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

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ABSTRACT

Schizophrenia is associated with disconnectivity in the brain although it is still unclear whether changes within or between hemispheres are of greatest importance. In this paper, an analysis of 152 schizophrenia patients compared with 122 healthy controls was carried out. Comparisons were also made with 39 depression patients and 37 controls to examine whether brain-wide changes in inter- or intra-hemispheric functional connectivity are most associated with the disorder and can distinguish it from depression. The authors developed new techniques (first and second order symmetry) to investigate brain-wide changes in patients (45 regions per hemisphere) and their association with illness duration and symptom severity. Functional connectivity between the same regions in left- and right-hemispheres (first order symmetry) was significantly reduced as was that between the same pairs of regions in the left- and right-hemispheres (second order symmetry) or using all possible inter-hemispheric connections in schizophrenia patients. By contrast, no significant changes were found for brain-wide intra-hemispheric links. First order symmetry changes correlated significantly with positive and negative symptom severity for functional connections linked via the anterior commissure and negative symptoms for those linked via the corpus callosum. Support vector machine analysis revealed that inter-hemispheric symmetry changes had 73–81% accuracy in discriminating schizophrenia patients and either healthy controls or depressed patients. In conclusion, reduced brain-wide inter-hemispheric functional connectivity occurs in schizophrenia, is associated with symptom severity, and can discriminate schizophrenia patients from depressed ones or healthy controls. Brain-wide changes in inter-hemispheric connections may therefore provide a useful potential biomarker for schizophrenia.

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1. Introduction

Schizophrenia is a complex syndrome mainly defined by positive symptoms of psychosis, such as paranoid delusions and auditory hallucinations (Wing and Agrawal, 2007). It is increasingly viewed as a developmental disorder (Insel, 2010) with onset of first major symptoms

occurring mainly between 20 and 28 years in men and 26 to 32 years in women (Castle et al., 1991), with a prodromal period of some years (Broome et al., 2005; Broome et al., 2012). Wernicke first proposed that schizophrenia was a disorder of functional disconnection in the brain (Wernicke, 1906) and this concept has re-emerged more recently (Friston and Frith, 1995). Many brain imaging studies have now reported either structural or functional connectivity evidence for widespread disconnection in resting-state brain networks, most notably in the default network (Garrity et al., 2007; Greicius, 2008; Huang et al., 2010; Liang et al., 2006; Lui et al., 2009; Lynall et al., 2010). We have recently shown evidence for weakening of functional connectivity between the two brain hemispheres involving a number of cortical and limbic regions (Guo et al., 2012). Structural changes in the anterior part of the corpus callosum (CC) are thought to be the most likely cause (Crow, 1998;

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Innocenti et al., 2003) of inter-hemispheric disconnection in schizophrenia and are even observed in non-psychotic high-risk offspring of schizophrenia patients (Francis et al., 2011). A post-mortem reduction in CC fiber numbers has also been reported to occur in female but not male schizophrenia patients (Highley et al., 1999a). While complete surgical section of the CC reduces functional resting state inter-hemispheric connectivity (Johnston et al., 2008), evidence from individuals with congenital callosal agenesis shows that functional connections can develop even in the absence of the CC (Tyszka et al., 2011). Anterior commissure (AC) size has also been shown to be reduced in schizophrenia by a diffusion tensor imaging study (Choi et al., 2011) and reduced fiber numbers have been reported in female but not male patients (Highley et al., 1999b). However, as yet the potential functional importance of these AC changes in schizophrenia is unknown. A consequence of reduced inter-hemispheric connectivity in schizophrenia may be impaired hemispheric co-operation and this has been shown in the language domain (Mohr et al., 2008).

While there have also been extensive functional and structural studies revealing altered connectivity within both left and right hemispheres in schizophrenia (Garrity et al., 2007; Greicius, 2008; Guo et al., 2012; Huang et al., 2010; Liang et al., 2006; Lui et al., 2009; Lynall et al., 2010) it is currently unclear whether inter or intra-hemispheric changes play the major role.

We have recently conducted a brain wide functional connectivity analysis on schizophrenia patients showing both intra and inter-hemispheric changes associated with illness duration and symptom severity (Guo et al., 2012). Here we have used data from this same subject set, together with that one from another hospital, to assess the relative importance of brain-wide changes in inter- as opposed to intra-hemisphere functional connectivity. Inter-hemispheric connections were analyzed using novel approaches quantifying both first (direct inter-hemispheric connections) and second (correlations between pairs of structures in the two hemispheres) order symmetry. We have also investigated the relative contributions of CC and AC connected structures to inter-hemispheric changes since, as discussed above, these are the major inter-hemispheric fiber tracts associated with schizophrenia. We have also conducted a similar analysis on another previously published dataset from depressed patients and their healthy controls (Tao et al., 2011) and finally, we have used support vector machine (SVM) approaches to establish accuracy in identifying schizophrenia patients compared to healthy controls and depressed patients.

2. Methods

2.1. Subjects

Our analysis included datasets from two schizophrenia and one unipolar depression patient groups and their respective healthy control groups. Two of the three datasets have been described in detail in previous publications (Guo et al., 2012; Tao et al., 2011). For schizophrenia, one patient group was recruited at the National Taiwan University Hospital (group 1) (Guo et al., 2012) and the other from Second Xiangya Hospital of Central South University in China (group 2). In total there were 152 patients with schizophrenia (84 males/68 females), identified by structured interviews with an experienced psychiatrist at each of the two hospitals and using DSM-IV diagnostic criteria. None of the patients had co-morbidities with other axis-1 disorders. Illness durations ranged from 6 months to 20 years (mean ± SD: 4.06 ± 5.43 years). The patients had a mean age of 27.11 ± 9.57 years and education duration of 13.66 ± 2.55 years. Two patients were left handed and 150 were right handed (Edinburgh Handedness Inventory). Symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) administered by hospital psychiatrists either one week before or after the MRI scan. A total of 26 patients had no PANSS records due to incomplete records or because they did not have a PANSS assessment carried out. Only 22 patients (from group 2) were treatment naïve,

the remaining 130 were all taking antipsychotic medication (see Supplementary Table S1).

122 (60 males/62 females) healthy control subjects were also recruited by the two hospitals (60 from Xiangya Hospital and 62 from National Taiwan University Hospital) aged 28.54 ± 7.76 years and mean education duration of 14.42 ± 2.92 years. One subject was left handed and 121 right handed. All controls were assessed by structured interviews with experienced psychiatrists in accordance with DSM-IV criteria as being free of schizophrenia and other axis I disorders. None had any neurological diseases or suffered from clinically significant head trauma or had a history of any substance dependence. Written informed consent was obtained from all individual participants, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Board (IRB) of the two hospitals. The patient and control groups were well matched by gender (χ^2 test, p = 0.316) and age (t test, p = 0.182) although the controls had a slightly longer education duration (t test, p = 0.022). Patient and healthy control demographics are shown in Table 1 and details of each dataset in Supplementary Table S2.

The depression group also involved patients from Second Xiangya Hospital used in a previous resting state fMRI study (Tao et al., 2011). Subjects were 15 treatment-naïve adult patients with first episode major depression (7 females/8 males; mean age 28.27 ± 7.45) and 24 with treatment-resistant major depression (16 females/8 males; mean age 27.83 ± 7.86 years). Subject demographic details are given in Supplementary Table S2. No patients had co-morbidities with other axis-1 disorders. A total of 37 age, gender and education duration matched healthy control subjects (14 females/23males; mean age 28.22 ± 6.47 years) were used. Patients and healthy controls were excluded if they had any of the following: (I) a history of neurological diseases or other serious physical diseases; (II) a history of electroconvulsive therapy; (III) history of substance (that is drugs, alcohol and other psychoactive substance) abuse; (IV) comorbidities with other disorders (no evidence for schizoaffective disorder or axis II, personality disorders and mental retardation); and (V) any contra-indications for MRI.

Patients and healthy controls in all three datasets were recruited and scanned over the same time period.

2.2. Imaging acquisitions and data preprocessing

Although data were obtained from patients and healthy controls in two different hospitals and using two different MRI scanners the resting-state fMRI protocol, number of images per scan, movement criterion and correction and data preprocessing techniques were similar. Individuals were instructed to close their eyes during the scan without falling asleep and scan the resting-state scan duration was 6 min. To further confirm similarities between the data obtained via the different MRIs we made statistical comparisons between all the healthy control groups scanned.

For the group 1 dataset, all subjects underwent a structural and functional MRI scan in a single session using a 3 T MR system (TIM

Table 1
Demographic and clinical characteristics of schizophrenia patients and controls.

	Schizophrenia patient (n = 152)	Controls (n = 122)	p value
Age (year)	27.11 ± 9.57	28.54 ± 7.76	0.182
Education (year)	13.66 ± 2.55	14.42 ± 2.92	0.022
Sex (M/F)	84/68	60/62	0.316
Illness duration (year) (n = 149)	4.06 ± 5.43	n.a.	n.a.
PANSS aggregate score (n = 142)	71.46 ± 26.69	n.a.	n.a.
PANSS—positive scale (n = 126)	15.82 ± 6.81	n.a.	n.a.
PANSS—negative scale (n = 126)	17.52 ± 8.05	n.a.	n.a.
PANSS—general psychopathology scale (n = 126)	33.17 ± 12.25	n.a.	n.a.

Trio, Siemens). A total of 180 volumes of EPI images were obtained axially, (repetition time, 2000 ms; echo time, 24 ms; slices, 34; thickness, 3 mm; no gap; field of view (FOV), 256 × 256 mm², resolution, 64 × 64; flip angle, 90°).

For the group 2 dataset, image data were acquired using a 1.5 T Siemens MRI scanner. A total of 180 volumes of EPI images were obtained axially (repetition time, 2000 ms; echo time, 40 ms; slices, 20; thickness, 5 mm; gap, 1 mm; field of view (FOV), 240 × 240 mm²; resolution, 64 × 64; flip angle, 90°).

Prior to preprocessing, the first 10 volumes of these two datasets were discarded to allow for scanner stabilization and the subjects' adaptation to the environment. fMRI data preprocessing was then conducted by SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and a Data Processing Assistant for Resting-State fMRI (DPARSF). In all cases head movements did not exceed the criterion of greater than ±1.5 mm or ±1.5°. The remaining functional scans were first corrected for within-scan acquisition time differences between slices and then realigned to the middle volume to correct for inter-scan head motions. Subsequently, the functional scans were spatially normalized to a standard template (Montreal Neurological Institute) and resampled to 3 × 3 × 3 mm³. After normalization, BOLD signal of each voxel was firstly detrended to abandon linear trend and then passed through a band-pass filter (0.01–0.08 Hz) to reduce low-frequency drift and high-frequency physiological noise. Finally, nuisance covariates including head motion parameters, global mean signals, white matter signals and cerebrospinal signals were regressed out from the BOLD signals. For the depression subject database the same protocols were used as for schizophrenia database 2.

After data preprocessing, the time series were extracted in each ROI by averaging the signals of all voxels within that region. In our present study, the automated anatomical labeling atlas (AAL) was used to parcellate the brain into 90 regions of interest (ROIs) (45 per hemisphere). The names of the ROIs and their corresponding abbreviations are listed in Supplementary Table S3.

In view of recent evidence for a potential contribution of movement to functional connectivity measures even after the standard precautions detailed above we additionally applied a DVARS motion scrubbing protocol to eliminate any final images identified as having motion artifact (see Power et al., 2012). Using this approach the rate of change in the BOLD signal is measured across the entire brain for each frame of data. A temporal mask is then generated for each region of interest, marking frames whose DVARS exceeds 3. We choose those frames with a number of masks greater than 20 out of the total 90 of temporal masks to generate a final temporal mask for each subject. The temporal mask was then applied to eliminate marked frames from the analysis. The proportion of data removed within each subject was very small (10%–40% in only a total of 38 subjects see Supplementary Fig. S1).

2.3. First and second order symmetry

The simplest measure of symmetry between the hemispheres is the correlation (functional connectivity) between the same ROIs in the left and right, i.e., 45 pairs in the whole brain. In the majority of cases this value is higher than functional connectivity between any two ROIs which are not symmetric (see Guo et al., 2012). A Fisher's r-to-z transformation was utilized to convert each correlation coefficient r_{ij} into Z_{ij} to improve the normality. Here we use the mean Z value of all 45 pairs and call it first order symmetry (see Fig. 1A). For every subject, we define S_1 as the measure of first order symmetry:

$$S_1 = \frac{1}{45} \sum_{i=1}^{45} z(i, i+45) \qquad (1)$$

where $z(i, i+45)$ is Fisher's r-to-z transformation of the ordinary Pearson correlation coefficient between the left ROI i and the
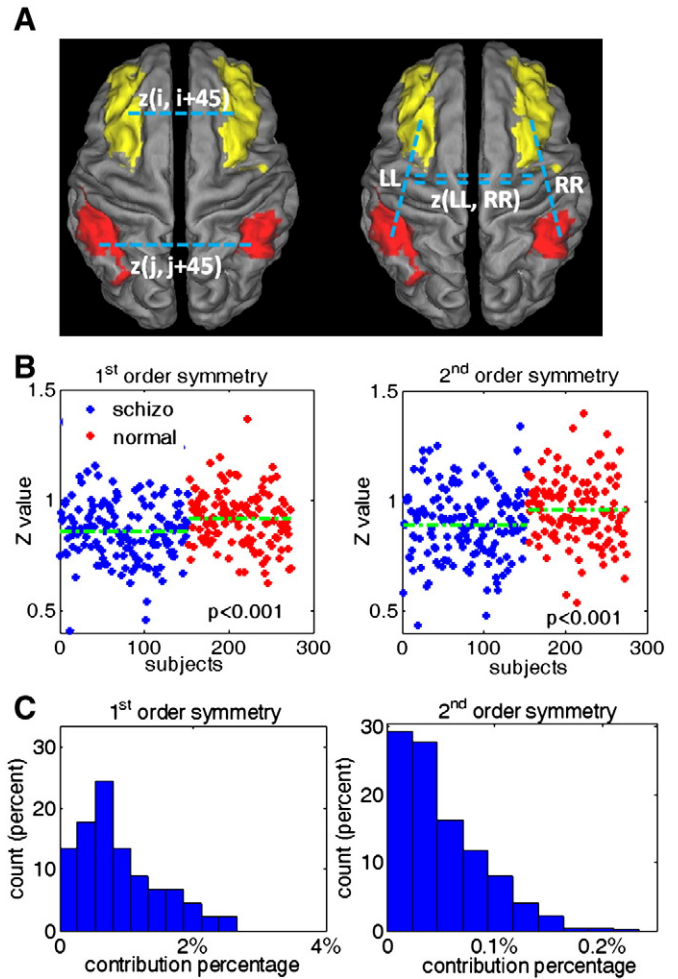

Fig. 1. Reduced inter-hemispheric connectivity in schizophrenia patients. (A) Illustration of first order (left) and second order symmetry (right). First order symmetry is the mean z-values for all 45 pairs of functional connectivities. Second order symmetry is the symmetry between any two pairs of connectivity within the left- and right-hemispheres. (B) z-Values in schizophrenia patients and healthy controls for first order (left) and second order symmetry (right). (C) Contribution percentage of the significant altered links to overall first order (left) and second order symmetry (right).

corresponding right ROI i. Further we examined the symmetry between the left- and right-hemispheric functional networks, i.e., the symmetry between any two pairs of connections within the left- and right-hemispheres, as shown in Fig. 1A. $LL = z(i,j)$, $i = 1, ..., 45$, and $j = 1, ..., 45$, $j \neq i$ represent the Fisher's r-to-z transformation of the Pearson correlation coefficients between ROI i and ROI j within the left-hemisphere and $RR = z(i + 45, j + 45)$ between ROI i and ROI j within the right-hemisphere. There are $C_{45}^2 = 990$ pairs of links in total, and if the left and right hemispheres have similar functional networks the correlation between LL and RR will be large. Then we can define the correlation between LL and RR to measure the symmetry between the left- and right-hemispheric functional networks. A Fisher's r-to-z transformation is also utilized to improve the normality. For every subject, second order symmetry S_2 is defined by:

$$S_2 = z(LL, RR). \qquad (2)$$

2.4. Percentage contribution to first and second order symmetry

For every subject, first order symmetry S_1 represents the mean z-values of all 45 symmetric pairs of ROIs in the left- and right-hemispheres. Similarly, second order symmetry S_2 represents the

correlation between the intra-hemispheric correlation patterns. In order to calculate the between-group difference in the contribution of a particular link k to the first order symmetry, we have the formula:

$$\text{Contribution}_1(k) = \frac{\left| \frac{1}{t_1} \sum_{t=1}^{t_1} z(t,k) - \frac{1}{t_2} \sum_{t=1}^{t_2} z(t,k) \right|}{\sum_{k=1}^{45} \left| \frac{1}{t_1} \sum_{t=1}^{t_1} z(t,k) - \frac{1}{t_2} \sum_{t=1}^{t_2} z(t,k) \right|}, k = 1,\dots,45 \quad (3)$$

where $z(t,k)$ is the Fisher's r-to-z transformation of Pearson correlation coefficient for subject t and a particular link k, t_1 is the number of patients and t_2 is the number of healthy controls. For second order symmetry, we use the following formula to calculate the between-group difference in the contribution of a functional network k:

$$\text{Contribution}_2(k)$$
$$= \frac{\left| \frac{1}{t_1} \sum_{t=1}^{t_1} (zl(t,k) - zr(t,k)) - \frac{1}{t_2} \sum_{t=1}^{t_2} (zl(t,k) - zr(t,k)) \right|}{\sum_{k=1}^{990} \left| \frac{1}{t_1} \sum_{t=1}^{t_1} (zl(t,k) - zr(t,k)) - \frac{1}{t_2} \sum_{t=1}^{t_2} (zl(t,k) - zr(t,k)) \right|}, k = 1,\dots,990$$
$$(4)$$

where $z\,l(t,k)$ and $z\,r(t,k)$ represent the strength of the network k for subject t within the left- and right-hemispheres respectively.

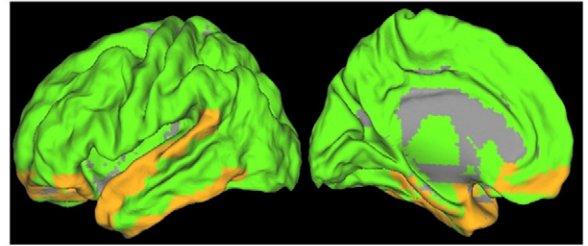### 2.5. Corpus callosum vs. anterior commissure links

According to non-human primate and human studies (Demeter et al., 1990; Paul et al., 2007; Schmahmann and Pandya, 2006) the ROIs considered to connect primarily via the AC are: amygdala, parahippocampal gyrus, olfactory bulb, all 4 regions of orbitofrontal cortex, superior and inferior temporal gyri and medial and superior temporal poles (11 in total). The remaining 34 ROIs were considered to be connected via the CC (see Fig. 2A). In view of previous findings of structural changes occurring particularly in the anterior part of the CC (Crow, 1998; Francis et al., 2011; Highley et al., 1999a; Innocenti et al., 2003) we also carried out some analyses contrasting this (8 connected regions, inferior frontal gyrus (opercular and triangular), medial frontal gyrus, superior frontal gyrus (dorsal and medial), rectus gyrus and anterior and medial cingulate gyri) with the remaining part of the CC (26 connected regions).

2.6. Support vector machine (SVM) classifier

The SVM is a learning machine for a two-class classification problem. Since first proposed by Vapnik as a logistical extension of statistical learning theory, SVM has become widely used in many areas because of their ability to handle very high-dimensional data, and their accuracy in the classification and prediction. Because of these properties, they have proven useful in the analysis of functional magnetic resonance imaging data.

SVM conceptually implements the idea that vectors are non-linearly mapped to a very high dimension feature space. In the feature space, a linear separation surface is created to separate the training data by minimizing the margin between the vectors of the two classes. The training ends with the definition of a decision surface that divides the space into two sub-spaces. Each sub-space corresponds to one class of the training data. Once the training is completed, the test data are mapped to the feature space. A class is then assigned to the test data depending on which sub-space they are mapped to. In this paper, a SVM toolkit named libsvm written by Lin Chih-Jen from Taiwan University (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) is used. A radial basis function (RBF) is selected as a kernel function ($t = 2$) and parameter C is fixed to 10 to trade-off learning and extend ability while other parameters are kept as default values.
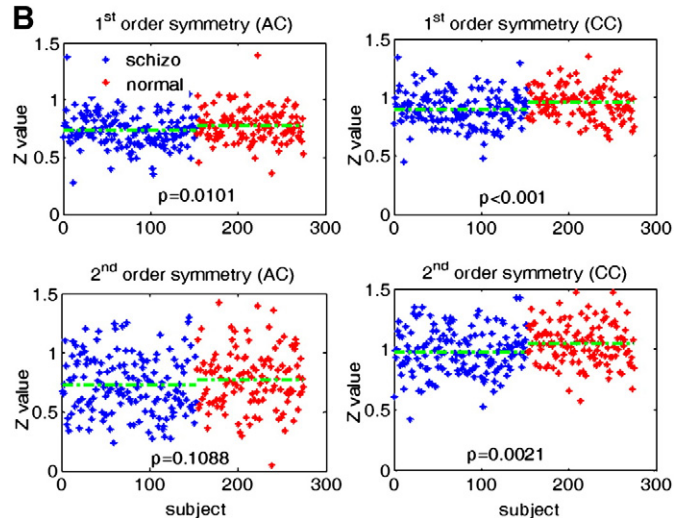

Fig. 2. First and second order symmetry of corpus callosum and anterior commissure connected functional links. (A) Neuroanatomical localization of corpus callosum vs. anterior commissure connected ROIs with anterior commissure (AC) connected regions shown in orange and those connected via the corpus callosum (CC) in green. (B) Plots show differences (z-values) in first and second order symmetry of functional connections in schizophrenia patients (blue) and healthy controls (red) and associated p-values.

We also used permutation tests for statistical assessment of classifier performance (see Golland and Fischl, 2003; Ojala and Garriga, 2010). Choosing the generalization rate as the statistic, permutation tests are employed to estimate the statistical significance of the observed classification accuracy. In permutation testing, the class labels of the training data are randomly permuted prior to training. Leave one out cross validation is then performed on the permuted training set, and the permutation was repeated 1000 times. It is assumed that a classifier is learned reliably from the data when the generalization rate r_0 obtained by the classifier trained on the real class labels exceeds the 95% confidence interval of the classifier trained on randomly relabelled class labels. For any value of the estimated r_0, the appropriate p-value represents the probability of observing a classification prediction rate of no less than r_0.

3. Results

3.2. Comparisons between the two schizophrenia patient and healthy control groups

There were a number of significant demographic differences between subject groups in the two datasets summarized in Supplementary Table S2. For healthy control groups the average age and education duration were significantly higher in the group 2 compared with the group 1 dataset. In the schizophrenia groups, illness duration and PANSS scores were also higher in group 2 compared with the

group 1 dataset. The depression patients and their healthy control group did not differ significantly from the combined schizophrenia groups and their healthy controls for age and sex although in both cases education duration was slightly but significantly less in both the depression patients and their healthy controls (see Table S2). In view of some demographic differences between the groups (age and education duration), in the following group comparisons, we take age, and education into account by including them as confound variables in an ANCOVA. There were no significant differences between the healthy control groups for any of the inter- or intra-hemispheric measures analyzed (Supplementary Table S4) suggesting that neither age nor education duration differences per se are likely to have a significant impact on them. No significant differences in signal to noise were found in the BOLD data between schizophrenia patient and healthy control groups in the two datasets, alone or combined, or between the two datasets (t-tests − dataset 1: schizophrenia vs healthy controls: p = 0.2751; dataset2: schizophrenia vs healthy controls: p = 0.6061; datasets 1 and 2 combined: schizophrenia vs healthy controls: p = 0.4737; patients and healthy controls in dataset 1 vs dataset 2: p = 0.7738). Additionally both of the schizophrenia groups showed similar overall significant changes in first and second order symmetry (see Supplementary Fig. S2) although the magnitude of changes was significantly greater in dataset 2 than in dataset 1 (see Table S4). Thus to increase statistical power we have carried out our main analysis of results using the combined data from the two healthy control and schizophrenia groups.

3.3. Reduced first and second order symmetry in schizophrenia and depression

Functional maps were constructed for the 152 schizophrenia patients and 122 healthy controls from the two groups. Fig. 1B shows that both first symmetry and second order symmetry are reduced in schizophrenia patients. First order symmetry is considerably reduced ($z_1 = 0.8596$ for patients, $z_1 = 0.9158$ for healthy controls, p < 0.001), implying that synchronization between the hemispheres is weakened. Second order symmetry is also reduced ($z_2 = 0.7108$ for patients, $z_2 = 0.7415$ for healthy controls, p < 0.001), implying that the difference between the left and right functional networks is enlarged. Fig. 1C shows that there are many different links making minor contributions to the first and second symmetry changes. Supplementary Fig. S2 shows that both first symmetry and second order symmetry were significantly altered in each individual group of schizophrenia patients (first order symmetry: dataset 1 − p = 0.033; dataset 2 − p = 0.0262; second order symmetry: dataset 1 − p = 0.0088; dataset 2 − p = 0.0130). In view of some previous evidence for sex differences in inter-hemispheric connections in schizophrenia (Highley et al., 1999a,b) we carried out a separate analysis for male and female patients. This did not reveal any significant difference in either first ($t^{150} = -0.5719$, p = 0.5682) or second ($t^{150} = -0.9348$, p = 0.3514) order symmetry between male and female patients.

When we sub-divided ROIs into those connected via either the CC or AC this revealed that both had significantly reduced first order symmetry in schizophrenia patients (AC: p = 0.0101; CC: p < 0.001) but only the CC group showed reduced second order symmetry (AC: p = 0.1088; CC: p = 0.0021) (see Fig. 2B). When we sub-divided the CC into an anterior and medial/posterior part this revealed that connections involving both showed significantly reduced first order symmetry (anterior: p = 0.0371 and medial/posterior: p < 0.0001) although for second order symmetry only the medial/posterior-based connections were significant (anterior: p = 0.1838 and medial/posterior: p = 0.0014).

Next we analyzed correlations between first and second order symmetry changes and illness duration and symptom severity (PANSS scores). There were no overall significant correlations between the first and second order symmetry of functional connections via AC, CC or AC + CC and illness duration (correlations between +0.05 and

−0.12; p = from 0.15 to 0.86). To determine if significant changes occurred across all illness durations we calculated symmetry changes at short (0 to 2 years, 79 subjects), medium (3 to 9 years, 50 subjects) and long term (10 + years, 23 subjects). Fig. 3A and B shows that first order symmetry is reduced in schizophrenia patients across all illness durations for functional connections via AC + CC, although CC-based connections were more affected than AC ones. The same pattern was also seen for second order symmetry (see Supplementary Fig. S3 for individual datasets). When the CC was sub-divided, the medial/posterior part was most strongly correlated with illness duration for both first order symmetry and second order symmetry although there was no significant difference between anterior and medial/posterior connected regions (data not shown).

Correlations between symmetry and PANSS positive and negative scores are shown in Fig. 3C and Supplementary Table S5. First order symmetry was significantly negatively correlated with the PANSS positive and negative scores for AC connected regions (positive: r = −0.2480, p = 0.0051; negative: r = −0.2271, p = 0.0106), negative scores for CC (negative: r = −0.2091, p = 0.0188) and positive and negative scores for AC + CC (positive: r = −0.1781, p = 0.0460; negative: r = −0.2276, p = 0.0104). For second order symmetry there was a significant negative correlation with positive PANSS scores for AC connected regions (r = −0.1850, p = 0.0381) but no correlations with negative PANSS scores. When the CC was sub-divided into connections involving the anterior and middle/posterior parts the latter showed a significant negatively correlation with negative PANSS scores (r = −0.1993, p = 0.0252) and the former a non-significant trend (r = −0.1698, p = 0.0574). Overall the patients in group 2 showed stronger correlations with symptom severity than those in group 1 (Supplementary Table S5), possibly due to patients in group 1 having significantly lower and a narrower range of PANSS scores than those in group 2.

To address the possibility that anti-psychotic medication was influencing symmetry changes we compared the 22 medication free subjects with the remaining 130 receiving medication. This showed no significant difference in first order symmetry (p = 0.2784) although second order symmetry was significantly reduced in the medicated patients for CC connected regions (p = 0.047) and showed an overall trend in AC + CC ones (p = 0.055 − see Supplementary Fig. S4). We found no evidence for a correlation between first (r = −0.122, p = 0.404) or second (r = 0.097, p = 0.506) order symmetry and daily drug doses (converted to chlorpromazine equivalents) in the 49 medicated patients from group 2 where we had daily medication dose details (see Supplementary Fig. S5).

A similar analysis of first and second order symmetry changes in depressed compared to healthy subjects did not find any significant differences in first order symmetry (p = 0.1480) and a small difference in second order (p = 0.0415 − Supplementary Fig. S6).

3.4. Inter vs. intra-hemispheric links

In order to compare the relative importance of intra-compared to inter-hemispheric functional changes in the brain in schizophrenia we also calculated brain-wide changes in both. For every subject, there are 4005 different links, where $45 * 45 = 2025$ are inter-hemispheric links and 990 links are within each hemisphere. For every subject, we obtained the strength of left- and right-hemispheric links by averaging z-scores of corresponding links. Fig. 4A and B shows that in contrast to overall functional connectivity for all inter-hemispheric links (p < 0.001) there were no overall changes in intra-hemispheric ones in schizophrenia patients (left: p = 0.1122; right: p = 0.7230). A similar pattern was found in depression although overall inter-hemispheric changes were less marked (inter-hemispheric: p = 0.0205; left hemisphere p = 0.3876; right hemisphere p = 0.8879 − see Supplementary Fig. S6).
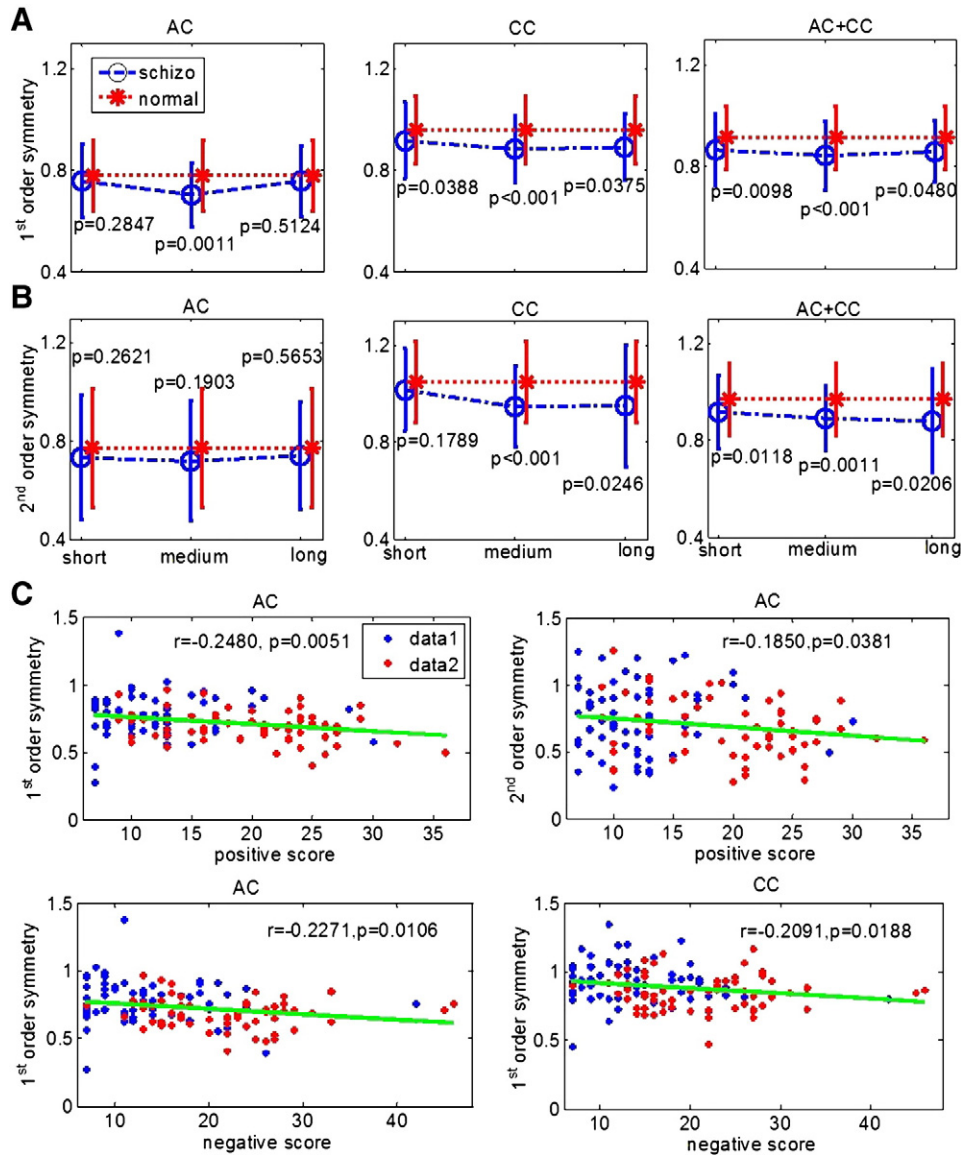
Fig. 3. Associations between altered functional connections via the corpus callosum and anterior commissure and illness duration and symptom severity. Mean ± SD z-values comparing first (A) and second (B) order symmetry in schizophrenia patients (blue) at short, medium and long illness durations vs healthy controls for functional connections involving the corpus callosum (CC) and anterior commissure (AC). (C) Correlations between first and second order symmetry z-values in schizophrenia patients and positive and negative PANSS scores for functional connections involving either the corpus callosum (CC) or anterior commissure (AC).

3.5. Support vector machine analysis

In SVM analysis, we used Fisher z-values for each symmetric pair of ROIs in the left- and right-hemispheres (first order symmetry) and also for matched pairs of intra-hemispheric links (second order symmetry) as features with each condition (AC, CC, AC + CC). A summary of the SVM analyses carried out is given in Table 2. It can be seen that in terms of discrimination accuracy the leave one out calculation showed that with both datasets combined, using AC + CC connections there was 73.4% (permutation test, $p < 0.001$) accuracy in identifying individual schizophrenia patients and healthy controls with AC connections alone being 65.3% ($p < 0.001$) and CC 68.6% ($p < 0.001$). Specificity and sensitivity values showed that 73–79% of individuals in the schizophrenia group were accurately identified compared to 56–66% of healthy controls. When the two datasets were analyzed separately similar results were obtained although discrimination accuracies were generally higher for dataset 1 than dataset 2. Table 2 also shows that the SVM accuracy in discriminating individual schizophrenia patients and

those with depression was 79.6% ($p < 0.001$) for AC, 80.6% ($p < 0.001$) for CC and 80.6% ($p < 0.001$) for AC and CC combined. Sensitivity and specificity values showed that in this case 100% of individuals could be identified from the schizophrenia group but none of the depression ones using AC connections, and 95% of them using CC or AC + CC connections compared with only 25% from the depression group.

4. Discussion

Overall our results have demonstrated for the first time that brain-wide functional networks between the two hemispheres are significantly weakened in schizophrenia, but not in depression patients, whereas there is no similar generalized weakening of functional connections within hemispheres. Reduced first and second order of symmetry was found in inter-hemispheric networks as well as in functional connectivity across all possible functional inter-hemispheric connections. Changes in the symmetry of inter-hemispheric connections via the AC and CC occurred, although while both correlated negatively
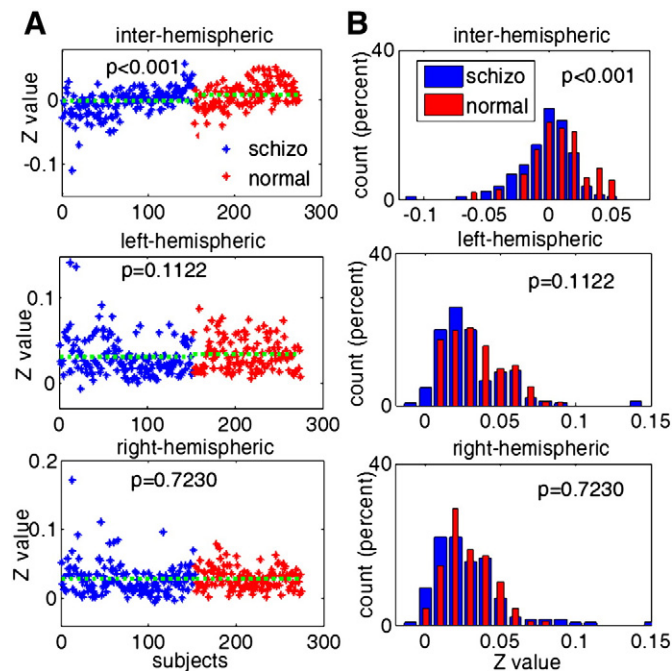
A

B

Fig. 4. Comparison of brain-wide intra- and inter-hemispheric functional connectivity changes. (A) z-Values of all possible functional inter-hemispheric and intra-hemispheric links for every subject showing that only brain-wide inter-hemispheric links are significantly altered in schizophrenia patients ($p < 0.001$). (B) Histograms showing distributions of z-values for inter-hemispheric and intra-hemispheric links.

with negative symptom severity, only the AC-based connections correlated negatively with positive symptom severity. Overall SVM analysis revealed that symmetry changes involving both AC and CC connections had 73% discrimination accuracy in identifying individual schizophrenia patients and healthy controls and 81% in identifying them and depressed patients. The sensitivity of discriminating schizophrenia patients per se was 79% when grouped with the healthy controls and 95–100% when grouped with depression patients.

While some previous studies have reported that structural connections between the two hemispheres are only reduced in female schizophrenia patients (Highley et al., 1999a,b), we did not find any significant difference in overall changes in first or second order symmetry between male and female schizophrenia patients. This may reflect a considerable age difference between the patients in our study and those in post-mortem ones, the later being around 60–70 years old. However, our findings are also based on functional connectivity measures and

Table 2
Results of SVM classifier.

vs. healthy controls		Accuracy (p value)	Specificity	Sensitivity
1. Classification results for schizophrenia patients vs. healthy controls				
Combined dataset (1 + 2)	AC	65.33% (<0.001)	55.74%	73.03%
	CC	68.61% (<0.001)	60.66%	75%
	AC + CC	73.36% (<0.001)	66.39%	78.95%
Dataset 1	AC	64.89% (<0.001)	72.58%	57.97%
	CC	74.81% (<0.001)	70.97%	78.26%
	AC + CC	83.21% (<0.001)	85.51%	80.65%
Dataset 2	AC	58.04% (<0.001)	43.33%	68.67%
	CC	62.94% (0.005)	53.33%	69.88%
	AC + CC	66.43% (<0.001)	58.33%	72.29%
2. Classification results for depression patients vs. schizophrenia patients				
Dataset 1 + 2	AC	79.58% (<0.001)	0	100%
	CC	80.63% (<0.001)	25.64%	94.74%
	AC + CC	80.63% (<0.001)	25.64%	94.74%

while these can be contributed to by altered structural connectivity we did not confirm this in the current study. Indeed, they could also be contributed to by gray matter changes or even changes in synaptic transmission. Clearly it will be important to establish in the future if the global inter-hemispheric symmetry changes in functional connectivity we have found in schizophrenia are a cause, or consequence of, structural changes in connecting fibers.

The precise functions of communication between the two brain hemispheres are still a matter of debate. Human studies have shown that where communication between the two brain hemispheres is reduced, or prevented due to surgery or callosal agenesis, many cognitive, emotional and motor functions can still be performed independently by each hemisphere (Paul et al., 2007). However, although some specialized functions such as language and face recognition have clear evidence for asymmetric processing there is also evidence that inter-hemispheric co-operation and integration are important for aspects of higher cognitive function and emotional control. Thus any disorder which produces inter-hemispheric disconnection is likely to be associated with significant impairments in these domains (Schulte and Müller-Oehring, 2010; van der Knaap and van der Ham, 2011). There is also still a debate as to whether inter-hemispheric transfer of information primarily involves excitatory or inhibitory interactions (Bloom and Hynd, 2005; Schulte and Müller-Oehring, 2010), although in either case weakened connections between the hemispheres would lead to impaired communication. A global reduction in symmetry of inter-hemispheric connections could result in increased functional lateralization and/or reduced inter-hemispheric co-operation. Both of these have been reported to occur in schizophrenia (Mohr et al., 2008; Oertel-Knöchel and Linden, 2011).

For the schizophrenia patients in the group 1 dataset we previously reported that the key pathway showing altered functional connectivity comprised midline cortical and mirror neuron regions involved in aspects of self processing (Guo et al., 2012). One of the main symptoms of schizophrenia involves a disturbed sense of self, particularly in terms of misattributions of agency (Sass and Parnas, 2003) and it has been proposed that inter-hemispheric connectivity may also contribute to self-processing (Uddin, 2011). Thus both specific local intra-hemispheric changes together with a global weakening of functional inter-hemispheric links may contribute to deficits in self-related processing in schizophrenia. However, schizophrenia also involves cognitive, emotional and visuomotor dysfunction (Dazzan and Murray, 2001; Foussias and Remington, 2010; Joyce and Huddy, 2004; Taylor et al., 2011; Fusar-Poli et al., 2012) which are known to be affected by reduced connectivity between the two brain hemispheres following CC damage (Bloom and Hynd, 2005; Lungu and Stip, 2012; Schulte and Müller-Oehring, 2010).

Importantly first order, and to a lesser extent second order symmetry changes in the schizophrenia patients were correlated with symptom severity. Both positive symptom severity and negative symptom severity were negatively correlated with the degree of symmetry in connections via the AC and for negative symptoms via the CC. This was much more evident in patients in database 2 who had significantly greater symptom severity than those in database 1. Overall, correlations were strongest between AC-based functional connections supporting our findings in our previous study of patients in database 1 showing that the strength of inter-hemispheric links between two AC connected structures, the amygdala, and superior orbitofrontal cortex, correlated negatively with severity of some PANSS positive or negative symptoms (Guo et al., 2012). Symptom severity has also been shown to correlate with reduced CC size in both anterior and posterior parts, in schizophrenia (Walterfang et al., 2008; Whitford et al., 2010). Our preliminary analysis dividing the CC into anterior and medial/posterior subdivisions revealed reduced symmetry in functional connections via both although they were more significant in the medial/posterior part. Negative correlations with negative symptom severity were also stronger for functional connections via the medial/posterior CC. Significant

brain wide changes in inter-hemispheric connections occurred in patients irrespective of illness duration, although here a more consistent pattern was seen in CC than AC-based functional connections, especially those involving medial/posterior CC. Overall though it must be emphasized that our sub-division of AC and CC connected regions using AAL defined structures is a relatively crude approach and a more fine-detailed analysis might show more localized and complex patterns of change.

We confirmed that in a sub-group of first-episode, treatment-naïve patients reduced symmetry in brain-wide inter-hemispheric functional connectivity also occurred. Furthermore in 49 patients from the second schizophrenia group where we had information on daily medication doses we found no significant correlation between first or second order symmetry and the magnitude of the dose (using chlorpromazine equivalents). Thus it is unlikely that our results were caused by antipsychotic medication effects and that functional brain-wide inter-hemispheric disconnection occurs at the earliest stages of the disorder. This is in agreement with studies reporting reduced fractional anisotropy in the CC in first-episode psychosis (Price et al., 2007). There is also evidence for reduced CC volume in non-psychotic high-risk offspring of schizophrenia patients (Francis et al., 2011) suggesting that reduced functional inter-hemispheric connectivity may identify individuals at risk, although this requires confirmation.

Given the large number of studies reporting significant altered functional connectivity between specific pairs of brain regions within hemispheres associated with schizophrenia and depression it might seem surprising that we did not find significant overall changes in intra-hemispheric functional connectivity. However, this presumably reflects the fact that while the proportion of significant changes in inter vs intra-hemisphere functional connections may be relatively similar, that showing a pattern of reduced functional connectivity in these disorders may be relatively higher for inter-hemispheric connections. Indeed, our previous studies on the schizophrenia patients from dataset 1 (Guo et al., 2012) and depression patients from dataset 3 (Tao et al., 2011) showed that both decreased and increased functional connectivity occurred within the two hemispheres, whereas all the changes involving connections between counterparts in the two hemispheres were of reduced connectivity. Thus as a global biomarker only the inter-hemispheric functional connectivity changes are significant because they show a similar pattern of reduced strength in schizophrenia.

Altered inter-hemispheric connectivity may be a hallmark of a number of psychiatric disorders and has been reported in autism (Lo et al., 2011), depression (Xu et al., 2012) and anxiety (Compton et al., 2008). It has also been found in disorders of consciousness (Ovadia-Caro et al., 2011). However, in our current study we found evidence for only modest brain-wide changes in depressed patients. Despite evidence for weakened inter-hemispheric connectivity in depression as well, our SVM analysis revealed 81% discrimination accuracy for the groups of schizophrenia and depressed patients using the inter-hemispheric symmetry measures and for AC-based connections all of the schizophrenia patients could be individually identified and 95% of them for CC-based ones. Indeed, this accuracy was actually slightly higher than where schizophrenia patients and healthy control subjects were discriminated, although it might possibly reflect the lower number of depression patients in the study. Thus overall, brain-wide reductions in inter-hemispheric functional connectivity may prove a potentially useful schizophrenia biomarker which can help to distinguish it both from healthy control subjects and from other psychiatric disorders such as depression.

The advantage of using global features as biomarkers is that they are more stable than local ones since they are an average of many different local features. Given the variability of local feature changes reported to date in schizophrenia (Garrity et al., 2007; Greicius, 2008; Guo et al., 2012; Huang et al., 2010; Liang et al., 2006; Lui et al., 2009; Lynall et al., 2010), a global feature might be more effective in identifying

consistent changes which are relatively independent of the many potential confounding variables between patient and control groups and factors such as illness duration and medication. Indeed, the fact that we observed broadly similar changes in two independent groups of schizophrenia patients despite some significant demographic differences lends support to this. However, such global feature changes may be less effective in discriminating between sub-types of a disorder, where more discrete local feature changes might prove more useful. One solution may therefore be to use combinations of both.

A potential limitation of the current study is that the two groups of schizophrenia patient and their respective controls were scanned using machines with different field strengths (1.5 vs 3 T) and that there were also some demographic differences in terms of age and education duration. A previous study has reported that it is possible to combined 1.5 and 3 T data, with the lower field strength being found only to reduce detection power but not specificity (Han and Talavage, 2011). Importantly we found no overall significant differences between either the healthy controls or the patient groups in terms of brain-wide symmetry measures which is why we considered it appropriate to combine them and achieve more statistical power. There were also no significant differences in BOLD signal to noise ratios either between subject groups scanned on the same MRI machine or scanned using different ones. We also found that including age and education duration as nuisance variables did not alter the overall significance of our first and second order symmetry results. While we did find that patients in database 1 had significantly reduced first-order symmetry changes for functional connections via both the AC and CC compared with patients in database 2, the patients in database 1 also had significantly lower symptom severity and the first order symmetry of both AC and CC-based connections is negatively correlated with symptom severity. Thus it would be expected that overall symmetry changes should be lower in database 1 patients due to their lower symptom severity. However, we cannot completely rule out some contribution from the significant demographic differences between the two patient groups or the use of two different MRI machines with different field strengths. On the other hand the fact that neither of these factors had a major influence on our findings serves to further underline the stability of using global measures such as brain-wide symmetry as biomarkers.

Overall our results show that reduced inter-hemispheric symmetry changes in schizophrenia are most associated with the disorder. These symmetry changes occur across illness durations and are negatively correlated with positive and negative symptom severity. Overall, symmetry changes had good prediction accuracy for discriminating schizophrenia patients from either healthy controls or depression patients within our datasets. Thus global inter-hemispheric changes in schizophrenia may be an important potential biomarker.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2013.06.008.

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References

Bloom, J.S., Hynd, G.W., 2005. The role of the corpus callosum in interhemispheric transfer of information: excitation or inhibition. Neuropsychology Review 15, 59–71.

Broome, M.R., Woolley, J.B., Tabraham, P., Johns, L.C., Bramon, E., Murray, G.K., Pariante, C., Mcguire, P.K., Murray, R.M., 2005. What causes the onset of psychosis? Schizophrenia Research 79, 23–34.

Broome, M., Dale, J., Marriott, C., Merino, C., Bortolotti, L., 2012. Neuroscience, continua and the prodromal phase of psychosis. In: Fusar-Poli, P., Borgwardt, S., Mcguire, P.K. (Eds.), Vulnerability to Psychosis: From Psychopathology to Neurosciences. Routledge.

Castle, D., Wessely, S., Der, G., Murray, R.M., 1991. The incidence of operationally defined schizophrenia in Camberwell, 1965–84. The British Journal of Psychiatry 159, 790–794.

Choi, H., Kubicki, M., Whitford, T.J., Alvarado, J.L., Terry, D.P., Niznikiewicz, M., McCarley, R.W., Kwon, J.S., Shenton, M.E., 2011. Diffusion tensor imaging of anterior commissural fibers in patients with schizophrenia. Schizophrenia Research 130, 78–85.

Compton, R.J., Carp, J., Chaddock, L., Fineman, S.L., Quandt, L.C., Ratliff, J.B., 2008. Trouble crossing the bridge: altered interhemispheric communication of emotional images in anxiety. Emotion 8, 684–692.

Crow, T.J., 1998. Schizophrenia as a transcallosal misconnection syndrome. Schizophrenia Research 30, 111–114.

Dazzan, P., Murray, R.M., 2001. Neurological soft signs in first episode psychosis: a systematic review. The British Journal of Psychiatry 178, 506–517.

Demeter, S., Rosene, D.L., Van Hoesen, G.W., 1990. Fields of origin and pathways of the interhemispheric commissures of the temporal lobe of macaques. The Journal of Comparative Neurology 302, 29–53.

Foussias, G., Remington, G., 2010. Negative symptoms in schizophrenia and Occam's razor. Schizophrenia Bulletin 36, 359–369.

Francis, A., Bhojraj, T.S., Prasad, K.M., Kulkarni, S., Montrose, D.M., Eack, S.M., Keshavan, M.S., 2011. Abnormalities of the corpus callosum in non-psychotic high risk offspring of schizophrenia patients. Psychiatry Research 191, 9–15.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clinical Neuroscience 3, 89–97.

Fusar-Poli, P., Desete, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, O., Stieglitz, R., Vita, A., Mcguire, P.S.B., 2012. Cognitive functioning in prodromal psychosis: a meta-analysis. JAMA Archives of General Psychiatry 69, 562–571.

Garrity, A.G., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D., 2007. Aberrant "default mode" functional connectivity in schizophrenia. The American Journal of Psychiatry 164, 450–457.

Golland, P., Fischl, B., 2003. Permutation Tests for Classification: Towards Statistical Significance in Image-Based Studies, Information Processing in Medical Imaging. Springer, Berlin/Heidelberg 330–341.

Greicius, M., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Current Opinion in Neurology 21, 424–430.

Guo, S.X., Kendrick, K., Rongjun, Yu, Wang, H.L., Feng, J.F., 2012. Key functional circuitry altered in schizophrenia involves parietal regions associated with sense of self. Human Brain Mapping. http://dx.doi.org/10.1002/hbm.22162.

Han, K., Talavage, T.M., 2011. Effects of combining field strengths on auditory functional MRI group analysis: 1.5 T and 3 T. Journal of Magnetic Resonance Imaging 34, 1480–1488.

Highley, J.R., Esiri, M.M., McDonald, B., Cortina-Borja, M., Herron, B.M., Crow, T.J., 1999a. The size and fibre composition of the corpus callosum with respect to gender and schizophrenia: a post-mortem study. Brain 122, 99–110.

Highley, J.R., Esiri, M.M., McDonald, B., Roberts, H.C., Walker, M.A., Crow, T.J., 1999b. The size and fiber composition of the anterior commissure with respect to gender and schizophrenia. Biological Psychiatry 45, 1120–1127.

Huang, X.Q., Lui, S., Deng, W., Chan, R.C.K., Wu, Q.Z., Jiang, L.J., Zhang, J.R., Jia, Z.Y., Li, X.L., Li, F., Chen, L., Li, T., Gong, Q.Y., 2010. Localization of cerebral functional deficits in treatment-naïve, first-episode schizophrenia using resting-state fMRI. NeuroImage 49, 2901–2906.

Innocenti, G.M., Ansermet, F., Parnas, J., 2003. Schizophrenia, neurodevelopment and corpus callosum. Molecular Psychiatry 8, 261–274.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193.

Johnston, J.M., Vaishnavi, S.N., Smyth, M.D., Zhang, D., He, B.J., Zempel, J.M., Shimony, J.S., Snyder, A.Z., Raicle, M.E., 2008. Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. Journal of Neuroscience 28, 6453–6458.

Joyce, E., Huddy, V., 2004. Defining the cognitive impairment in schizophrenia. Psychological Medicine 34, 1151–1155.

Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H., Hao, Y., 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. NeuroReport 17, 209–213.

Lo, Y.-C., Soong, W.-T., Gau, S.S.-F., Wu, Y.-Y., Lai, M.-C., Yeh, F.-C., Chiang, W.-Y., Kuo, L.-W., Jaw, F.-S., Tseng, W.-Y.I., 2011. The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion specturm imaging tractography. Psychiatry Research 192, 60–66.

Lui, S., Li, T., Deng, W., Huang, X., Jiang, L., Ma, X., Chen, H., Zhang, T., Li, X., Li, D., Zou, L., Tang, H., Zhou, X.J., Mechelli, A., Collier, D.A., Sweeney, J.A., Li, T., Gong, Q., 2009. Association of cerebral deficits with clinical symptoms in antipsychotic-naïve first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. The American Journal of Psychiatry 166, 196–205.

Lungu, O., Stip, E., 2012. Agenesis of corpus callosum and emotional information processing in schizophrenia. Front Psychiatry. http://dx.doi.org/10.3389/fpsyt.2012.00001.

Lynall, M.E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., Muller, U., Bullmore, E., 2010. Functional connectivity and brain networks in schizophrenia. Journal of Neuroscience 30 (28), 9477–9487.

Mohr, B., Pulvermüller, F., Rockstroh, B., Endrass, T., 2008. Hemispheric cooperation — a crucial factor in schizophrenia? Neurophysiological evidence. NeuroImage 41, 1102–1110.

Oertel-Knöchel, V., Linden, D.E.J., 2011. Cerebral asymmetry in schizophrenia. The Neuroscientist. http://dx.doi.org/10.1177/1073858410386493.

Ojala, M., Garriga, G.C., 2010. Permutation tests for studying classifier performance. Journal of Machine Learning Research 11, 1833–1863.

Ovadia-Caro, S., Nir, Y., Soddu, A., Ramot, M., Hesselmann, G., Vanhaudenhuyse, A., Dinstein, I., Tshibanda, J.-F.L., Boly, M., Harel, M., Laureys, S., Malach, R., 2011. Reduction in interhemispheric connectivity in disorders of consciousness. PLoS One 7, e37238.

Paul, L.K., Brown, W.S., Adolphs, R., Tyszka, J.M., Richards, L.J., Mukherjee, P., Sherr, E.H., 2007. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nature Reviews Neuroscience 8, 287–299.

Power, J.D., Barnes, K.A., Snyder, A.Z., Bradley, L.S., Steven, E.P., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage 59 (3), 2142–2154.

Price, G., Cercignani, M., Parker, G.J.M., Altmann, D.R., Barnes, T.R.E., Barker, G.J., Joyce, E.M., Ron, M.A., 2007. Abnormal brain connectivity in first episode psychosis: a diffusion MRI tractography study of the corpus callosum. NeuroImage 35, 458–466.

Sass, L.A., Parnas, J., 2003. Schizophrenia, consciousness, and the self. Schizophrenia Bulletin 29, 427–444.

Schmahmann, J.D., Pandya, D.N., 2006. Fiber Pathways of the Brain. Oxford University Press, Oxford.

Schulte, T., Müller-Oehring, E.M., 2010. Contribution of callosal connections to the interhemispheric integration of visuomotor and cognitive processes. Neuropsychology Review 22, 174–190.

Tao, H., Guo, S., Ge, T., Kendrick, K.M., Xue, Z., Liu, Z., Feng, J., 2011. Depression uncouples brain hate circuit. Molecular Psychiatry. http://dx.doi.org/10.1038/mp.2011.127.

Taylor, S.F., Kang, J., Brege, I.S., Tso, I.F., Hosanagar, A., Johnson, T.D., 2011. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. Biological Psychiatry. http://dx.doi.org/10.1016/j.biopsych.2011.09.007.

Tyszka, J.M., Kennedy, D.P., Adolphs, R., Paul, L.K., 2011. Intact bilateral resting-state networks in the absence of the corpus callosum. Journal of Neuroscience 31, 15154–15162.

Uddin, L.Q., 2011. Brain connectivity and the self: the case of cerebral disconnection. Consciousness and Cognition 20, 94–98.

van der Knaap, L.J., van der Ham, I.J.M., 2011. How does the corpus callosum mediate interhemispheric transfer? A review. Behavioural Brain Research 223, 211–221.

Walterfang, M., Wood, A.G., Reutens, D.C., Wood, S.J., Chen, J., Velakoulis, D., McGorry, D., Pantelis, C., 2008. Morphology of the corpus callosum at different stages of schizophrenia: cross-sectional study in first-episode and chronic illness. The British Journal of Psychiatry 192, 429–434.

Wernicke, C., 1906. Grundrisse der Psychiatrie. Thieme, Leipzig, Gemrnay.

Whitford, T.J., Kubicki, M., Schneiderman, J.S., O'Donnell, L.J., King, R., Alvarado, J.L., Khan, U., Markant, D., 2010. Corpus callosum abnormalities and their association with psychotic symptoms in patients with schizophrenia. Biological Psychiatry 68, 70–77.

Wing, J.K., Agrawal, N., 2007. Concepts and Classification of Schizophrenia, in Schizophrenia, In: Hirsch, S.R., Weinberger, D.R. (Eds.), Second edition. Blackwell Science Ltd, Oxford, UK. http://dx.doi.org/10.1002/9780470987353.ch1.

Xu, K., Jiang, W., Ren, L., Ouyang, X., Jiang, Y., Wu, F., Kong, L., Womer, F., Liu, Z., Blumberg, H.P., Tang, Y., Wang, F., 2012. Impaired interhemispheric connectivity in medication-naïve patients with major depressive disorder. Journal of Psychiatry & Neuroscience. http://dx.doi.org/10.1503/jpn.110132.