Supplementary Materials

Brain-wide functional inter-hemispheric disconnection is a potential biomarker for schizophrenia and distinguishes it from depression

Shuixia Guo, Keith M. Kendrick, Jie Zhang,

Matthew Broome, Yongjun Yu, Zhening Liu, Jianfeng Feng

Our analysis included three datasets: two schizophrenia datasets and one depression dataset. Schizophrenia dataset 1 was recruited at the National Taiwan University Hospital and schizophrenia dataset 2 and depression dataset was recruited at Second Xiangya Hospital of Central South University in China. Here we mainly present our results from the two schizophrenia datasets separately rather than combined as in the main paper.

1. Effects of using DVARS "motion scrubbing" on data

In view of the fact that inter-hemispheric connections are generally longer than intra-hemispheric ones and might therefore be more susceptible to motion artifacts, particularly in schizophrenia and depression, we used DVARS "motion scrubbing" (as described in Power et al., 2012) in addition to standard movement control criteria for fMRI data from all subjects. Following DVARS only a very small proportion of data (10 - 40%) was removed from a total of 38 subjects out of 274 subjects across the combined schizophrenia datasets (see Fig. S1) and which made very little difference to the overall results. Indeed, applying this procedure resulted in a slight improvement in the overall significance of our findings.

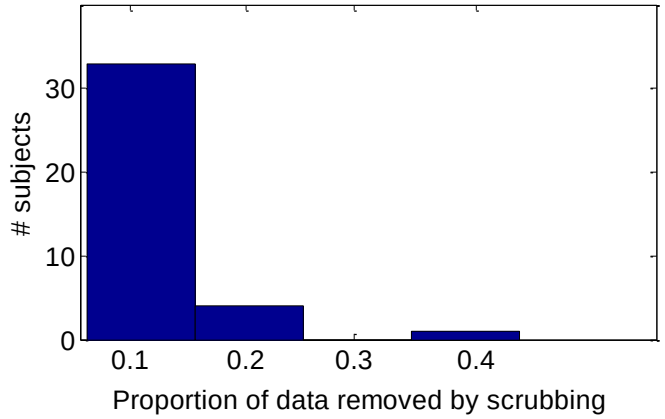


Figure S1: Histogram showing the proportion of image data removed as a result of applying DVARS motion scrubbing. It can be seen that very little of the fMRI data obtained from patients and healthy controls were contaminated by significant motion artifact.

2. Symmetry measures in the two schizophrenia datasets

From analysis of the two individual schizophrenia datasets it can clearly be seen that both first and second order symmetry are considerably reduced in both compared with healthy controls. This shows that synchronization between the left and right hemispheres is consistently reduced in the two schizophrenia patient groups despite some demographic differences between them (although for analysis we included education duration and age as nuisance covariates). Figure S2 shows the symmetry results for the two datasets separately and Figure S3 shows effects of illness duration in the different datasets. Details of drug treatments are given in Table S1 and demographic and symptom differences between the two groups are given in Table S2. Table S3 gives abbreviations for the 45 brain regions analyzed in each brain hemispheres, Table S4 shows first and second order symmetry changes in the two datasets divided into connections via the anterior commissure (AC) and corpus callosum (CC), Table S5 gives correlations between symmetry changes and positive and negative PANSS scores.

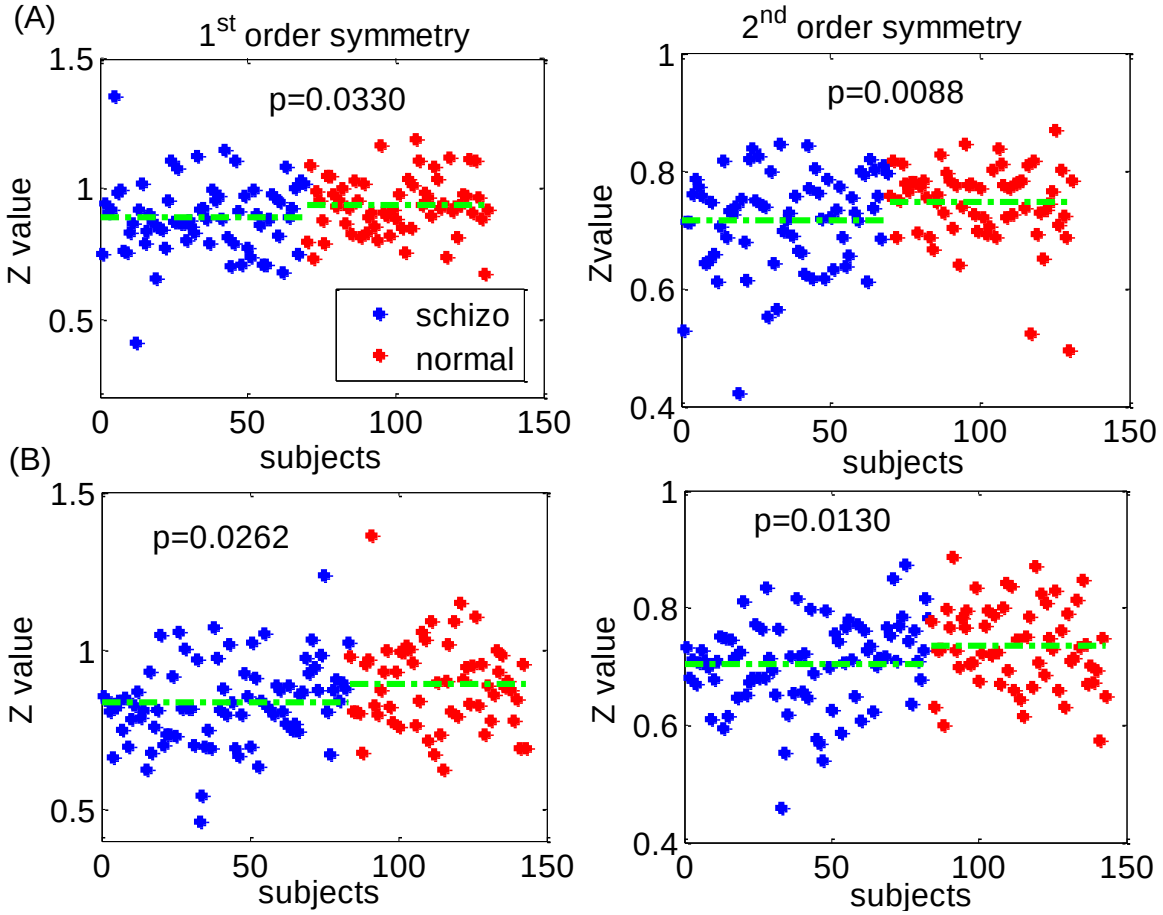


Figure S2: Symmetry Results for each of the two Schizophrenia Datasets. Results show first and second order symmetry schizophrenia patients (blue) and healthy controls (red) for dataset 1 (A) and dataset 2 (B). It can be seen that z-values for both first order and second order symmetry are significantly reduced in both groups, justifying them being combined in the main text.

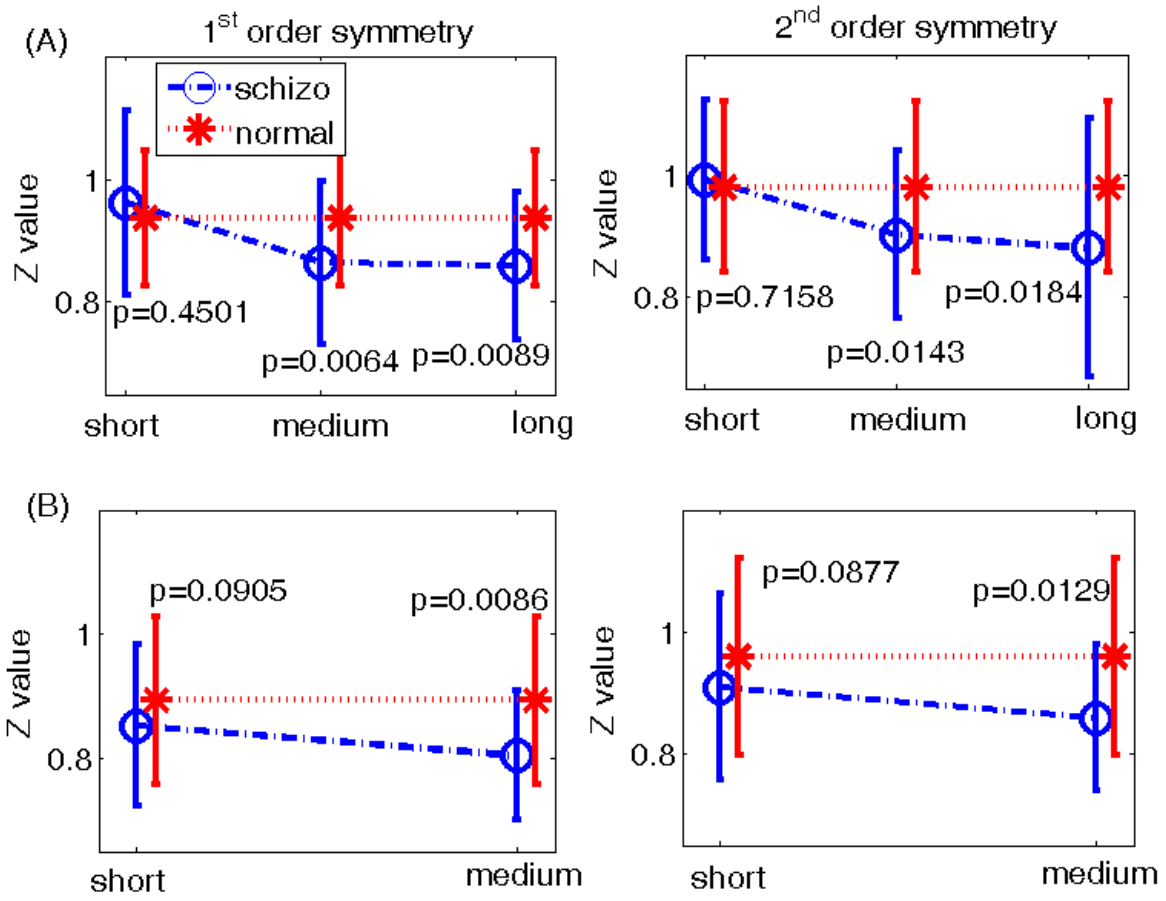


Figure S3: Effects of illness duration on first and second order symmetry in schizophrenia patients. (A) For dataset 1 first order symmetry and second order symmetry z-values (mean ± SD) are significantly reduced at both medium and long illness durations (B) For dataset 2 no patients had a long illness duration but significantly reduced first and second order symmetry occurred for medium illness durations with a trend towards this for short durations.

3. Effects of medication in schizophrenia patients

Table S1 gives a breakdown of the different types of medications for the schizophrenia patients in combined datasets 1(n = 69) and 2 (n = 83). In dataset 2, 22 patients were treatment naive and this allowed us to carry out a comparison of first and second order symmetry between them and the

remaining medicated patients. This analysis revealed no significant difference between the medicated and unmedicated groups for brain-wide first order symmetry, although a small significant difference for second order symmetry for CC connected regions, with medicated patients showing a slight reduction in z-scores (see Fig S3).

To investigate a potential influence of medication dose on first and second order symmetry we analyzed data from patients in dataset 2 where we had the drug and dose information from individual patients (drug dose information was not available for patients in dataset 1). In dataset 2, 9 patients (15%) were receiving first generation antipsychotics (FGAs) (sulpiride or haloperidol); 42 patients (69%) were receiving second generation antipsychotics (SGAs) (clozapine, risperidone, quetiapine, olanzapine, or aripiprazole), and 10 patients (16%) were receiving combination therapy (combining an FGA and an SGA). Daily-dose information was provided for a total of 49 of these patients and converted to chlorpromazine equivalents (50~1500 mg/day). The mean dosages of treatments with FGAs, SGAs and combination therapy were 822.9 mg/day, 384.6 mg/day and 572.3 mg/day respectively. The mean medication duration for these patients was 36.8 weeks (2 ~ 144 weeks). We found no correlation between chlorpromazine equivalent doses and brain wide first or second order symmetry in this group of patients (see Fig. S5).

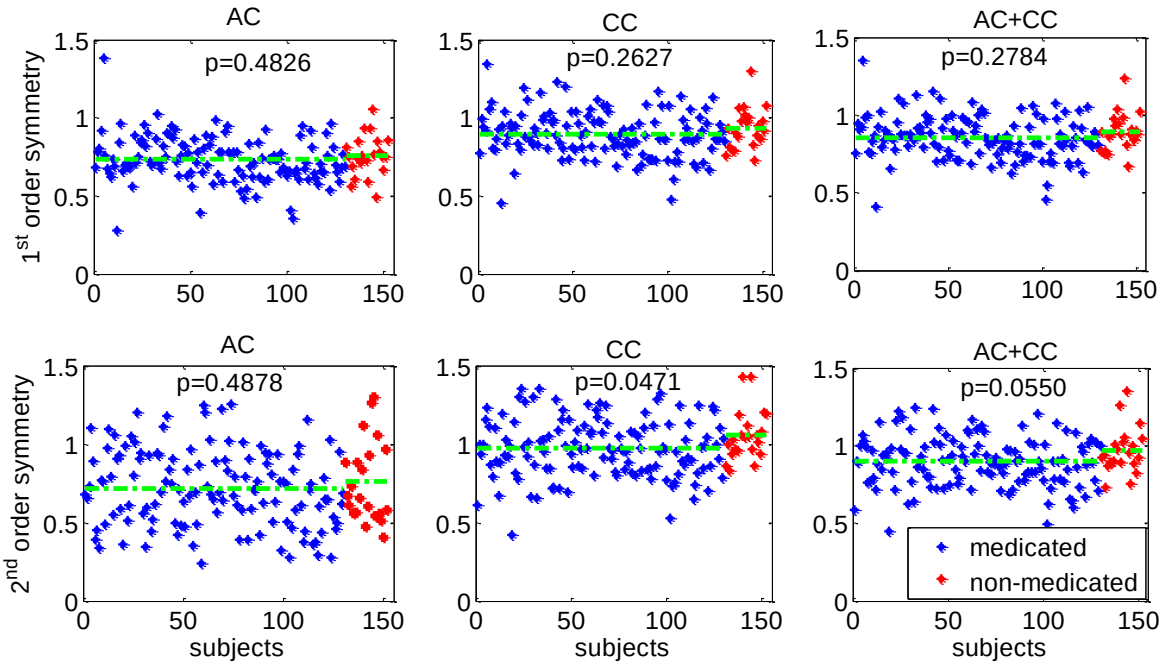


Figure S4: Comparison between treatment naive (n=22) and medicated (n=130) schizophrenia patients for first and second order symmetry measures. Z-values showing no significant differences were found between unmedicated and medicated patients for first order symmetry for connections via the anterior commissure (AC), corpus callosum (CC) or AC+CC (top). For second order symmetry there is a small significant difference for CC connected regions, with symmetry reductions being stronger in the medicated patients.

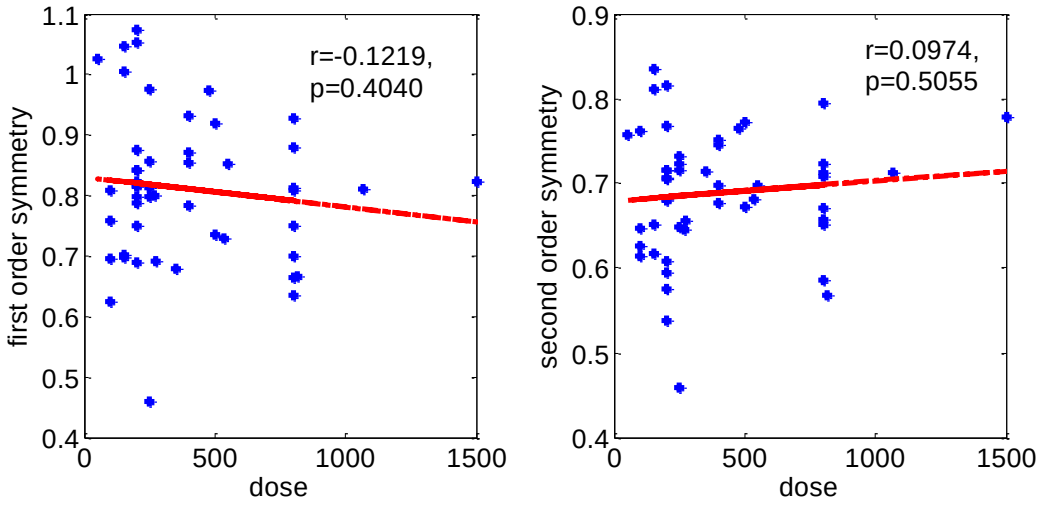
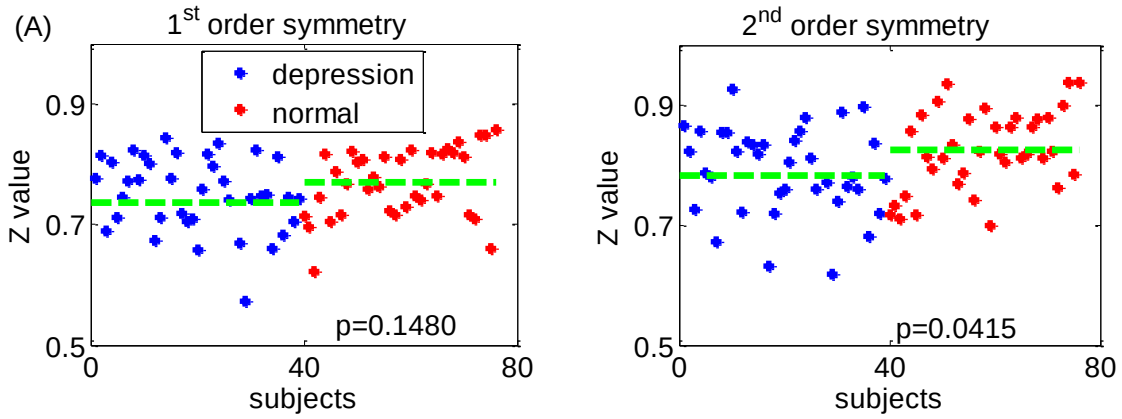


Figure S5. No correlation between brain-wide first (left panel) and second (right panel) order symmetry z-values and medication dose (given in chlorpromazine equivalents) in 49 schizophrenia patients from dataset 2.

4. Comparisons with depression patients

In the depression dataset, there are 39 patients diagnosed according to DSM-IV, and their scores on the 17-item version of Hamilton Rating Scale for Depression (HRSD), and 37 matched healthy controls recruited at the Second Xiangya Hospital of Central South University in China. Figure S6 shows brain-wide first and second order symmetry and overall inter-hemispheric links are slightly but significantly reduced. Similar to schizophrenia, depression was not associated with altered brain-wide intra- hemispheric links.



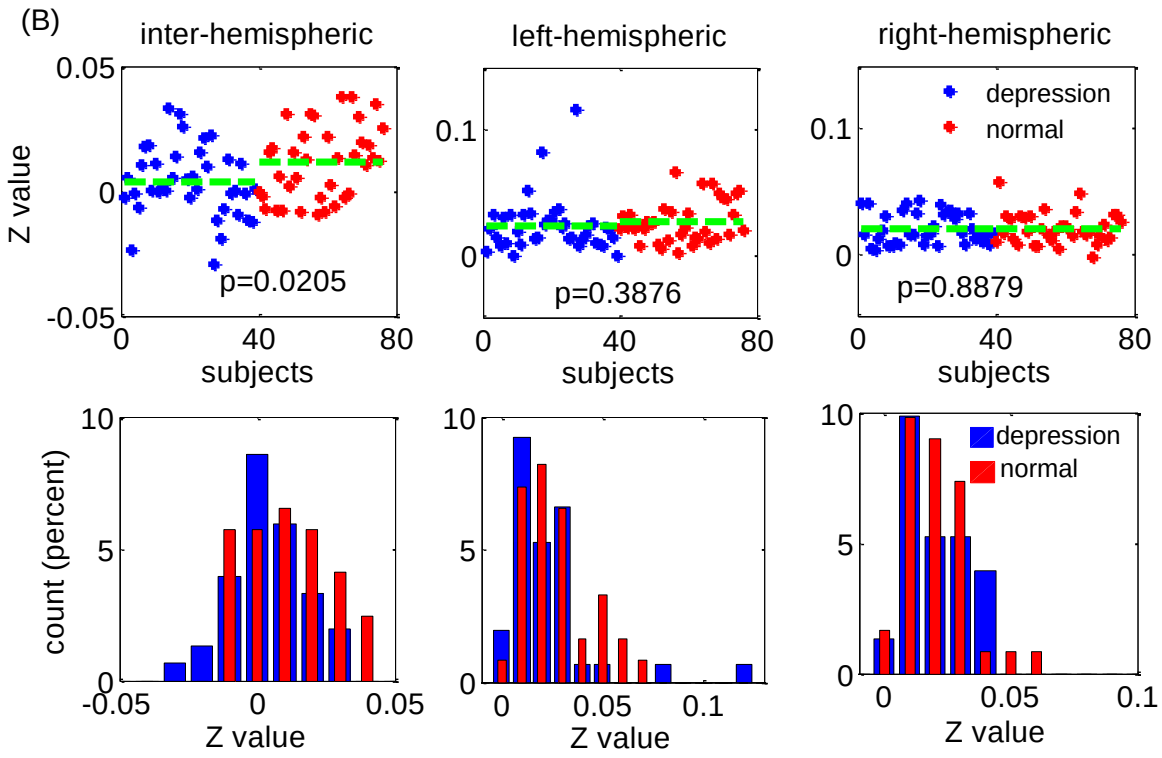


Figure S6: Reduced Inter-hemispheric Connectivity in Depression Patients. (A) First (left) and second (right) order symmetry changes in the depression dataset. (B)The strength of inter-hemispheric and intra-hemispheric links for every subject. It can be seen that the key functional change in depression patients is for brain-wide inter-hemispheric links (p=0.0205), with no significant changes in brain-wide intra-hemispheric links (left: p=0.3876; right: p=0.8879). Histograms show the distribution of the z-values in depression patients and healthy controlsfor inter-hemispheric and intra-hemispheric links.

TABLE S1: Treatment details of two datasets of schizophrenia patients.

Treatment	Patient number
first generation antipsychotics (FGAs) (sulpiride or haloperidol)	13
second generation antipsychotics (SGAs) (clozapine, risperidone, quetiapine, olanzapine, or aripiprazole)	107
combination therapy (combining an FGA and an SGA)	10
treatment naïve	22

TABLE S2: Demographic and clinical characteristics of threedatasets used.

1. Schizophrenia Dataset 1			
	patients (n = 69)	Controls (n = 62)	P value
Age (year)	31.95 ±9.60	29.87 ±8.62	0.2836
Education (year)	14.19 ±2.16	15.29 ±2.39	0.0064
Sex (M/F)	35/34	25/37	0.2328
Illness duration(year)	7.17 ±6.61	n.a.	n.a.
PANSS-positive scale (n = 64)	11.92 ±4.6	n.a.	n.a.
PANSS-negative scale (n = 64)	13.60 ±9.64	n.a.	n.a.
PANSS-general psychopathology scale(n=64)	27.28 ±9.63	n.a.	n.a.
2. Schizophrenia Dataset 2			
	patients (n = 83)	Controls (n = 60)	P value
Age (year)	23.1916 ±8.45	27.2 ±6.6	0.0056
Education (year)	12.7229 ±2.75	13.5 ±3.2	0.1120
Sex (M/F)	49/34	35/25	0.9334
Illness duration(year)	1.375 ±1.34	n.a.	n.a.
PANSS-positive scale (n =62)	19.84 ±6.31	n.a.	n.a.
PANSS-negative scale (n = 62)	21.56 ±7.66	n.a.	n.a.
PANSS-general psychopathology scale(n=62)	39.24 ±11.75	n.a.	n.a.
3. Depression Dataset			
	patients (n = 39)	Controls (n = 37)	P value
Age (year)	27.99 ±7.7	28.22 ±6.47	0.964
Education (year)	12.00 ± 3.58	13.32 ±3.29	0.306
Sex (M/F)	23/16	14/23	0.087
Illness duration(year)	2.42 ±3.26	n.a.	n.a.
HAMD	24.97 ±5.07	n.a.	n.a.

4. Statistical comparisons betweenthe two different groups of schizophrenia and healthy control subjects (i.e. Datasets 1 vs Dataset 2).

	Schizophrenia patients (p value)	Controls (p value)
Age (year)	<0.001	0.0550
Education (year)	<0.001	<0.001
Sex (M/F)	0.3080	0.0471
Illness duration(year)	<0.001	n.a
PANSS-positive scale (n = 64)	<0.001	n.a
PANSS-negative scale (n = 64)	<0.001	n.a
PANSS-general psychopathology scale (n= 64)	<0.001	n.a

5. Statistical comparisons of schizophrenia (datasets 1 and 2 combined) and

depressionpatients and their respective healthy control groups

	Schizophrenia vs depression patients (p value)	Schizophrenia controls vs depression controls (p value)
Age (year)	0.9054	0.7464
Education (year)	<0.05	0.0222
Sex (M/F)	0.2471	0.3641

TABLES3: The Names and Abbreviations of the Regions of Interest (ROIs)

Regions	Abbr.	Regions	Abbr.
Amygdala	AMYG	Orbitofrontal cortex (middle)	ORBmid
Angular gyrus	ANG	Orbitofrontal cortex (superior)	ORBsup
Anterior cingulate gyrus	ACG	Pallidum	PAL
Calcarine cortex	CAL	Paracentral lobule	PCL
Caudate	CAU	Parahippocampalgyrus	PHG
Cuneus	CUN	Postcentralgyrus	PoCG
Fusiform gyrus	FFG	Posterior cingulate gyrus	PCG
Heschl gyrus	HES	Precentralgyrus	PreCG
Hippocampus	HIP	Precuneus	PCUN
Inferior occipital gyrus	IOG	Putamen	PUT
Inferior frontal gyrus (opercula)	IFGoperc	Rectus gyrus	REC
Inferior frontal gyrus(triangular)	IFGtriang	Rolandic operculum	ROL
Inferior parietal lobule	IPL	Superior occipital gyrus	SOG
Inferior temporal gyrus	ITG	Superior frontal gyrus (dorsal)	SFGdor
Insula	INS	Superior frontal gyrus (medial)	SFGmed
Lingual gyrus	LING	Superior parietal gyrus	SPG
Middle cingulate gyrus	MCG	Superior temporal gyrus	STG
Middle occipital gyrus	MOG	Supplementary motor area	SMA
Middle frontal gyrus	MFG	Supramarginalgyrus	SMG
Middle temporal gyrus	MTG	Temporal pole (middle)	TPOmid
Olfactory	OLF	Temporal pole (superior)	TPOsup
Orbitofrontal cortex (inferior)	ORBinf	Thalamus	THA
Orbitofrontal cortex (medial)	ORBmed		

Table S4: Statistical analysis of different symmetry measures in the different schizophrenia and healthy control groups for connections via the anterior commissure (AC) or corpus callosum (CC).

1. t-test, p values for comparisons between two healthy control groups for schizophrenia patients			
	AC	CC	AC+CC
First order symmetry	0.4612	0.0519	0.0639
Second order symmetry	0.9629	0.4788	0.4279
2. t-test, p values for comparisons between the two schizophrenia patient groups			
	AC	CC	AC+CC
First order symmetry	0.0082	0.0253	0.0129
Second order symmetry	0.2216	0.5825	0.2434
3. ANOVA p values from comparing all three groups of healthy controls (i.e. controls for both schizophrenia and depression patients).			
	AC	CC	AC+CC
First order symmetry	0.6787	0.1407	0.2011
Second order symmetry	0.9787	0.6786	0.4117

Table S5. Correlations between first and second order symmetry changes in anterior commissure (AC) and corpus callosum (CC) connected regions and symptom severity (positive and negative PANSS scores) in the two schizophrenia datasets.

1. combined data (dataset 1 + dataset 2)			
	AC	CC	AC+CC
First vs positive	-0.2480 (0.0051)	-0.1413 (0.1145)	-0.1781 (0.0460）
First vs negative	-0.2271 (0.0106)	-0.2091 (0.0188)	-0.2276 (0.0104)
Second vs positive	-0.1850 (0.0381)	-0.0766 (0.3941)	-0.1370 (0.1260)
Second vsnegative	-0.0699 (0.4364)	-0.0641 (0.4760)	-0.1006 (0.2625)
2. dataset 1			
	AC	CC	AC+CC
First vs positive	0.0356 (0.7801)	0.1187 (0.3503)	0.1039 (0.4138)
First vs negative	-0.1314 (0.3007)	-0.1441 (0.2559)	-0.1497 (0.2379)
Second vs positive	0.0461 (0.7178)	0.0700 (0.5828)	0.0446 (0.7266)
Second vsnegative	0.0823 (0.5180)	-0.0931 (0.4642)	-0.0769 (0.5460)
3. dataset 2			
	AC	CC	AC+CC
First vs positive	-0.2751 (0.0305)	-0.0504 (0.6975)	-0.1103 (0.3934)
First vs negative	-0.0890 (0.4916)	-0.0247 (0.8489)	-0.0428 (0.7414)
Second vs positive	-0.2655 (0.0370)	-0.0142 (0.9125)	-0.0681 (0.5990)
Second vsnegative	-0.0602 (0.6423)	0.1568 (0.2236)	0.1113 (0.3891)

NOTE:Numbers given are for Pearson correlations with p values in brackets (uncorrected for multiple comparisons). Shaded boxes indicate significant correlations.

References:

Power JD, Barnes KA, Snyder AZ, Bradley LS, Steven EP. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion, Neuroimage, 2012, 59(3): 2142-2154.