temporal sulcus, WN: within-network

**Networks:** CON: cingulo-opercular network, DAN: dorsal attention network, DMN: default mode network, FPN: frontoparietal network, SM: somatomotor network, UA: unassigned, VAN: ventral attention network

*Non-significant correlations are boldfaced.*
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