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Key Functional Circuitry Altered in Schizophrenia Involves Parietal Regions Associated with Sense of Self

Shuixia Guo,[1] Keith M. Kendrick,[2] Rongjun Yu,[3] Hsiao-Lan Sharon Wang,[4] and Jianfeng Feng[5,6]*

[1]*College of Mathematics and Computer Science, Key Laboratory of High Performance Computing and Stochastic Information Processing, Ministry of Education of China, Hunan Normal University, Changsha, Hunan, China*
[2]*Key Laboratory for Neuroinformation, Ministry of Education of China, School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 610054, China*
[3]*School of Psychology and Center for Studies of Psychological Application, South China Normal University, Guangzhou, China*
[4]*Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei 100, Taiwan*
[5]*Centre for Computational Systems Biology, School of Mathematical Sciences, Fudan University, Shanghai, China*
[6]*Department of Computer Science, University of Warwick, Coventry, United Kingdom*

Abstract: There is still no clear consensus as to which of the many functional and structural changes in the brain in schizophrenia are of most importance, although the main focus to date has been on those in the frontal and cingulate cortices. In the present study, we have used a novel holistic approach to identify brain-wide functional connectivity changes in medicated schizophrenia patients, and functional connectivity changes were analyzed using resting-state fMRI data from 69 medicated schizophrenia patients and 62 healthy controls. As far as we are aware, this is the largest population reported in the literature for a resting-state study. Voxel-based morphometry was also used to investigate gray and white matter volume changes. Changes were correlated with illness duration/symptom severity and a support vector machine analysis assessed predictive validity. A network involving the inferior parietal lobule, superior parietal gyrus, precuneus, superior marginal, and angular gyri was by far the most affected (68% predictive validity compared with 82% using all connections) and different components correlated with illness duration and positive and negative symptom severity. Smaller changes occurred in emotional memory and sensory and motor processing networks along with weak-

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*Correspondence to: Jianfeng Feng, Centre for Computational Systems Biology, School of Mathematical Sciences, Fudan University, Shanghai, People's Republic of China. E-mail: jianfeng64@gmail.com

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ened interhemispheric connections. Our findings identify the key functional circuitry altered in schizophrenia involving the default network midline cortical system and the cortical mirror neuron system, both playing important roles in sensory and cognitive processing and particularly self-processing, all of which are affected in this disorder. Interestingly, the functional connectivity changes with the strongest links to schizophrenia involved parietal rather than frontal regions. *Hum Brain Mapp 35:123–139, 2014.*

Key words: schizophrenia; functional connectivity; VBM; partial correlation; network

INTRODUCTION

Schizophrenia is a complex syndrome including a large number of indicators and symptoms although mainly defined by psychosis, paranoid delusions, and auditory hallucinations [Insel, 2010]. It is increasingly thought of as a developmental disorder with onset of first major symptoms normally occurring in late adolescence or early adulthood although with a prodromal period likely to cover many years prior to this [Insel, 2010]. Schizophrenia is arguably the most serious, debilitating, and distressing mental illness suffered by humans and we are far from reducing our susceptibility to it [Hegarty et al., 1994], or achieving a successful long-term therapy with sustained recovery within the first five years of a psychotic episode being reported to be only 14–16% [Harrison et al., 2001; Robinson et al., 2004]. We still have a poor understanding of the biological bases for this disorder and current drug treatments while reasonably successful in controlling psychotic symptoms are far less effective at improving cognitive and emotional dysfunction symptoms of the disorder and as such patients are still unable to maintain employment or function normally in society [Marwaha et al., 2007].

Increasing attention is being focused on identifying the changes in brain structure and functional circuitry which are responsible both for susceptibility to schizophrenia and for generating its key debilitating symptoms, particularly those related to cognitive and emotional dysfunction [Insel, 2010; Zhang and Raichle, 2010]. As such it will be important both to establish the progressive developmental changes which lead to the emergence of the full schizophrenic syndrome and also those underlying the cognitive and emotional dysfunctions that are often resistant to current anti-psychotic drugs. To date, a number of task-related studies have been carried out indicating differences between schizophrenia patients and healthy controls [Garrity et al., 2007; Ragland et al., 2009; Taylor et al., 2011] although there is increasing interest in establishing core functional changes in brain circuitry during resting-state [Greicius, 2008; Huang et al., 2008; Jafri et al., 2008; Lynall et al., 2010]. Results from the latter studies have so far not revealed a consistent pattern of changes although alterations in the so called "default" circuit, most notably the prefrontal and cingulate cortices, and overall evidence for increased disconnectivity and reduced integration are most commonly reported. Variable alterations in local and global encoding efficiency have also been described [Liu et al., 2008; Yoon et al., 2008] and structural studies have shown altered gray matter (GM) and white matter (WM) volumes/densities in a variety of different brain regions [Lui et al., 2009] and altered connectivity [van den Heuvel et al., 2010; Zhou et al., 2008].

Previous studies attempting to use resting-state functional Magnetic Resonance Imaging (fMRI) to establish functional connectivity changes in the brains of schizophrenia patients have used either seed-based or independent component analysis (ICA)-based approaches. Seed-based analysis is a hypothesis-driven approach, which means the foci (seeds) of the disorder must be specified *a priori,* it is therefore a biased approach lacking a global and independent view. On the other hand, ICA is often used to discover spatial-temporal independent components based on separation of variance; however, the components identified are often difficult to interpret. Different from these methods, in our previous article, we have developed a brain-wide association method for determining whole brain functional connectivity changes in patient populations using resting-state fMRI data [Tao et al., 2011]. This uses an unbiased holistic approach which makes no *a priori* assumptions about which structures and connections will be affected, but assumes a degree of inter-relatedness. Our first use of this approach identified a novel key functional pathway which was altered in both the brains of first episode and treatment-resistant depressed patients [Tao et al., 2011]. We have now used this same approach in the current study in schizophrenia patients suffering from significant cognitive and emotional dysfunction despite treatment with anti-psychotic drugs. We deliberately chose patients with a wide range of different illness durations and antipsychotic treatments in order to better identify key changes common to a wide spectrum of conditions. In addition, we have used voxel-based morphometry (VBM) to assess GM and WM volume changes in the brains of these same patients and investigated whether they correlate with functional changes.

Overall, we hypothesized that by utilizing our novel data-driven approach for establishing brain-wide changes in cortical and sub-cortical connectivity in a large group of medicated schizophrenia patients with a range of illness durations, we would identify the key connectivity changes associated with this disorder. In addition, we have directly

addressed the question of the extent to which functional connectivity and structural changes are correlated in schizophrenia patients. Our results have revealed that the key functional pathway altered in schizophrenia patients involves components of the default network and cortical mirror neuron system involved with various aspects of processing the sense of self and these correlate with illness duration and symptom severity. There is also evidence for reduced inter-hemispheric connectivity. While there is also widespread evidence of reduced GM volumes in the brains of schizophrenic patients, there were no correlations following correction between these and illness duration or symptom severity. GM changes also did not correlate with altered functional connectivity in the key pathways affected in the patients.

METHODS

Subjects

From July 2009 to December 2011, we recruited 69 patients with chronic schizophrenia, with 35 males and 34 females who were identified according to the DSM-IV diagnostic criteria by qualified psychiatrists at the National Taiwan University Hospital. Exclusion criteria included the presence of DSM-IV Axis I diagnoses of other disorders such as bipolar disorder, history of any substance dependence, or history of clinically significant head trauma. Patient and healthy control demographics are shown in Table I. Illness durations ranged from a few months to 30 years (mean ± SD: 7.17 ± 6.61 years). All patients were being treated with a range of antipsychotics (see Supporting Information Table S1 for details) with the most common being Abilify (aripiprazole—$n = 20$) or Zyprexa/ZyprexaZydis ($n = 12$). Their average age was 31.6 ± 9.6 years and they had a mean education duration of 14.2 ± 2.16 years. Only two of the patients were left handed and the other 67 were right handed according to the Edinburgh Handedness Inventory. Symptom severity was measured using the Positive and Negative Syndrome Scale (PANSS) assessment which was given to all schizophrenic participants either one week before the MRI scan or one week after it. However, five patients were not able to complete their PANSS assessment because of their poor health condition.

Sixty-two (25 males and 37 females) healthy control subjects were also recruited. Their average age was 29.9 ±8.62 years, and their mean education duration was 15.3 ± 2.39 years. One of the subjects was left handed and the remaining 61 right handed. All of the controls were assessed in accordance with DSM-IV criteria as being free of schizophrenia and other Axis I disorders. None of them had any neurological diseases or suffered from clinically significant head trauma and none had a history of any substance dependence. Written informed consent was obtained from all individual participants, and all of the research procedures and ethical guidelines were followed in accordance with the Institutional Review Board (IRB) of the National Taiwan University Hospital. The patient and control groups were well matched by gender ($\chi^2 = 1.4234$, $P = 0.2328$) and age (t-test, $P = 0.2836$) although the controls had a slightly longer education duration (t-test, $P = 0.0064$).

TABLE I. Subject demographics

	Schizophrenia 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	11.92 ± 4.71	n.a.	n.a.
PANSS-negative scale	13.61 ± 6.33	n.a.	n.a.
PANSS-general psychopathology scale	27.28 ± 9.64	n.a.	n.a.
PANSS-Total	52.81 ± 16.68	n.a.	n.a.
PANSS-supplement aggression risk subscale score	4.08 ± 2.29	n.a.	n.a.

Demographic information for the patient and control groups. Mean and standard deviation are provided for continuous variables (e.g., age, education, and PANSS scales). PANSS = Positive and Negative Syndrome Scale ($n = 69$ patients with $n = 64$ for PANSS scores).

Imaging Acquisitions and Data Preprocessing

All subjects underwent a structural and functional MRI scan in a single session using a 3T MR system (TIM Trio, Siemens, Erlangen, Germany). A 32 channel head coil was used as the RF signal receiver. Sponges were used to fix subjects' heads within the coil to prevent motion artifacts. All images were acquired parallel to anterior-commissure-posterior-commissure line with an auto-align technique. The total scan time for each subject was about 10 min.

The resting-state fMRI was performed with a gradient-echo echo planar sequence. Subjects were asked to relax and think of nothing in particular and to keep their eyes closed, although they were requested not to fall asleep. Wakefulness was assessed throughout the recording via an intercom link to the scanner chamber. The fMRI acquisition parameters were as follows: repetition time (TR) = 2000 ms, echo time (TE) = 24 ms, field of view (FOV) = 256 × 256 mm^2, matrix = 64 × 64, slice thickness = 3 mm and flip angle = 90°. For each participant, 34 trans-axial slices with no gap were acquired to encompass the whole brain volume. The scan time of the resting-state fMRI was approximately 6 min.

Prior to preprocessing, the first 10 volumes 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) [Chao-Gan and Yu-Feng, 2010].

TABLE II. 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	Parahippocampal gyrus	PHG
Cuneus	CUN	Postcentral gyrus	PoCG
Fusiform gyrus	FFG	Posterior cingulate gyrus	PCG
Heschl gyrus	HES	Precentral gyrus	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	Supramarginal gyrus	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		

Briefly, 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 $3 \times 3 \times 3$ mm^3. After normalization, blood oxygen level-dependent (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, WM signals, and cerebrospinal signals were regressed out from the BOLD signals. An automated anatomical labeling atlas [Tzourio-Mazoyer et al., 2002] was used to parcellate the brain into 90 regions of interest (ROIs) (45 in each hemisphere). The names of the ROIs and their corresponding abbreviations are listed in Table II. The time series of each ROI is extracted by averaging the time series of all voxels within it for our further analysis.

For the reference anatomical image, a magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire a whole brain high-resolution T_1-weighted MR image in a coronal view. The sequence parameters were TR/TE = 2000 ms/2.98 ms, inversion time = 900 ms, image matrix size = 192×256, spatial resolution = 1×1 mm^2, FOV = 192×256 mm^2, and slice thickness = 1 mm without gap. T_1 scan time is about 3 min and 36 sec. All T_1-weighted structural data were processed with VBM5 toolbox (Structural Brain Mapping Group, Jena, Germany; http://dbm.neuro.unijena.de/vbm) based on the SPM software package. First, the original T_1 image was segmented into GM, WM, and cerebrospinal fluid (CSF) probability maps. This procedure included a bias correction, correcting the image inhomogeneities to increase the contrast between the GM and WM voxel-value distribution and improve the quality of the segmentation. Further, all non-brain voxels are removed by rendering the lateral surface of the brain. The obtained transformation matrix was applied to the original T_1 image to create normalized T_1 images, which were segmented a second time. The resulting GM and WM images were modulated in order to preserve the volume of a particular tissue compartment within each voxel. The modulated images were smoothed with an 8-mm Full Width at Half Maximum (FWHM) isotropic Gaussian kernel. The resulting smoothed, modulated, normalized regions contained the average amount of GM and WM, which enabled the investigation of their absolute volume [Ashburner and Friston, 2000; Douaud et al., 2006]. In the traditional VBM analysis, voxelwise analysis is carried out to obtain the voxels with significant GM and WM differences between schizophrenia patients and healthy controls following correction. In this study, we aimed to test whether these structure changes were associated in any way with the functional changes. By using the same automated anatomical labeling atlas, we can extract the volumes of the GM and WM for each ROI by averaging the volumes of each voxels within it. Two sample *t*-tests with false discovery rate (FDR) correction were then used to assess whether there were significant volume differences between patients and healthy controls.

Construction of Whole-Brain Functional Network

After data preprocessing, the time series were extracted in each of the 90 ROIs by averaging the signals of all voxels within that ROI and then linearly regressing out the influence of head motion and global signals. Pearson correlation coefficients between all pairs of ROIs were first calculated. Significant correlations were detected with $P < 0.01$. A 90×90 correlation matrix was obtained for each subject. However, significant correlation between two ROIs may be spurious, i.e., a by-product of the correlations of the two ROIs with a third region and so to determine whether the correlation for the two ROIs is genuine, the third ROI should be kept constant. Statistically, this problem can be tackled by means of a partial correlation test where the effects of the third ROI on the relation between the other two ROIs are eliminated. By calculating partial correlation coefficients between all pairs of ROIs, with all the remaining ROIs being controlling variables, a 90×90 correlation matrix was obtained for each subject with $P < 0.01$. The population-level network can be obtained by summarizing all individual networks in the patient and healthy groups respectively, and thresholding them into binarized matrices with matched and reasonable sparsity values (defined as the total number of edges in a network divided by the maximum number of possible edges). In the analysis for this article, the sparsities of the healthy and patient group networks were 2.65% and 2.7%, respectively.

Measures of Functional Connectivity Effects

When studying the functional connectivity, we are interested in knowing not only whether a link between two ROIs has statistically significant difference between different groups, but also the effect of this relationship. The effect associated with a particular link can be calculated from the following score (risk difference):

$$s = \frac{L_{\mathrm{h}}^{\mathrm{link}}}{N_{\mathrm{h}}^{\mathrm{link}}} - \frac{L_{\mathrm{p}}^{\mathrm{link}}}{N_{\mathrm{p}}^{\mathrm{link}}}$$

where s is the risk difference for a particular link, $L_{\mathrm{p}}^{\mathrm{link}}$ is the number of times a link is present in the individual networks of patients, $N_{\mathrm{p}}^{\mathrm{link}}$ is the total number of patients, $L_{\mathrm{h}}^{\mathrm{link}}$ is the number of times a link is present in the individual networks of healthy controls, and $N_{\mathrm{h}}^{\mathrm{link}}$ is the total number of healthy controls. Obviously, a risk difference of 0 indicates that the link is equally likely to occur in both groups, a risk difference less than 0 indicates that the link is a dangerous factor and more likely to occur in the patient group, and a score greater than 0 indicates that the link is a protective factor and less likely to occur in the patient group. In order to obtain the statistically significance of the score for a particular link, a permutation test can be carried out.

In brief, the rationale behind our approach for establishing functional connectivity changes is to: (1) rank each link according to their "score," i.e., their risk difference; (2) select the top 10–20 links for further analysis, and (3) check the selected 10–20 links to see whether they are statistically significant and confirm significance using a permutation test. By adopting this approach, we avoid the necessity for multi-comparison corrections over all possible links by restricting analysis to the top 10–20 links identified by their risk differences.

Support Vector Machine Classifier

The support vector machine (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 [Williams et al., 2007]. Because of these properties, they have proven powerful in the analysis of functional magnetic resonance imaging data.

SVM conceptually implements the idea that vectors are nonlinearly 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 subspace. Each subspace 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 subspace they are mapped to. In this article, a SVM toolkit named libsvm written by Lin Chih-Jen from Taiwan university (http://www.csie.ntu.edu.tw/∼cjlin/libsvm/) is used. Radial basis function (RBF) is selected as kernel function ($t = 2$), parameter C is fixed to 10 which is used to trade-off learning and extend ability, and other parameters are kept as default values.

RESULTS

Canonical Template

The constructed six-community structure for the whole brain from healthy subjects is as previously described [Tao et al. 2011—see Supporting Information Fig. S1a]. These six communities have a clear biological significance which can be classified as the default mode network (DMN) (RNS1), the attention network (RSN2), the visual system (RSN3), the auditory system (RSN4), the sensory-motor areas (RSN5), and the subcortical network (RSN6).

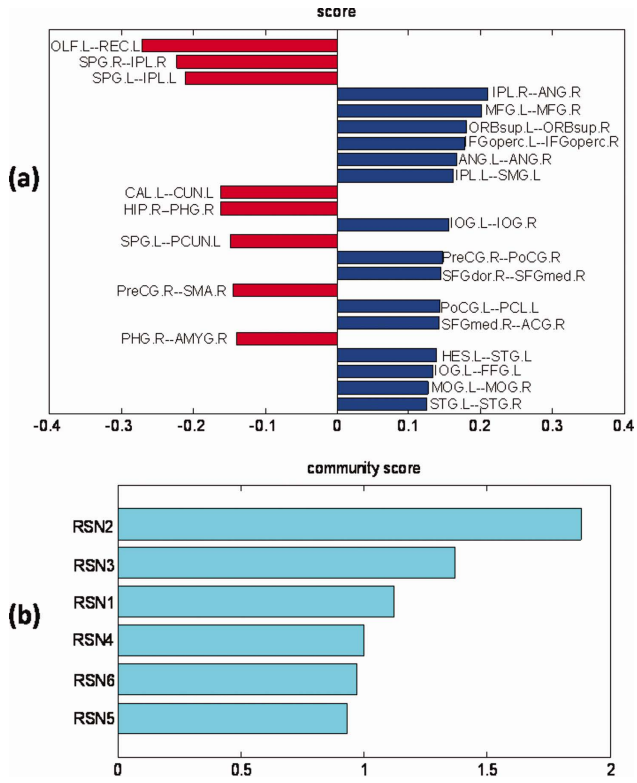

Figure 1.

Changes in individual links and community scores in schizophrenia patients. (**a**) Bar plot of the largest changes in connectivity scores between the networks for schizophrenia patients and healthy controls. (**b**) Summary of the score changes for links within each RSN. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Altered Connectivity in Schizophrenia Patients vs. Healthy Controls

Functional maps are constructed for 69 schizophrenia patients and 62 healthy controls. Figure 1a shows the scores for different links between the schizophrenia patient and healthy control networks and indicating links that are either strengthened or weakened. The summation of the scores for links within each RSN is shown in Figure 1b. Overall, the canonical network most affected in the schizophrenia patients was the attention network (RSN 2) followed by the visual (RSN 3) and default (RSN 1) ones.

To illustrate more clearly the connectivity changes in the schizophrenic patients, Figure 2a plots the altered links between the schizophrenia and healthy patient networks within and between the different RSNs with the two hemispheres merged into one. Additionally, Figure 2b shows the localization of the altered circuits in the brain. It can be seen that the three most altered individual links were those between the olfactory bulb (OLF) and rectus gyrus (REC) in the left hemisphere and bilaterally between the superior parietal gyrus (SPG) and inferior parietal lobule (IPL) which were all stronger in the schizophrenic patients. The most notable pattern of change in terms of stronger connections in the healthy subjects is between the same regions in the left and right hemispheres. Seven different regions show this altered pattern, including the medial frontal gyrus (MFG), superior orbitofrontal cortex (ORBsup), opercula inferior frontal gyrus (IFGoperc), angular gyrus (ANG), inferior and medial occipital gyri (IOG and MOG), and the superior temporal gyrus (STG).

For the next stage of analysis, we calculated the significance of overall changes in circuits in the two groups. With the large number of individual connections analyzed between 90 different brain structures, the changes for individual links could fail to be significant after making corrections for multiple comparisons. We, therefore, also carried out a permutation analysis on total scores for different circuits (the summation of the scores for all altered links within a circuit) to assess the significance of changes in schizophrenia patients. Table III gives the score and *P*-value for the circuits showing significant changes. It can be seen that by far the most altered circuit involves primarily connections between and within the default (RSN1), attention (RSN2), and auditory (RSN4) networks, including the IPL, SPG, precuneus (PCUN), supramarginal gyrus (SMG), and ANG with $s = 1.123$ ($P < 0.001$). Figure 2a,b shows that the IPL is at the centre of this altered circuit with its connections with the SMG and ANG being weakened and those with the SPG and PCUN being strengthened. Interestingly, we found significant correlations between the change in the score in this circuit and both illness duration and positive and negative PANSS scores although involving different components (see Tables IV and V). The IPL-SPG-PCUN component of the circuit, which is strengthened in schizophrenia patients, was significantly positively correlated (0.26, $P < 0.05$) with illness duration but not at all with PANSS scores (0.03 positive and 0.04 negative; $P > 0.05$). On the other hand, the IPL-ANG connection, which is weakened in patients, was strongly positively correlated with both PANSS positive and negative scores (0.43 and 0.35; $P < 0.01$) but not at all with illness duration (0.10, $P > 0.05$).

In order to provide a clearer assessment of the relationships between the different connections and schizophrenia symptoms we calculated ordinary Pearson correlations for each component with each of the PANSS questions (7 Positive, 7 Negative, and 16 General). This confirmed an absence of correlation with any question for the IPL-SPG-PCUN or IPL-SPG alone (see Supporting Information Tables S2 and S3). For the SPG-PCUN pathway, small positive correlations with general questions G4 (0.27—tension) and G15 (0.26—preoccupation) were found (Supporting Information Table S3). On the other hand, for the IPL-ANG connection, there were significant positive correlations with 6/7 positive and 5/7 negative PANSS questions and 6/16 general ones (see Supporting Information Table S2).

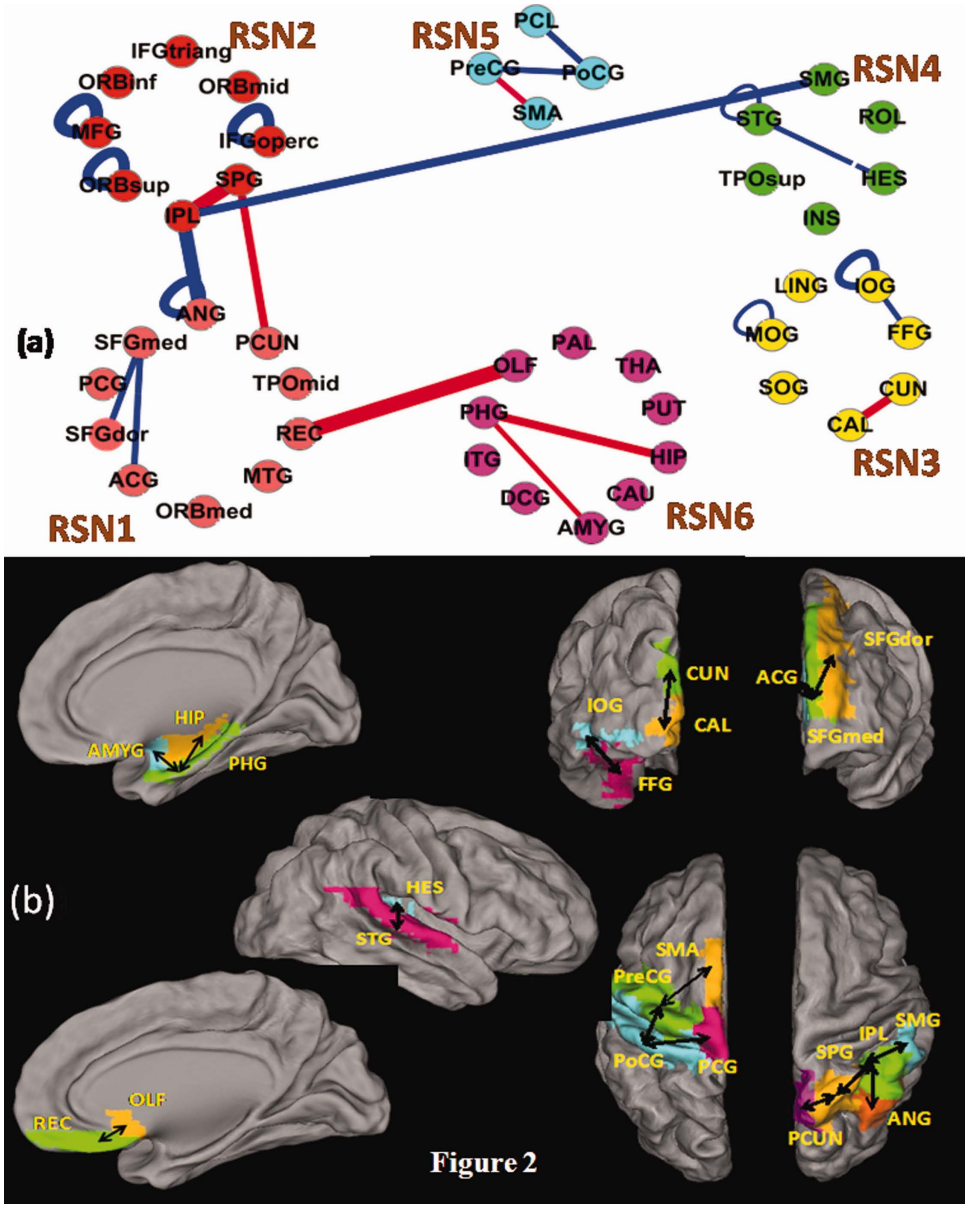

Figure 2.

Altered connections in schizophrenia patients displayed in a single hemisphere. (**a**) Functional network structure of the 6 RSN showing the connections which are increased in schizophrenia patients (red) and in normal healthy subjects (blue). (**b**) Brain images showing the location of the structures and circuits where changes have occurred. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Supporting Information Table S2 shows that the strongest significant correlations for changes in IPL-ANG were for P1 (0.27—delusions), P2 (0.34—conceptual disorganization), P4 (0.48—excitement), P7 (0.52—hostility), N2 (0.35—emotional withdrawal), N5 (0.29—difficulty in abstract thinking), N7 (0.40—stereotyped thinking), G14 (0.34—poor impulse control), G1 (0.28—somatic concern), and G15 (0.43—preoccupation). The IPL-SMG pathway (Supporting Information Table S3) showed overlap with IPL-ANG with significant correlations for P5 (0.30—grandiosity), P6 (0.27—suspiciousness/persecution), G1 (0.26—somatic concern), G11 (0.33—poor attention), and G15 (0.33—preoccupation) but unlike the IPL-ANG pathway also had significant correlations with N4 (0.30—passive/apathetic social withdrawal), G2 (0.33—anxiety), and G3 (0.30—guilt feelings).

TABLE III. The scores and *P*-values of significantly altered circuits

Circuit	Score	*P*-value
IPL-SPG-PCUN-SMG-ANG	1.1233	<0.0001
PreCG-PoCG-PCL-SMA	0.4350	0.004
HIP-PHG-AMYG	0.3014	0.005
IOG-FFG	0.2891	0.006
SFGdor-SFGmed-ACG	0.2871	0.005
REC-OLF	0.2719	0.000
HES-STG	0.2636	0.006
MFG-MFG	0.2024	0.0170
ORBsup-ORBsup	0.1802	0.0070
IFGoperc-IFGoperc	0.1781	0.0250
CAL-CUN	0.1620	0.0380

The other networks with significant changes included all sensorimotor structures (RSN 5), the pre- (PreCG) and post-central (PoCG) gyri, paracentral lobule (PCL), and supplementary motor area (SMA) with $s = 0.435$ ($P = 0.004$), subcortical (RSN 6), amygdala (AMYG), parahippocampal gyrus (PHG) and hippocampus (HIP) with $s = 0.301$ ($P = 0.005$) and visual networks (RSN 3) including the connection between the IOG and fusiform gyrus (FFG) ($s = 0.289$, $P = 0.006$) and calcarine cortex (CAL) and cuneus (CUN) ($s = 0.162$, $P = 0.038$). Additionally, there were changes within the default network involving the medial (SFGmed) and dorsal superior frontal (SFGdor) gyri and anterior cingulate cortex (ACG) ($s = 0.287$, $P = 0.005$), the attention network (RSN 2) between right and left MFG, inferior frontal gyrus (opercula—IFGoper) and ORBsup and auditory (RSN 4) networks; STG and Herschl's gyrus (HES) and in the olfactory pathway between the olfactory bulb (OLF—RSN 6) and rectal gyrus (REC—RSN 1) (see Table III). However, Table IV shows that none of these connectivity changes were significantly associated with illness duration, with the notable exception of the IOG-FFG (-0.21, $P = 0.003$). Only the HIP-PHG-AMYG (0.28, $P = 0.028$) connection change showed a significant positive correlation with negative PANSS scores (Table V). Analysis of this latter pathway, in terms of significant correlations with specific PANSS questions, showed that it was primarily the PHG-AMYG that was important (significant correlations with P2—conceptual disorganization, N1—blunted effect, N3—poor rapport, G1—somatic concern, G4—tension, G8—uncooperativeness, G11—poor attention, G13—disturbance of volition, G15—preoccupation, G16—active social avoidance—see Supporting Information Table S4).

Since a number of regions showed evidence for altered connectivity between the two hemispheres, a further partial correlation analysis was carried out just for inter-hemispheric connections for each of the 45 brain areas. This revealed significant reductions in correlation coefficients for nine regions (PCG in RSN 1; ORBsup and MFG in RSN 2; IOG in RSN 3; insula cortex (INS) in RSN 4; PoCG in RSN 5; and AMYG, pallidum (PAL) and thalamus (THA) in RSN 6 (see Fig. 3a–c). When the correlation coefficients for all nine regions were combined, they showed an overall negative correlation both with illness duration (-0.32, $P = 0.0079$) and negative PANSS (-0.25, $P = 0.0425$) (see Fig. 3d). However, when the individual correlations with PANSS scores were computed it was clear that it was only the amygdala connectivity change that correlated significantly and negatively with negative PANSS (-0.395, $P = 0.0012$) although not with positive PANSS (-0.16, $P = 0.20577$) or illness duration (-0.22, $P = 0.1081$). An analysis of correlations with individual PANSS questions revealed that for the amygdala significance was achieved for all the negative symptoms other than N5 (difficulty in abstract thinking). There was also a small

TABLE IV. Correlation between selected circuits and illness duration

Circuit	Correlation coefficient	Two tailed *P*-value
IPL-SPG-PCUN-SMG-ANG	0.1216	0.3719
IPL-SPG-PCUN	0.2635	0.0497
IPL-ANG	0.1012	0.4578
HIP-PHG-AMYG	−0.0469	0.7314
PHG-AMYG	−0.0540	0.6929
PreCG-PoCG-PCL-SMA	0.0867	0.5251
IOG-FFG	−0.3852	0.0034
SFGdor-SFGmed-ACG	0.2093	0.1215
REC-OLF	−0.0948	0.4871
HES-STG	−0.0405	0.7669
MFG-MFG	−0.0366	0.7890
ORBsup-ORBsup	−0.0944	0.4889
IFGoperc-IFGoperc	−0.0622	0.6488
CAL-CUN	−0.1088	0.4247

The significant level of the shaded entries is 0.05.

TABLE V. Correlation between selected circuits and the positive/negative PANSS score

Circuit	Correlation coefficient (P/N)	Two tailed *P*-value
IPL-SPG-PCUN-SMG-ANG	0.2599/0.2252	0.0381/0.0736
IPL-SPG-PCUN	0.0328/0.0413	0.7968/0.7459
IPL-ANG	0.4312/0.3498	0.0003/0.0046
HIP-PHG-AMYG	0.1699/0.1378	0.1795/0.2276
PHG-AMYG	0.1699/0.2755	0.1795/0.0276
PreCG-PoCG-PCL-SMA	0.1433/0.2220	0.2585/0.0779
IOG-FFG	−0.1442/−0.1995	0.2557/0.1140
SFGdor-SFGmed-ACG	−0.1154/ 0.1670	0.3641/0.1872
REC-OLF	0.1362/0.0065	0.2831/0.9593
HES-STG	−0.0850/−0.0764	0.5045/0.5484
MFG-MFG	−0.0219/−0.1220	0.8638/0.3367
ORBsup-ORBsup	0.0665/−0.1627	0.6014/0.1990
IFGoperc-IFGoperc	−0.0383/−0.0714	0.7638/0.5751
CAL-CUN	−0.0969/−0.2080	0.4463/0.0990

The significant level of the shaded entries is 0.05.

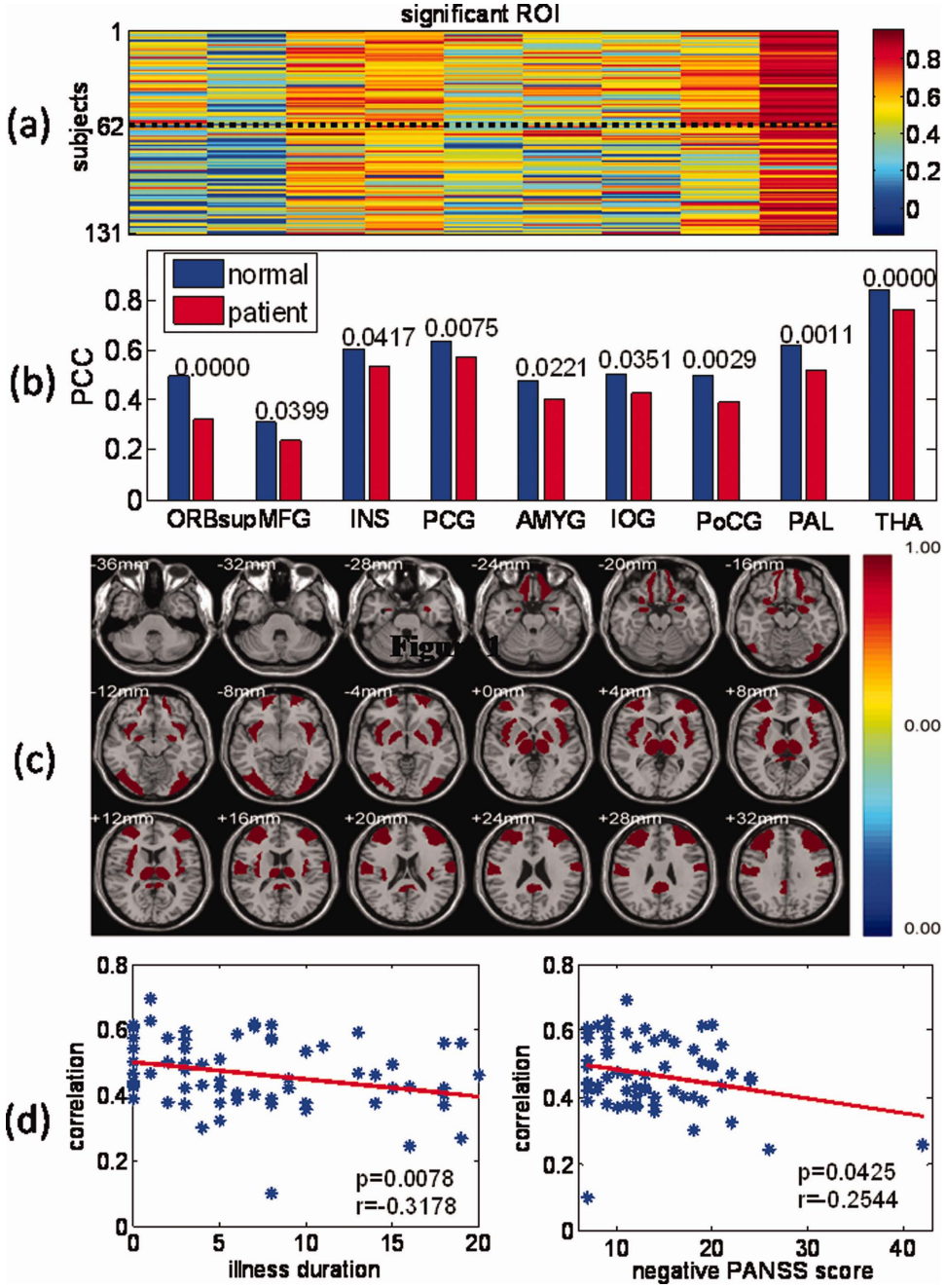

Figure 3.

Significant ROIs with altered interhemispheric partial correlation coefficients between schizophrenia patients and control subjects. (**a**) Shows a pseudocolor plot of comparisons between all individual healthy subjects (1–62) and schizophrenia patients (63–131). (**b**) Histograms show specific brain regions with significantly altered interhemispheric connectivity—*P* value is given above each set. (**c**) Location of these significant ROIs. (**d**) Correlation of the mean correlation coefficients (MCC) of these significant ROIs and the illness duration/negative PANSS score. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

significant correlation with P3 (−0.25, $P = 0.0472$ - hallucinatory behavior) and with G4 (−0.31 - tension), G6 (−0.29 - depression), G7 (−0.39 - motor retardation), G8 (−0.311 - uncooperativeness), G13 (−0.30 - disturbance of volition) and G15 (−0.34 - preoccupation). For the remaining 8 ROIs with weakened interhemispheric connections only

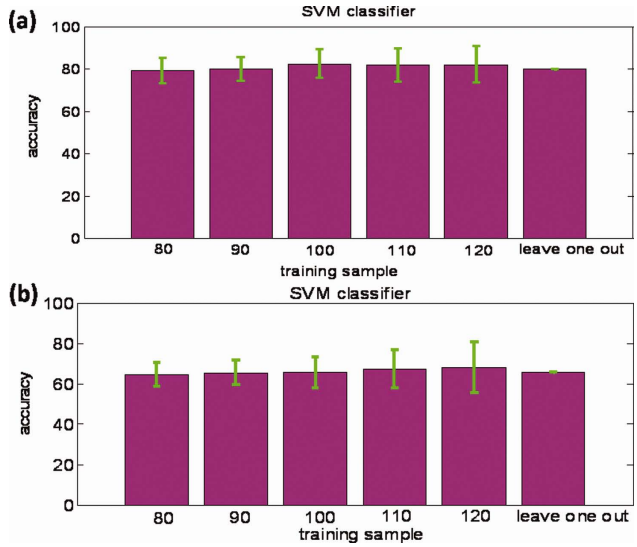

Figure 4.

Predictive value of connectivity changes for identifying schizophrenia patients. (**a**) Histogram shows (mean ± SD)% accuracy in the SVM classifier analysis using all connection changes in the group of schizophrenia patients compared with healthy controls across a range of training samples and when one connection is randomly left out. The table gives mean percentage values for specificity and sensitivity as well as accuracy. (**b**) Same as (a) but just for the circuit most changed in schizophrenia patients (IPG-SPGPCUN-SMG-ANG). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the ORBsup, INS and THA showed any significant correlations with a small number of PANSS question scores (see supplementary Tables S5–7).

In view of the wide range of illness durations, and the possibility that there might be different patterns of altered networks over time, we also performed a secondary analysis where patients were divided into groups with either short (up to 2 years), medium (3–9 years), or long (10–20 years) illness durations. Supporting Information Table S8 shows that the same general pattern of significant changes occurred in most of the networks in the three patient groups, and particularly in the key IPL-SPG-PCUN-SMG-ANG one. The IOG-FFG came close showing a significant difference across the three groups ($P = 0.069$), with the 0–2 year illness duration group showing a much smaller and non-significant change compared with controls.

A range of different antipsychotic treatments were being given to the patients and around 30% of them were receiving Abilify (aripiprazole) which, unlike the other treatments being used, can have a partial agonist effect at the dopamine D2 receptor [Kessler, 2007]. To determine whether treatment with Abilify produced different effects to the other drugs, we compared the strength of functional connectivity changes in the groups of patients receiving either Abilify or not. Results showed no significant differences in any of the altered pathways (see Table S9 in the Supporting Information section).

Predictive Value of Connectivity Changes in Schizophrenia Patients

In order to test the performance of the most changed circuit (IPL-SPG-PCUN-SMG-ANG), we compared the discrimination accuracy of this circuit with the overall circuit. In the present study, SVM is used to discriminate between subjects belonging to patients and healthy controls. For different training samples, we first selected the correlation coefficients of those links with the significant P value of the difference between two groups less than 0.002 among all possible links and repeated it for 1,000 times. The trained SVM is then applied to the remaining test data and a mean rate of correct classification for the test data is obtained. It can be seen from Figure 4a and Table VI that the classification accuracy is 82.4%. Next, we only select the correlation coefficients of the links in the most changed circuit (IPL-SPG-PCUN-SMG-ANG) as features to obtain the result which is shown in Figure 4b with a classification accuracy being 68.2%. The result shows that the IPL-SPG-PCUN-SMG-ANG circuit makes a strong contribution to the overall predictive value.

Gray and White Matter Changes in Schizophrenia Patients

Table VII and Figure 5 show that 58 out of the 90 ROIs show significantly decreased (GM) volumes in schizophrenia patients compared with controls and none show an increase. The two functional canonical networks showing

TABLE VI. Classification results of SVM classifier

Training sample	80	90	100	110	120	Leave one out
Classification results for all connection changes						
Accuracy	79.2157%	80.1220%	82.4194%	81.9524%	82.1429%	80.0000%
Specificity	74.9600%	77.1000%	78.6667%	78.4000%	79.5000%	73.0000%
Sensitivity	83.3077%	83.0000%	85.9375%	85.1818%	84.5455%	87.0000%
Classification results for IPL-SPG-PCUN-SMG-ANG circuit alone						
Accuracy	64.63%	65.66%	65.74%	67.48%	68.18%	66%
Specificity	50.36%	50.45%	53.67%	55.5%	56%	50%
Sensitivity	78.35%	77.29%	77.06%	78.36%	78.33%	82%

TABLE VII. The ROIs with significantly decreased GM volume in the schizophrenia group

	ROI	Control	Patient	*P* value		ROI	Control	patient	*P* value
RSN1	SFGdor.L	0.8523	0.7696	0.0030	RSN3	CUN.L	0.5354	0.5047	0.0028
	SFGdor.R	0.9789	0.8795	0.0008		LING.L	0.9084	0.8658	0.0012
	SFGmed.L	0.7543	0.6531	0.0002		LING.R	0.9136	0.8602	0.0002
	SFGmed.R	0.5920	0.5173	0.0001		SOG.L	0.3807	0.3528	0.0019
	ORBmed.L	0.2813	0.2535	0.0000		SOG.R	0.4091	0.3821	0.0041
	ORBmed.R	0.3481	0.3190	0.0000		MOG.L	1.1673	1.1153	0.0026
	REC.L	0.3629	0.3384	0.0001	RSN4	ROL.L	0.3365	0.3165	0.0009
	REC.R	0.3196	0.3014	0.0011		INS.L	0.7804	0.7356	0.0007
	ACG.L	0.6319	0.5924	0.0020		INS.R	0.8026	0.7469	0.0002
	MTG.L	2.0728	1.9791	0.0009		SMG.L	0.4407	0.4152	0.0005
	MTG.R	1.9294	1.8437	0.0007		SMG.R	0.7243	0.6870	0.0023
	TPOmid.L	0.2860	0.2673	0.0027		HES.L	0.1118	0.1063	0.0055
	TPOmid.R	0.4118	0.3855	0.0028		STG.L	1.0079	0.9406	0.0002
RSN2	ORBsup.L	0.3122	0.2971	0.0048		STG.R	1.2448	1.1670	0.0002
	ORBsup.R	0.3244	0.3054	0.0008		TPOsup.L	0.3844	0.3124	0.0000
	MFG.L	1.4759	1.3689	0.0022		TPOsup.R	0.4159	0.3607	0.0002
	MFG.R	1.6561	1.5182	0.0003	RSN5	PreCG.L	0.9133	0.8285	0.0004
	ORBmid.L	0.3098	0.2930	0.0008		PreCG.R	0.8845	0.7996	0.0005
	ORBmid.R	0.3709	0.3494	0.0005		PoCG.L	1.0180	0.9281	0.0018
	IFGoperc.L	0.3177	0.2915	0.0008		PoCG.R	0.9847	0.9034	0.0056
	IFGoperc.R	0.4642	0.4158	0.0000	RSN6	PHG.L	0.4792	0.4632	0.0029
	IFGtriang.L	0.7453	0.6774	0.0001		PHG.R	0.5685	0.5471	0.0011
	IFGtriang.R	0.6043	0.5636	0.0035		AMYG.L	0.1216	0.1176	0.0050
	ORBinf.L	0.6215	0.5889	0.0020		CAU.L	0.2738	0.2511	0.0026
	ORBinf.R	0.6229	0.5803	0.0003		CAU.R	0.2774	0.2574	0.0050
	IPL.L	0.8843	0.8195	0.0023		THA.L	0.1904	0.1635	0.0001
	IPL.R	0.5109	0.4728	0.0020		THA.L	0.2149	0.1834	0.0001
RSN3	CAL.L	0.9285	0.8727	0.0007		ITG.L	1.3283	1.2669	0.0005
	CAL.R	0.6982	0.6638	0.0057		ITG.L	1.5372	1.4730	0.0008

The significance threshold following FDR correlation is 0.0057; C = healthy control subjects, P = schizophrenia patients. The actual volume is *1.0*e*+004.

the greatest effects were the auditory network (RSN 4) where all structures were affected, and the attention network (RSN 2) where all regions other than the SPG had reduced GM volumes. In the remaining four networks, around half of the structures in each showed changes. In the key IPL-SPG-PCUN-SMG-ANG and HIP-PHG-AMYG networks showing the greatest functional connectivity change in schizophrenia patients, the IPL, SMG, and PHG bilaterally, and left AMYG, showed significantly reduced GM volumes in patients. However, none of the GM volumes in these regions correlated significantly with either illness duration or PANSS scores and also did not correlate significantly with the strength of functional connectivity links in either patients (IPL-ANG = −0.16, IPL-SMG = −0.18, IPL-SPG = 0.20, PHG-AMYG = 0.16, AMYG-AMYG = 0.004, $P > 0.1$ in all cases) or healthy subjects (IPL-ANG = −0.03, IPL-SMG = −0.03, IPL-SPG = −0.12, PHG-AMYG = −0.19, AMYG-AMYG = −0.06, $P > 0.2$ in all cases). By calculating ordinary Pearson correlation, the GM volumes of three ROIs including the IFGoperc, inferior orbitofrontal cortex (ORBinf), and superior orbitomedial cortex (ORBmed) correlated negatively with illness duration (see Fig. 5). However, when the other GM volumes are treated as covariates, these three ROIs are no longer significant. No GM changes in any ROI correlated significantly with PANSS scores. Only four ROIs showed increased WM volumes in the schizophrenia patients (right PreCG, left PoCG, left triangular region of the IFG, and left CUN—see Fig. 5). None of these showed a significant correlation with illness duration or PANSS scores.

DISCUSSION

Overall, our results have demonstrated that across a range of illness durations from several months to 20 years the key functional network showing significant changes in the brains of schizophrenic patients is one involving components of the default network and the cortical mirror neuron system. Both systems are associated with a range of sensory and cognitive functions, particularly those involving self-processing and a sense of agency and changes were both correlated with illness duration and symptom severity and had a high predictive value for identifying schizophrenic patients compared with healthy controls. However, interestingly the components of both

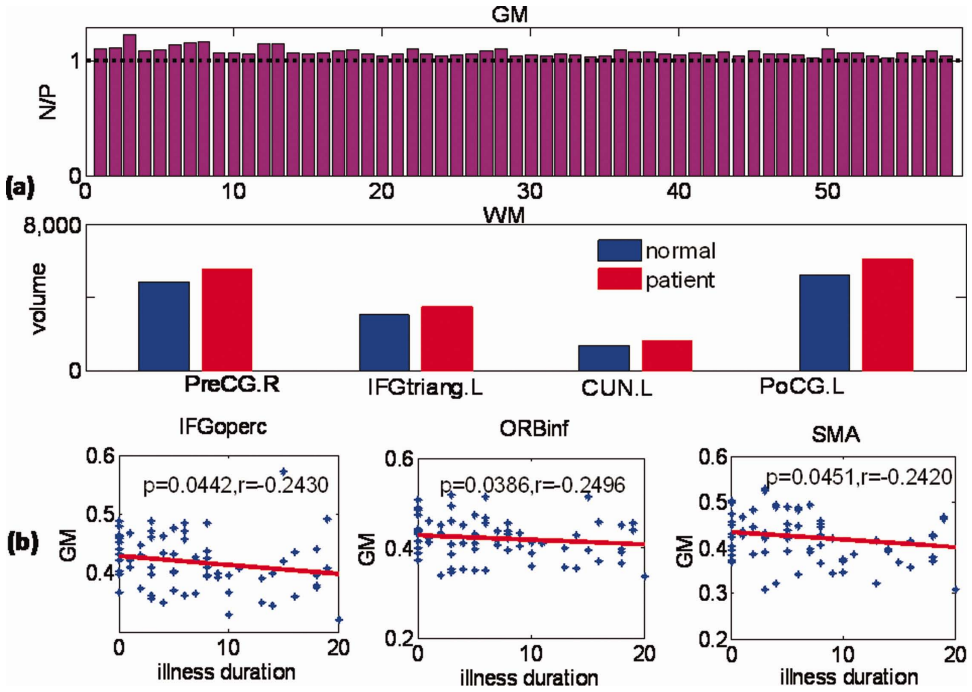

Figure 5.

GM and WM changes in schizophrenia patients. (**a**) The detected ROIs with significant GM and WM volume difference between patients and healthy controls. There are 58 ROIs with significant GM difference in which the ratios of GM volume of healthy controls over patients are all larger than 1, the sequence and names of the ROIs are as listed in Table II. There are four ROIs with significant WM volume difference in which the volume of healthy controls are all smaller than the patients. (**b**) ROIs which have significant correlation between GM and illness duration. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

networks which were most strongly linked with schizophrenia did not include the frontal cortex but mainly parietal regions.

Studies investigating the neural circuitry underlying the sense of self have generally employed paradigms involving self-recognition, self-referential judgments, self-appraisal, and judgments of personality traits, and such information is clearly of great importance not only for evaluating one's own behavior but also for providing a basis for comparison with the behavior of others [Gillihan and Farah, 2005; Legrand and Ruby, 2009; Uddin et al., 2007]. Research to date has emphasized the importance of a number of different regions within the default circuit in the brain containing a number of frontal and parietal regions characterized by high resting-state activity and commonly showing deactivation during task conditions. Indeed, since they show higher activity during the resting state, when it is assumed there is a high level of self-awareness, and this is decreased by any tasks requiring attention (where self-awareness is assumed to be reduced), this has led to the proposal that they are involved in self-processing [see Buckner et al., 2008; Fox and Raichle, 2007]. As such the default circuit has been proposed to be important for self-referential and mental activity [Cavanna and Trimble, 2006; Gusnard et al., 2001]. The main default circuit brain regions implicated in self-relevant information processing includes a group of cortical midline structures including the medial frontal cortex, anterior PCUN, posterior cingulate gyrus, temporal pole, and temporoparietal junction. There is, however, some debate as to the extent to which they are actually more selectively activated by "self" compared with "other" related tasks [Christoff et al., 2011; Legrand and Ruby, 2009]. This same default midline system is also apparently involved in evaluating the mental states of both self and others and as such is central to mental state attribution (theory of mind), social cognition, memory recall, and inferential reasoning [Gilihan and Farah, 2005; Legrand and Ruby, 2009; Uddin et al., 2007]. Christoff et al. [2011] have argued that most studies on self-related processing focus on the self as "an object of attribution" as opposed to "the knowing subject and agent," i.e., the difference between "me" where the self is identified through its physical and mental attributes and "I" where the self is the subjective knower and agent. They have therefore proposed that this cortical midline system forms part of a comparator which acts to

distinguish self through "reafference" (afferent, sensory signals arising as a result of an individual's own efferent motor command processes) from non-self through "exafference" (afferent sensory signals arising as a result of environmental events). In this way, the self becomes "I" the subject and agent of perception rather than "Me" the object of perception or attribution [Christoff et al., 2011].

In addition to the cortical midline structures in the default circuit that have been associated with internal, "mental self" processing it has been proposed that components of the cortical mirror neuron system may play an important role, particularly in the context of the external "physical self" primarily through motor simulation mechanisms [Uddin et al., 2007]. Uddin et al. propose that the fronto-parietal mirror neuron system functions as bridges between self and other through a process whereby recognition of the actions of others supports self-representation. Importantly, the cortical midline and mirror neuron systems are interconnected at two main points via connections between the PCUN and intraparietal lobule and between medial frontal areas and the inferior frontal gyrus [Uddin et al., 2007].

Schizophrenia has long been recognized as being characterized by profound disturbances to the sense of self involving a loss of ability to direct thoughts and attribute action [Bleuler, 1950; Kircher and David, 2003; Kraepelin, 1896; Sass and Parnass, 2003]. It has also been proposed that schizophrenia is fundamentally a "self-disorder" and that this may provide a unifying account of the seeming heterogeneity of schizophrenia symptoms [Sass and Parnas, 2003]. Sass and Parnass have proposed that schizophrenia involves an ipseity disturbance, that is, of a "first person perspective of the world" which manifests itself through self-alienation, a diminished sense of subjective self-presence and a disturbed grip on and awareness of the salience and stability of external objects. The distinction between self and other can virtually disappear in schizophrenia patients [Sass and Parnas, 2003]. How do our current results relate to this? The key functional link altered in our schizophrenia patients, and correlated with the severity of both positive and negative PANSS scores, involves interconnections between closely related and adjacent structures, the IPL, ANG, and SMG. All of these regions have been reported to be involved in aspects of action awareness, sense of agency, or self-recognition [Farrer et al., 2004, 2008; Fuller Torrey, 2007; Macuga and Frey, 2011] and there is some evidence that they are involved in another common symptom of schizophrenia, illness unawareness [Fuller Torrey, 2007]. We also found significant correlations between specific illness symptoms involving disturbed sense of self and IPL-ANG functional connectivity (notably for presence of delusions, suspiciousness/persecution, somatic concern, and preoccupation). All of these regions have been reported to exhibit structural or functional changes in schizophrenia [Farrer et al., 2004, 2008; Fuller Torrey, 2007]. von Angyal as early as 1934 [von Angyal, 1934] observed that the IPL (including the SMG and ANG) were among the cortical regions most seriously damaged in schizophrenia patients. A recent study has also provided evidence that misattributions of agency in schizophrenia are due to impaired predictions concerning the sensory consequences of one's own actions [Synofzik et al., 2010] in line with proposed comparator model of self discussed above [Christoff et al., 2011]. Consistent with links between these regions and sense of self damage to this general temporoparietal area and parietal lobe epilepsy is also associated with occurrence of psychotic symptoms including delusions and hallucinations [Levine and Finkelstein, 1982; Salanova et al., 1995].

While a disturbed sense of self may be considered as a core symptom of schizophrenia there are clearly many other relevant symptoms and in that respect it is important that this same key circuit involving midline cortical and mirror system structures has also been implicated in disturbed sensory integration (including perceptual dysfunction, blunting of pain perception, stereognosis, graphesthesia, and double-simultaneous stimulation), awareness of body image (including right-left disorientation), and executive function (including attention and working memory deficits, dual-task management and decision making) [see Fuller Torrey, 2007]. The observation in our study that the disrupted link between IPL and ANG was particularly correlated with scores across almost all positive and negative PANSS questions and many general pathophysiology ones, further support is likely to contribute to a diverse range of symptoms, not just those involving the sense of self.

It is interesting to note that the SPG, PCUN, IPL, SMG, and ANG are amongst the last brain regions to reach full developmental maturity and to be larger and more complex in humans than in other species [Cavanna and Trimble, 2006; Fuller Torrey, 2007]. Indeed, the late development of these structures has probably contributed to their widely recognized individual variability in terms of anatomical landmarks [Bailey and Von Brodin, 1951; Ingalls, 1914]. Functional connections involving these regions are therefore potentially vulnerable to developmental and experiential changes over a long period, consistent both with the observed late onset of schizophrenia and its being considered as a developmental disorder [Insel, 2010]. Indeed, recent evidence has shown delayed and altered maturation of some brain regions in schizophrenia [Douaud et al., 2009].

Increased functional connectivity in the AMYG-PHG-HIP pathway in the schizophrenia patients is consistent with the widely reported hyper-responsivity to emotional stimuli and emotional memory changes in schizophrenia patients [Hall et al., 2007; Herbener, 2008] However, while the change between PHG and AMYG correlated positively with negative PANSS scores it did not correlate with illness duration. Similarly the raft of changes in face (IOG-FFG), vocal (HES-STG), and olfactory (REC-OLF) processing pathways are consistent with well established face [Chen et al., 2008; Kohler and Martin, 2006] and odor

recognition [Cumming et al., 2011; Turetsky et al., 2009] deficits and auditory hallucinations [Nenadic et al., 2010]. The altered connectivity between the CAL (V1) and CUN (V2) may also indicate reported dysfunction, in general, visual processing in schizophrenia [Butler and Javitt, 2005]. Changes in motor control networks involving Pre- and Post-CG, PCL, and SMA may reflect aspects of motor dysfunction common in schizophrenia patients [Dazzan and Murray, 2001].

The presence of interhemispheric connection differences in schizophrenia patients is also an issue of great interest. There is a large literature describing laterality changes in Schizophrenia [Crow, 1990; Crow et al., 1989] and abnormalities in the corpus callosum [Crow, 1998]. Our finding of reduced interhemispheric connectivity between a number of the ROIs which correlated with both illness duration and negative PANSS scores is consistent with other studies reporting either structural or functional changes in interhemispheric communication in schizophrenia [Crow, 1990, 1998; Crow et al., 1989; Ribolsi et al., 2009]. It also supports the general hypothesis that schizophrenia is characterized by an extensive pattern of disconnectivity in the brain. Overall, the strength of these functional interhemispheric connections was negatively correlated with illness duration and with negative PANSS scores. However, the major contribution to symptom severity was from the amygdala where connectivity strength between the left and right was strongly negatively correlated with six out of the seven PANSS negative questions (the only exception being lack of spontaneity and flow of conversation) as well as with many of the general pathophysiology ones. The strongest correlation here was for social interactions, including poor rapport, passive/apathetic social withdrawal, lack of spontaneity, and flow of conversation. Connections between the right and left amygdala may be important for controlling coordinated cognitive and emotional responses to threat [Hariri et al., 2003]. Face emotion perception is well known to be impaired in schizophrenia [Mandal et al., 1998] and there is a corresponding reduced activation to emotional faces in the bilateral amygdala [Li et al., 2010]. Part of this may be mediated by the changes between the amygdala and PHG as already discussed, but could also be contributed to by impaired functional connectivity between the left and right amygdala.

An interesting aspect of our findings is that different functional connections were found to correlate with illness duration and symptom severity. Thus in the main altered pathway, the IPL-ANG-SMG components were exclusively associated with symptom severity and the IPL-SPG-PCUN with illness duration. The IOG-FFG was only correlated with illness duration and the AMYG-AMYG and PHG-AMYG connections only with symptom severity. This suggests that illness progression and symptom severity may exert differential effects on functional pathways.

In broad agreement with many other studies [Brambilla et al., 2005; Brambilla and Tansella, 2007; Lui et al., 2009], we observed extensive structural changes in our schizophrenia patients using VBM. These changes were mainly in GM volume (in 58 out of 90 ROIs) although importantly there was no correlation between these and the key changes in functional connectivity we observed. Thus there appears to be no simple correspondence between structural and functional connectivity changes in schizophrenia. While one might perhaps anticipate that functional connectivity and GM volumes in different regions might correlate to some extent we are not aware of any study that has investigated this directly at a whole brain level. Also a recent study has reported only weak non-significant correlations between genetic factors contributing to functional connectivity and GM density in the default network, suggesting a degree of independent regulation [Glahn et al., 2010]. Possibly in our current study, the lack of correlation might reflect compensatory changes that have occurred in functional connectivity following progressive GM volume reductions or alternatively each may contribute independently to symptoms. A recent report has found that reduced GM and WM volumes correlate with dose and duration of anti-psychotic treatment more than with symptom severity in long-term patients [Ho et al., 2011]. While we did not investigate this possibility directly, the lack of correlations in our study between illness duration, symptom severity, and the structural changes we have observed could suggest they are more linked to the effects of anti-psychotic treatments than to the illness *per se*. Interestingly, also many of the structural changes we observed occur in frontal cortical regions which did not figure strongly in key functional connectivity changes.

Given the number of previous studies reporting links between structural and functional changes in the frontal cortex and schizophrenia [Hill et al., 2004; Insel, 2010; Yoon et al., 2008] it is perhaps surprising we found none that were particularly strongly correlated with the illness and none of the well established links between the frontal and parietal regions were implicated either. While this does not necessarily imply a lack of contribution by the changes in these frontal regions to either the development or expression of symptoms of schizophrenia it does suggest that it may not necessarily be the pre-eminent area contributing fundamentally to this disorder and that changes in the temporoparietal region should receive greater consideration in future studies.

A limitation of our study is that all the patients were being treated with a range of antipsychotic medications and these could have contributed to both functional and structural changes observed. Several studies have reported structural and function changes associated with both typical and atypical anti-psychotic treatments [Ho et al., 2011; Lui et al., 2010; Smieskova et al., 2009]. While we cannot rule out some contributory treatment effects a number of the structural and functional changes we have found have also been described in drug-naive patients [see Smieskova et al., 2009] or considered a high risk for developing psychosis [Meisenzahl et al., 2008]. We also found a

remarkably consistent pattern of changes in our patients over a long period of time despite receiving different types and durations of antipsychotic treatments. The atypical Abilify (aripiprazole), which has a somewhat different mode of action compared with other atypicals, in that it is a partial D2 receptor agonist [Kessler, 2007], was also associated with broadly similar patterns of functional and structural changes as all the other antipsychotics. Our patients were mostly being treated with second generation atypical rather than typical antipsychotics and it is the latter which are more associated with causing GM volume reductions [Ho et al., 2011], whereas atypicals are associated with increases [Smieskova et al., 2009].

The brain-wide association study (BWAS) as we reported here [see also Cheng et al., in press] is appealing in that the model is simple and the interpretations are straightforward. However, it also has some limitations. First of all, we ranked each functional link according to the value of its risk difference. We then selected and concentrated on a few top links with the most changed risk difference. The statistical significance of these top links was then assessed and their biological meanings are explored. Certainly, as in the genome-wide association study (GWAS), we can use different statistical quantities such as the odds ratio to rank the altered functional links. Different quantities, for example, the odds ratio and the risk difference, will give us different ranks, although the difference could be small, in particular, when the sample size is large enough. Alternatively, we can rank all altered functional links simply by their *P*-value and a multi-comparison correction was naturally introduced here. The pros and cons of these different approaches is an interesting topic and a detailed and theoretical investigation is beyond the scope of the current paper. On the other hand, although we confined ourselves to ROIs here, our approach can be pushed further to analyze voxel-wise differences by identifying the most changed voxels in the identified ROIs: a typical *post hoc* study. Of course, to choose which approach (including the ICA, seed-based method and methods mentioned above) to tackle your data was finally decided by cross-validations: either by independent data sets or further experiments. From our current results on independent data sets and genotyping results, we concluded that the approach presented in the current paper was the most successful.

In summary, our results using resting-state fMRI to analyze of functional connectivity changes in medicated schizophrenia patients have shown that by far the most affected pathway primarily includes parietal components of the medial cortical and mirror neuron systems involved in a number of self-processing and other sensory, cognitive and executive functions known to be impaired in this disorder. These changes were also widely correlated with a range of positive, negative, and general symptoms of schizophrenia. Additionally, we found evidence for reduced functional connectivity in brain regions involved in aspects of emotional memory processing and also between the two brain hemispheres. These were mainly correlated with negative symptoms. Interestingly, associated structural changes occurring in some of these regions did not correlate with these functional changes and there was no evidence for a major functional contribution from frontal cortical regions.

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