Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix

Preprocessing

Resting-state fMRI data were processed using procedures 1, 2 that were adapted from Fox et al. 3 and Van Dijk et al. 4. The following steps were performed: 1) slice timing correction (SPM2, Wellcome Department of Cognitive Neurology, London, UK); 2) rigid body correction for head motion with the FSL package 5, 6; 3) normalization for global mean signal intensity across runs; and 4) low-pass temporal filtering, head motion regression, and ventricular and white matter signal regression. Whole brain signal regression was also included in the processing stream, which can improve the correction of motion related artifacts 7, 8. All subjects included in this study had met the quality control criterion of slice-based temporal signal-to-noise ratio >100 9. Head motion is an important issue in resting-state fMRI data processing, which not only causes artifacts but can also reflect a neurobiological trait effect10. In the present study, we did not remove the image frames based on head motion because our recent exploration indicated that the data scrubbing might cause inflated connectivity estimates in specific regions 10.

The structural data were processed using the FreeSurfer version 4.5.0 software package as described in Yeo et al. 1. The structural and functional images were aligned using boundary-based registration11 within the FsFast software package (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast). The resting-state BOLD fMRI data were aligned to a spherical coordinate system via sampling from the cortical ribbon in a single interpolation (see Yeo et al. 1 for details).

Anti-correlation of AI Between Two Hemispheres

Since AI is defined as the contrast between intra- and inter-hemispheric connectivity, for any specific functional network that spans the two hemispheres, a strong negative correlation between the AI values in the left hemisphere portion and right hemisphere portion of the network would be expected. For example, assuming a network consisting of $N_l$ voxels in the left hemisphere and $N_r$ voxels in the right hemisphere, when each voxel is significantly correlated with every other voxel within the network, the mean AI in the left hemisphere portion is:

$$AI(l) = N_l / H_l - N_r / H_r$$
Where \( H_l \) and \( H_r \) are the total number of voxels in the left and right hemisphere, respectively.

For the right hemisphere portion of the network, the mean AI is given by:

\[
AI(r) = \frac{N_r}{H_r} - \frac{N_l}{H_l}
\]

Thus, in the extreme case where the voxels within the same network are 100% correlated, the AI values in left hemisphere portion and right hemisphere portion would be perfectly anti-correlated. However, in real data, the anti-correlation between \( AI(l) \) and \( AI(r) \) would always be weaker than -1. We have tested this based on 1,000 healthy subjects and found that as we expected, most functional networks demonstrated a significant anti-correlation between the left- and right hemispheric AI. The results are shown in Figure S6.

If the sub-networks in two hemispheres are completely disconnected, then each sub-network would only have intra-hemispheric connectivity. The AI values in the left hemisphere portion and right hemisphere portion are then given by:

\[
\begin{align*}
AI(l) &= \frac{N_l}{H_l} \\
AI(r) &= \frac{N_r}{H_r}
\end{align*}
\]

In such case, the AI values between the two hemispheres become uncorrelated. Therefore the anti-correlation of the AI values is a sensitive indication of the integrity of hemispheric interaction within a specific network.

**Reliability of AI**

To assess the test-retest reliability of AI we made use of a longitudinal data set that we previously published on \(^1\). This data set consists of 23 subjects each of which underwent 5 scanning sessions within six months (7, 14, 30, 90 and 180 days from the enrollment). The group AI maps resulting from each of these 5 scanning sessions show a highly similar AI distribution (see Figure S5), with an overall reliability of 0.87 (estimated as the mean correlation coefficient of the 5 maps, left and right hemisphere combined). The analogous analysis was performed for the AI of subcortical regions and yielded an overall reliability of \( r=0.75 \) (left and right hemisphere combined).

We also tested the stability of AI distribution across 2 independent datasets of healthy individuals and
found that AI showed a very replicable and robust distribution across the discovery and replication data sets (n=500 each, see Figure 2 in Wang and colleagues\textsuperscript{14}).

\textit{Controlling for potential outliers in the anti-correlation analyses}

To control for potential outliers driving the loss of anti-correlation shown in Figure 3 we performed a standardized analysis of outliers at a 95% confidence interval (CI) and found that three out of 31 schizophrenia subjects had caudate AI values beyond the 95% CI in either the left and the right hemisphere or both, whereas none out of the healthy control AI values were identified as outliers. Removing these outliers reduced the effect size of differential anti-correlation in the two groups, in fact the difference between the correlations of AI values of the entire caudate nucleus failed to remain significant (before outlier removal: \( r_{\text{CON}}=-0.40, r_{\text{SCZ}}=-0.01, p=0.04 \), after outlier removal: \( r_{\text{CON}}=-0.40, r_{\text{SCZ}}=-0.13, p=0.19 \)). When looking at the caudate portion that is connected to the default network however, the effect remained stable even after removing the three outliers (before outlier removal: \( r_{\text{CON}}=-0.53, r_{\text{SCZ}}=0.04, p=0.005 \), after outlier removal: \( r_{\text{CON}}=-0.53, r_{\text{SCZ}}=-0.01, p<0.02 \)).

\textit{Support vector machine (SVM) classifier}

The SVM classification procedure consisted of two steps: the training step to determine the parameters of the classifier based on a training dataset of patients and controls, and the testing step to determine the accuracy of this classifier in an independent testing dataset. To divide our probands in training and testing datasets one patient and one control subject were randomly selected as the testing dataset and all the remaining subjects were used as the training cohort.

The training and testing of the support vector machine were carried out using the Statistics Toolbox in MATLAB (details of the training and testing functions can be found in the following webpages: http://www.mathworks.com/help/stats/svmtrain.html & http://www.mathworks.com/help/stats/svmclassify.html). Possible results of the testing were that either 0, or 1, or 2 of the testing subjects were classified correctly, corresponding to a classification accuracy of 0\%, 50\% or 100\%. The procedure was repeated 1000 times and the mean classification accuracy was computed. As the SVM approach should be based on an equal number of subjects in
each group we used 31 schizophrenia patients, and 31 randomly picked controls in each of the 1000 permutations.
### eTable 1. Demographic and Clinical Characteristics of the Participants

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 37, 6 female)</th>
<th>Schizophrenia (n = 31, 7 female)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age (y)</td>
<td>34.6</td>
<td>11.7</td>
</tr>
<tr>
<td>Mean parental education (y)</td>
<td>14.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Mean parental socioeconomic status&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Premorbid verbal IQ&lt;sup&gt;b&lt;/sup&gt;</td>
<td>110.2</td>
<td>6.5</td>
</tr>
<tr>
<td>Head motion (mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean slice SNR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>277</td>
<td>79</td>
</tr>
<tr>
<td>PANSS (pos)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (neg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS (total)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents</td>
<td></td>
<td></td>
</tr>
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</table>

Note: There were no significant differences between the 2 groups in mean age, parental education, parental socioeconomic status, premorbid verbal IQ, head motion and slice SNR during the scanning. Antipsychotic medications of the 31 patients were as follows: 1–2 atypical agents (aripiprazole, ziprazadone, risperidone, clozaril) (n = 22), typical agents (haldol) (n = 1), unmedicated (n = 8). PANSS, positive and negative symptom scale.

<sup>a</sup>Measured with the Hollingshead index.
<sup>b</sup>Measured with the Adult North American Reading Test.
<sup>c</sup>Mean relative displacement in millimeters.
<sup>d</sup>Mean slice signal-to-noise ratio across all resting state fMRI scan time points.
<table>
<thead>
<tr>
<th></th>
<th>CON (n=) mean / std</th>
<th>SCZ (n=) mean / std</th>
<th>p (two-sided t-test) CON vs. SCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right caudate AI (Figure 2)</td>
<td>-0.0014 / 0.0223</td>
<td>0.0163 / 0.0271</td>
<td>0.0043</td>
</tr>
<tr>
<td>Left caudate AI (Figure 2)</td>
<td>0.0316 / 0.0227</td>
<td>0.0158 / 0.0188</td>
<td>0.0031</td>
</tr>
<tr>
<td>Correlation between left/ right caudate AI (Figure 3)</td>
<td>r=-0.4056</td>
<td>r= 0.0137</td>
<td>0.0416 (arctool)</td>
</tr>
<tr>
<td>Difference between left/ right caudate AI (Figure 4)</td>
<td>0.0330 / 0.0377</td>
<td>-0.0005 / 0.0328</td>
<td>0.00004</td>
</tr>
</tbody>
</table>
**eTable 3. Replication of Main Results After Separating Medicated From Unmedicated Patients**

<table>
<thead>
<tr>
<th></th>
<th>CON mean/std</th>
<th>UNMED mean/std</th>
<th>MED mean/std</th>
<th>p CON vs. UNMED</th>
<th>p CON vs. MED</th>
<th>p UNMED vs. MED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right caudate AI (Figure 2)</td>
<td>-0.0014 / 0.0223</td>
<td>0.0117 / 0.0164</td>
<td>0.0179 / 0.0301</td>
<td>0.1239</td>
<td>0.0060</td>
<td>0.5848</td>
</tr>
<tr>
<td>Left caudate AI</td>
<td>0.0316 / 0.0227</td>
<td>0.0130 / 0.0187</td>
<td>0.0168 / 0.0192</td>
<td>0.0366</td>
<td>0.0121</td>
<td>0.6259</td>
</tr>
<tr>
<td>Correlation between left/ right caudate AI (Figure 3)</td>
<td>r=-0.4056</td>
<td>r=0.4031</td>
<td>r=0.0467</td>
<td>0.0598</td>
<td>0.0696</td>
<td>0.3159</td>
</tr>
<tr>
<td>Difference between left/ right caudate AI (Figure 4)</td>
<td>0.0330 / 0.0377</td>
<td>0.0012 / 0.0193</td>
<td>-0.0011 / 0.0367</td>
<td>0.0263</td>
<td>0.0011</td>
<td>0.8663</td>
</tr>
</tbody>
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**eTable 4. Replication of Main Results Using All Subjects With Only One Resting State Run**

<table>
<thead>
<tr>
<th></th>
<th>CON (n=24) mean / std</th>
<th>SCZ (n=26) mean / std</th>
<th>p (two-sided t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right caudate AI (Figure 2)</td>
<td>-0.0043 / 0.0223</td>
<td>0.0181 / 0.0315</td>
<td>0.0091</td>
</tr>
<tr>
<td>Left caudate AI (Figure 2)</td>
<td>0.0332 / 0.0247</td>
<td>0.0170 / 0.0198</td>
<td>0.0265</td>
</tr>
<tr>
<td>Correlation between left/ right caudate AI (Figure 3)</td>
<td>r=-0.3918</td>
<td>r= 0.1596</td>
<td>0.0494 (arctool)</td>
</tr>
<tr>
<td>Difference between left/ right caudate AI (Figure 4)</td>
<td>0.0376 / 0.0392</td>
<td>-0.0011 / 0.0345</td>
<td>0.0017</td>
</tr>
</tbody>
</table>
**eFigure 1.** The Loss of Anticorrelation Between Left- And Right-Sided Specialization Is Most Prominent in Association Subdivisions of the Caudate Nucleus

The caudate nucleus can be segmented into a subdivision that is strongly connected to cortical association networks (frontoparietal and default network) and a subdivision that is strongly connected to the limbic network. The loss of anti-correlation between left- and right-sided specialization of the caudate nucleus in schizophrenia patients, as shown in Figure 3, was most prominent in the association portion of the caudate nucleus. Specifically, the effect was strongest in the caudate portion connected to the default network (p<0.01). The limbic portion by contrast did not display a significant disease effect.
**eFigure 2.** Cortical Regions Most Strongly Connected to the Caudate Nucleus Fall Within the Anterior Midline Component of the Default Network

A. Seven cortical networks derived from a parcellation in 1000 healthy subjects.³⁸

B. Boundaries of the seven-network parcellation overlaid on the caudate correlation map derived from 1000 healthy subjects.

C. Mask of cortical areas that are most strongly connected to the caudate nucleus (r>0.25) in 1000 healthy subjects.
eFigure 3. Reduced Left-Right AI Difference in Caudate-Connected Cortical Regions is Caused by Decreased Left-Sided and Increased Right-Sided AI Values.

Within the cortical regions connected to the caudate nucleus, the left-sided AI value was decreased while the right-sided AI value was increased in schizophrenia patients (gray bars) as compared to healthy controls (white bars, p<0.01 and p<0.05, respectively).
eFigure 4. Hemispheric Specialization Is Associated With Cortical Expansion During Development

Hemispheric specialization derived from 1000 healthy subjects 33 and developmental cortical expansion between term born infants and healthy young adults showed a moderate, yet significant association (Spearman rank correlation r=0.39, p<0.0001).
**eFigure 5.** The Autonomy Index Is a Robust and Highly Replicable Measure of Hemispheric Specialization

AI was estimated in a longitudinal data set with five repeated sessions. The group AI maps resulting from each of these five scanning sessions (A-E) showed a highly similar AI distribution with an overall reliability of 0.87.
**eFigure 6.** Functional Networks Demonstrate a Significant Anticorrelation Between Left- and Right Hemispheric Specialization

AI values within the right-sided and left sided-portion of functional networks were correlated in 1000 healthy subjects. The plots for each of these functional networks showed a strong anti-correlation between left- and right-sided AI values.


