**Supplementary Material For**

**Characteristics of disrupted topological organization in**

**white matter functional connectome in schizophrenia**

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***This supplementary material includes as follows:***

**Methods and Materials:** fMRI Data preprocessing

**Methods and Materials:** data quality control

**Methods and Materials:** Rationale for each graphic parameter

**Methods and Materials:** Non-parametric permutation tests

**Methods and Materials:** Stability analysis

**Supplementary Materials: *fMRI data preprocessing***

The fMRI data preprocessing steps were the following. (1) First five volumes of time series were removed for signal equilibrium and to allow the participants to adapt at to the scanning noise. (2) Slice-time correction. (3) Realignment to the mean functional image was performed using a trilinear interpolation with degrees of freedom and coregistered with the anatomical image. Subjects with maximum motion >2 mm or 2° were excluded. (4) Removal of linear trends to correct for signal drift. (5) Nuisance signal (including 24-parameter motion correction and the mean CSF signals) was regressed out. The 24 motion parameters included six rigid-body motion parameters (x, y and z translations and rotations) and their values at the previous time point and the 12 corresponding squared values. (6) Temporal scrubbing using motion “spikes” (framewise displacement (FD) > 1) as separate repressors was performed to further eliminate the effect of motion noise. (7) Band-pass filtering was performed to reduce physiological noise to BOLD fluctuations. (8) To avoid mixing white-matter and gray-matter signals, spatial smoothing was performed separately on the white-matter or gray-matter masks. In detail, the individual T1 segmentation images were coregistered to the functional space for each participant for the identification of white-matter or gray-matter masks (the threshold was set at 0.5). The individual functional images were smoothed (FWHM = 4 mm) separately on the two masks. (9) Normalization to the standard MNI template and resampling to 3 mm3. Steps 1–8 were performed on each subject's original sampling space in order to distinguish white-matter and gray-matter signals at the individual level. Preprocessing was performed using SPM12 (www.fifil.ion. ucl.ac.uk/spm) and DPABI (http://rfmri.org/dpabi). In addition, we examined group-level head-motion differences between the schizophrenia patient group and healthy control group using the two-sample t-test. There was no significant difference in head motion between the two groups (P>0.05).

**Supplementary and Materials: *data quality control***

The data quality control (QC) steps are as follows:

(1) QC for MRI scanner. Regular quality assurance protocols are performed daily, which ensure scanner performance stability and acquisition quality.

(2) QC for data acquisition. Only those subjects who accomplish all of the T1, resting-state fMRI and DTI data acquisitions were reserved for data analysis.

(3) QC for raw images. Raw functional and structural images must be checked for large distortions, ghosting or other abnormalities.

(4) QC for spatial normalization. During the data processing, the individual FA image is spatially coregistered (normalized) to standardized space. After this normalization, we visually inspected the spatial normalization results.

(5) QC for head motion. During scanning, subjects with maximum motion > 2 mm or 2° were excluded.

These quality control steps allow us to exclude those subjects with poor quality and generate a subject list for following analysis.

**Supplementary Materials: *Rationale for each graphic parameters***

The mathematical definitions of graphic parameters are list as below (Chen, Hu, Chen, & Feng, 2019; Rubinov & Sporns, 2010):

***Clustering coefficient:*** The clustering coefficient of a node *i* is quantified as the extent to which the neighborhoods are connected with each other or not, and is calculated with the following equation:

in which the *C(i)* is the clustering coefficient of a node *i*; the *ei* is the number of edges in the sub-graph *Gi*, and *Ki* represents the number of nodes connected to node *i*.

The network clustering coefficient is calculated by the average of *C(i)* across all nodes in the network, whose formula is list as below:

***Shortest path length:***The path length between node *i* and node *j* could be quantified as the sum of edge lengths along this path. The shortest path length (*Lij*) is calculated as the shortest path length between node *i* and node *j*. The shortest path length for a network is defined as the average *Lij* across all the paired nodes of the network. The formula is:

where *N* is the number of nodes of a graph; *Lij* is the shortest path length between the nodes *i* and node *j*.

The shortest path length can measure the ability for information propagation, with a larger value denoting the lower propagation efficiency.

**Small-worldness:** To characterize the small-worldness of a network, the clustering coefficient and the shortest path length of a network are normalized as Gamma (*γ*) and Lambda (*λ*),whose formula are as below:

where the *Cp(random)* and *Lp(random)*represent the clustering coefficient and the shortest path length for a random network. For each individual brain network, a set of 100 comparable random networks with similar degree sequence and symmetric adjacency matrix were generated in this study.

The small-worldness (*σ*) was initially proposed by Watts and Strogatz, indicating a typical network that has similar path length but higher clustering than a random network (Watts & Strogatz, 1998), that is *γ*>1, *λ*≈1. These two conditions can also be summarized into a scalar quantitative measurement, the small-worldness, *σ*=*γ*/*λ*, which is typically>1 (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Humphries, Gurney, & Prescott, 2006).

***Local efficiency:*** Local efficiency for a node *i* could be quantified for the information processing efficiency with the following equation:

in which the *Ljk* is the shortest path length between nodes *j* and *k* in the *Gi*, the *Gi* represents the subgraph composed of the nearest neighbors of the node *i*.

The local efficiency of a network *Eloc(net)* is defined as the average efficiency of the local subgraphs, which reflects the ability of local communication in a network:

***Hierarchy:*** Hierarchy is a natural topological property in many actual networks, particularly in brain networks. In a hierarchy network, the nodes with a low degree typically showed a higher clustering coefficient compared with high-degree nodes, yielding the efficient communication within the network (Smith, Abdala, Koizumi, Rybak, & Paton, 2007). The hierarchy coefficient could be quantified in the distribution of the ratio, and is defined as follows:

*C~k−β*

where the *C* indicates the clustering coefficient and the *k* is the degree of a node for the network. The coefficient of hierarchy *(β)* is computed by fitting a linear regression using the ratio between log-transformed *C* and log-transformed *k*.

***Synchronization:*** Network synchronization is quantified by the eigenratio of the Laplacian matrix (coupling matrix) of a graph (Barahona & Pecora, 2002). This definition is based on a linear stability analysis. In short, the Laplacian of a graph A=(aij) is obtained as L=D－A, where D=(dii) is a diagonal matrix with node-degrees in the diagonal entries. λi are the eigenvalues of the Laplacian matrix, ordered as 0 = λ1 ≤ λ2 ≤ … ≤ λN, where N is the number of nodes in the network. The eigenratio λN/λ2 is a measure for the degree of synchronization properties of the network: the smaller the eigenratio, the more synchronizable the network.

**Methods and Materials: *non-parametric permutation tests***

To further examine the associations between the altered nodal metrics (*Knodal*, *Enodal* and *Bnodal*) and FA values, the WM tracts with altered nodal metrics were extracted and then Spearman rank correlation analysis was employed to evaluate the correlation between the nodal metrics and FA for altered WM tracts in each group. We conducted an analysis to test the group interaction that whether the difference in correlations between SZ and HC groups is significant using the non-parametric permutation tests. In brief, we firstly calculated the correlation coefficient between Enodal and FA values in the SZ and HC group separately. Subsequently, we computed the real difference value of the correlation coefficient between the SZ and HC groups. Next, we randomly assigned the group labels across all subjects and divided all subjects into two random groups. In each random group, we calculated the correlation coefficient between Enodal and FA values. Then, we re-calculated the difference value of the correlation coefficient between the two random groups. Finally, this randomization procedure was repeated 100,000 times, and thus yielded a distribution of the null hypothesis. According the location of the real difference value within distribution of the null hypothesis, a p-value was assigned to the real difference.

In addition, one could make a case that even without a correlation in either group, there may still be a significant group difference in correlation. To test that, an exploratory analysis was performed to examine the interaction effect in all ROIs (see below Table S1).

Table S1. Group difference in correlations of FA and nodal metrics (Bnodal, Knodal and Enodal) between SZ and HC groups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Number | WM ROI name | Abbreviation | Interaction effect P value | | |
| Bnodal | Knodal | Enodal |
| 1 | Middle cerebellar peduncle | mCBLP | 0.0961 | 0.0191\* | 0.0396\* |
| 2 | Pontine crossing tract | PC | 0.6188 | 0.6606 | 0.8678 |
| 3 | Genu of corpus callosum | GCC | 0.8867 | 0.1162 | 0.0378\* |
| 4 | Body of corpus callosum | BCC | 0.0815 | 0.5790 | 0.8874 |
| 5 | Splenium of corpus callosum | SCC | 0.7561 | 0.1439 | 0.0859 |
| 6 | Fornix | FX | 0.0246\* | **0.007\*\*** | **0.0056\*\*** |
| 7 | Corticospinal tract R | CST.R | 0.3966 | 0.6239 | 0.4296 |
| 8 | Corticospinal tract L | CST.L | 0.4409 | 0.1183 | 0.0465\* |
| 9 | Medial lemniscus R | ML.R | 0.1764 | 0.8276 | 0.5824 |
| 10 | Medial lemniscus L | ML.L | 0.4827 | 0.7929 | 0.4903 |
| 11 | Inferior cerebellar peduncle R | iCBLP.R | 0.8334 | 0.6404 | 0.6009 |
| 12 | Inferior cerebellar peduncle L | iCBLP.L | 0.7037 | 0.6980 | 0.3657 |
| 13 | Superior cerebellar peduncle R | sCBLP.R | 0.1116 | 0.3449 | 0.8557 |
| 14 | Superior cerebellar peduncle L | sCBLP.L | 0.7247 | 0.1742 | 0.0251\* |
| 15 | Cerebral peduncle R | CBRP.R | 0.2078 | 0.0140\* | **0.0037\*\*** |
| 16 | Cerebral peduncle L | CBRP.L | 0.8241 | 0.2419 | 0.0459\* |
| 17 | Anterior limb of internal capsule R | ALIC.R | 0.5885 | 0.2036 | 0.0370\* |
| 18 | Anterior limb of internal capsule L | ALIC.L | 0.6337 | 0.2402 | 0.1489 |
| 19 | Posterior limb of internal capsule R | PLIC.R | 0.1272 | 0.0370\* | **0.0012\*\*** |
| 20 | Posterior limb of internal capsule L | PLIC.L | 0.2249 | 0.2230 | 0.0265\* |
| 21 | Retrolenticular part of internal capsule R | RLIC.R | 0.1118 | 0.9532 | 0.7469 |
| 22 | Retrolenticular part of internal capsule L | RLIC.L | 0.1681 | 0.0527 | 0.2293 |
| 23 | Anterior corona radiata R | ACR.R | 0.5806 | 0.3639 | 0.1742 |
| 24 | Anterior corona radiata L | ACR.L | 0.8811 | 0.7523 | 0.2582 |
| 25 | Superior corona radiata R | SCR.R | 0.7888 | 0.6208 | 0.3709 |
| 26 | Superior corona radiata L | SCR.L | 0.2545 | 0.6189 | 0.1524 |
| 27 | Posterior corona radiata R | PCR.R | 0.9079 | 0.6272 | 0.3373 |
| 28 | Posterior corona radiata L | PCR.L | 0.8162 | 0.5811 | 0.1289 |
| 29 | Posterior thalamic radiation R | OR.R | 0.8787 | 0.0217\* | **0.0078\*\*** |
| 30 | Posterior thalamic radiation L | OR.L | 0.9683 | 0.1380 | 0.0642 |
| 31 | Sagittal stratum R | SS.R | 0.9599 | 0.3782 | 0.2019 |
| 32 | Sagittal stratum L | SS.L | 0.7988 | 0.6661 | 0.9070 |
| 33 | External capsule R | EC.R | 0.7013 | 0.4543 | 0.6879 |
| 34 | External capsule L | EC.L | 0.5567 | 0.7420 | 0.5083 |
| 35 | Cingulum (cingulate gyrus) R | CGG.R | 0.4203 | 0.7747 | 0.2205 |
| 36 | Cingulum (cingulate gyrus) L | CGG.L | 0.8216 | 0.1626 | 0.4480 |
| 37 | Cingulum (hippocampus) R | CGH.R | 0.0198 | 0.1127 | 0.1140 |
| 38 | Cingulum (hippocampus) L | CGH.L | 0.6053 | 0.6185 | 0.1897 |
| 39 | Fornix (cres) / Stria terminalis R | FXC.R | 0.9385 | 0.2092 | 0.0972 |
| 40 | Fornix (cres) / Stria terminalis L | FXC.L | 0.9398 | 0.1100 | 0.0423\* |
| 41 | Superior longitudinal fasciculus R | SLF.R | 0.7266 | 0.5667 | 0.0779 |
| 42 | Superior longitudinal fasciculus L | SLF.L | 0.6218 | 0.4173 | 0.0960 |
| 43 | Superior fronto-occipital fasciculus R | SFO.R | 0.853 | 0.8519 | 0.6855 |
| 44 | Superior fronto-occipital fasciculus L | SFO.L | 0.8778 | 0.6042 | 0.5249 |
| 45 | Uncinate fasciculus R | UF.R | 0.5788 | 0.7475 | 0.7314 |
| 46 | Uncinate fasciculus L | UF.L | 0.2148 | 0.6368 | 0.6583 |
| 47 | Tapetum R | TAP.R | 0.6723 | 0.7151 | 0.2495 |
| 48 | Tapetum L | TAP.L | 0.3813 | 0.8814 | 0.4898 |

\* P<0.05; \*\* P<0.01

**Methods and Materials: *Stability analysis***

An additional ten-folds cross-validation was used to estimate the stability of the main results. In details, all subjects were randomly divided into ten folds, of which nine folds were used to compare the group differences between SZ and HC using the permutation test. The ten-folds cross-validation procedures were repeated 100 times to avoid the outcomes of the stability analysis depending on the exact instance of the 10-fold data split. The stability rate was the proportion of 1000 (10 folds × 100 iterations) outcomes with significant difference.

Results showed that the differences in GM network synchronization and WM network hierarchy had a excellent stability rate (> 0.9). The differences in GM shortest path length and local efficiency had a high stability rate (> 0.8). The differences in GM cluster coefficient and WM local efficiency, small-worldness exhibited a moderate stability rate (> 0.7). The differences in cluster coefficient and synchronization for the WM functional network had a fair stability rate (> 0.6). As for the nodal level, all group differences exhibited a high stability rate (>0.8).

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