

## “Brain Connectivity Deviates by Sex and Hemisphere in the First Episode of Schizophrenia”—A Route to the Genetic Basis of Language and Psychosis?

Qiang Wang<sup>1,2,21</sup>, Jie Zhang<sup>3,4,21</sup>, Zhaowen Liu<sup>5,6,7,21</sup>, Tim J Crow<sup>8,21</sup>, Kai Zhang<sup>9,21</sup>, Lena Palaniyappan<sup>10,11</sup>, Mingli Li<sup>1,2</sup>, Liansheng Zhao<sup>1,2</sup>, Xiaojing Li<sup>1,2</sup>, Wei Deng<sup>1,2</sup>, Wanjun Guo<sup>1,2</sup>, Xiaohong Ma<sup>1,2</sup>, Wei Cheng<sup>3,4</sup>, Liang Ma<sup>12</sup>, Lin Wan<sup>8,13</sup>, Guangming Lu<sup>9,14</sup>, Zhening Liu<sup>15</sup>, Jijun Wang<sup>16</sup>, Jianfeng Feng<sup>\*,3,4,17–20</sup>, and Tao Li<sup>\*,1,2</sup>

<sup>1</sup>Mental Health Center and Psychiatric Laboratory, the State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Chengdu, PR China; <sup>2</sup>West China Brain Research Center, West China Hospital of Sichuan University, Chengdu, PR China; <sup>3</sup>Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, PR China; <sup>4</sup>Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education, PR China; <sup>5</sup>Life Science Research Center, School of Life Science and Technology, Xidian University, Xi'an, PR China; <sup>6</sup>Engineering Research Center of Molecular and Neuro Imaging Ministry of Education, School of Life Science and Technology, Xidian University, Xi'an, PR China; <sup>7</sup>School of Computer Science and Technology, Xidian University, Xi'an, PR China; <sup>8</sup>POWIC, University Department of Psychiatry, Warneford Hospital, Oxford, UK; <sup>9</sup>Department of Computer and Information Sciences, Temple University, Philadelphia, PA; <sup>10</sup>Robarts Research Institute, University of Western Ontario & Lawson Health Research Institute, London, ON, Canada; <sup>11</sup>Centre for Translational Neuroimaging, Institute of Mental Health, University of Nottingham, Nottingham, UK; <sup>12</sup>Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing, PR China; <sup>13</sup>Interdisciplinary Sciences, Academy of Mathematics and Systems Science, Chinese Academy of Sciences, Beijing, PR China; <sup>14</sup>Department of Medical Imaging, Jinling Hospital, Nanjing University School of Medicine, Nanjing, PR China; <sup>15</sup>Mental Health Center, Xiangya Hospital, Central South University, Changsha, PR China; <sup>16</sup>Shanghai Key Laboratory of Psychotic Disorders (No. 13dz2260500), Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, PR China; <sup>17</sup>Department of Computer Science, University of Warwick, Coventry, UK; <sup>18</sup>Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, PR China; <sup>19</sup>Shanghai Center for Mathematical Sciences, Shanghai, PR China; <sup>20</sup>Zhongshan Hospital, Fudan University, Shanghai, PR China

<sup>21</sup>These authors contributed equally to the work.

\*To whom correspondence should be addressed; Jianfeng Feng: Department of Computer Science, University of Warwick, and Institute of Science and Technology for Brain Inspired Intelligence, Fudan University, Shanghai, PR China; tel:+86-21-65648379, e-mail: [jianfeng64@gmail.com](mailto:jianfeng64@gmail.com) and Tao Li: Mental Health Center, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, PR China; tel: +86-28-85423561, e-mail: [litaohx@scu.edu.cn](mailto:litaohx@scu.edu.cn)

Schizophrenia is genetic in origin and associated with a fecundity disadvantage. The deficits in schizophrenia have been attributed to variation related to the human capacity for language or brain laterality. How sex influences the relative connectivity of the 2 hemispheres is a route to understanding these 2 functions. Using resting-state functional magnetic resonance imaging (fMRI) we searched for sex- and hemisphere-specific changes in whole-brain functional-connectivity in multi-site datasets (altogether 672 subjects including 286 patients, all right-handed) in the first-episode schizophrenia (illness duration  $\leq 1$  year, mostly drug naive) and in chronic stages of schizophrenia (illness duration  $> 1$  year), respectively. We used meta-analyses to integrate data from different sources concerning individuals at the same illness stage. We found first-episode male patients are predominantly left-lateralized in aberrant connectivity with a focus on Broca's area. Female patients show a lesser degree of lateralization than males, but to the right particularly in orbital frontal cortex. In the chronic stage, the focus of aberrant connectivity shifted from anterior to posterior structures with prominent involvement

of the thalamus and pre- and post-central gyri bilaterally and in both sexes. While the “deviant connectivity” is right-sided in both the first-episode and the chronic stages in females, in males there is a shift between stages from the left to the right hemisphere. We hypothesized that the pathophysiology of schizophrenia may lie in the interaction between sex and lateralization, ie, in genetic mechanisms located on the X and Y chromosomes, intrinsic to the evolution of language.

*Key words:* resting-state fMRI/whole-brain functional connectivity analysis/sex-effect/lateralization/language/PCDH11XY/sexual selection

### Introduction

In 1861, Broca<sup>1</sup> recognized that a component of the faculty of articulate speech is localized in the frontal lobes and in the left hemisphere. In a presentation to the Montpellier Medical Society, Dax<sup>2</sup> had reported lateralization of speech 25 years before and by 1839, Pierre Gratiolet

had described the cortical gyri as developing in the frontal lobe on the left before the right, and in the occipital lobe on the right before the left.<sup>3</sup> In 1877, Broca<sup>4</sup> proposed that asymmetry was specific to the human brain, ie, to say that it defined the species and enabled the faculty of language. That hypothesis has proven controversial.

Within 2 years of Broca's conjecture, in what was perhaps the first evolutionary hypothesis of the origins of psychosis and in relation to a postmortem study of brain weight Crichton-Browne<sup>5</sup> wrote that "it seemed not improbable that the cortical centres that are the last organized, which are the most highly evolved and voluntary, and which are supposed to be located on the left side of the brain, might suffer first in insanity". An evolutionary theory is required to explain a lifetime prevalence of schizophrenia approaching 1% becoming more uniform across populations as diagnostic criteria are more strictly drawn,<sup>6</sup> associated with a fecundity disadvantage<sup>7</sup> and in the absence of environmental precipitation. Why does the disorder persist? Why is the genetic variation not selected out?

Differences between the sexes in the onset of schizophrenia have been held to reflect the operation of sexual selection in man.<sup>8</sup> Onsets occur throughout the reproductive phase of life with a sex difference—earlier in males—perhaps by as much as 2–3 years depending on the diagnostic criteria, and outcome is generally worse.<sup>9</sup> The interaction with laterality may hold the key to etiology. Although there has been research on sex differences in functional lateralization in healthy individuals<sup>10–13</sup> and on changes in cerebral lateralization in schizophrenia,<sup>14–16</sup> there has been little on the interaction between sex and laterality in relation to resting-state functional connectivity in disease. Though task functional magnetic resonance imaging (fMRI) may reveal more specific information of functional brain laterality in schizophrenia, in the current work, we focused on resting-state fMRI because it allows for a broader sampling of patient populations, and also that the whole-brain network architectures in task-state fMRI have a high level of similarity with those of resting-state fMRI.<sup>17</sup>

In addition, existing work of laterality of schizophrenia usually calculate the laterality index for a given pair of homologous structures [ie, (left-right)/(left +right)], and focused more on structural fMRI<sup>18</sup> than functional fMRI.<sup>19,20</sup> In comparison, here we first identified the significantly altered resting state functional connectivity, and then seek the laterality patterns of the altered functional connectivity.

Specifically, in a meta-analysis of resting-state fMRI of a total of 672 subjects we address these issues at the onset (illness duration  $\leq 1$  year) and with progression of schizophrenia (illness duration  $> 1$  year). In previous work, we identified functional connectivity change in the inferior frontal gyrus in drug naïve first-episode patients, and in the thalamus in chronic schizophrenia,<sup>21</sup> without specifying the influence of sex. We formulated the hypothesis that if schizophrenia is "the price that *Homo sapiens* pays

for the faculty of language" the developmental course of the illness should be critically dependent on the sex and laterality of the affected individual.

## Materials and Methods

### *Data Quality Control*

To ensure data quality, a control protocol was set up with exclusion criteria as follows: (1) Subjects with poor structural scans, or without complete demographic information and the Positive and Negative Syndrome Scale (PANSS) scores, or age  $< 16$  years old. (2) Head movement: subjects with  $> 10\%$  displaced frames in a scrubbing procedure or maximal motion between volumes in each direction  $> 3$  mm, and rotation about each axis  $> 3^\circ$  were excluded. Patients and controls were screened in each dataset so that the total root mean square displacements did not show significant differences. (3) Left-handed subjects were excluded.

### *Subjects and Data Acquisition*

Resting-state functional scans were collected from 814 subjects (428 patients with schizophrenia and 386 healthy control subjects). Our data is comprised of patient and healthy control data from 5 sources: (1) Huaxi hospital in China (163 schizophrenia patients and 150 healthy controls, first-episode)<sup>22</sup>; (2) Xiangya hospital in China (83 schizophrenia patients and 60 healthy controls)<sup>23</sup>; (3) The Center for Biomedical Research Excellence (COBRE, 71 patients and 74 controls)<sup>24</sup>; (4) The National Taiwan University Hospital in Taiwan (13 first-episode patients and 56 chronic patients, and 62 healthy controls)<sup>25</sup>; (5) Nottinghamshire and Leicestershire community-based mental health teams (42 patients and 40 controls).<sup>26</sup> After quality control, 672 subjects, involving 286 patients with schizophrenia and 386 controls were recruited; patients' demographics are provided in [table 1](#). Here, first-episode patients were defined as having illness duration less than a year, while chronic patients were defined as having illness duration longer than a year. Medication details can be found in the supplement data acquisition.

All patients were identified according to the DSM-IV diagnostic criteria by qualified psychiatrists using all available clinical information including a diagnostic interview, clinical case notes, and clinician's observations. Symptom severity was measured using the PANSS assessment. All healthy subjects were assessed in accordance with DSM-IV criteria as being free of schizophrenia and other axis I disorders, and none had neurological diseases, head trauma, or substance abuse. Written informed consent was obtained from all individual participants, and all of the research procedures and ethical guidelines were approved by the local research ethics committee of the West China Hospital, Second Xiangya Hospital, the Institutional Review Board (IRB) of the Hartford Hospital and Yale University, the IRB of the National Taiwan University Hospital, and

**Table 1.** Demographic and Clinical Characteristics of Patient in Datasets 1# to 5#

Sites	Group	<i>N</i>	Age (Year)	Positive Scale	Negative Scale	General Scale	Duration of Illness (Year)	Medication
1# Huaxi (FE)	Male (C)	80	24.7 ± 7.7					
	Female (C)	70	27.1 ± 9.6					
	Male (P)	53	23.2 ± 6.4	25.1 ± 6.1	19.4 ± 7.8	45.7 ± 9.1	0.29 ± 0.28	All drug-naïve
	Female (P)	60	25.6 ± 8.8	25.7 ± 5.2	18.8 ± 6.2	49.6 ± 8.5	0.19 ± 0.25	All drug-naïve
2# Xiangya (FE)	Male (C)	32	26 ± 5.2					
	Female (C)	25	26.6 ± 6.0					
	Male (P)	26	24.6 ± 5.8	20.2 ± 8.1	23.1 ± 9.7	40.0 ± 14.8	0.42 ± 0.33	14 drug-naïve
	Female (P)	13	25.3 ± 8.0	18.1 ± 4.4	21.1 ± 4.6	39.0 ± 10.0	0.54 ± 0.34	5 drug-naïve
2# Xiangya (chronic)	Male (C)	30	25.3 ± 4.5					
	Female (C)	22	25.1 ± 4.4					
	Male (P)	18	24.7 ± 5.4	21.0 ± 7.3	20.0 ± 6.4	38.7 ± 10.2	2.7 ± 1.1	14 drug-naïve
	Female (P)	13	25.0 ± 7.2	17.1 ± 6.2	18.5 ± 5.3	35.4 ± 9.6	2.9 ± 1.2	5 drug-naïve
3# COBRE (chronic)	Male (C)	44	35.5 ± 11.5					
	Female (C)	21	32.5 ± 9.3					
	Male (P)	33	36.8 ± 14.0	14.8 ± 4.2	15.1 ± 5.3	29.8 ± 8.4	17.0 ± 13.5	Medicated
	Female (P)	9	37.3 ± 12.1	15.6 ± 6.2	13.3 ± 4.7	29.6 ± 8.0	15.6 ± 9.7	
4# Taiwan (FE)	Male (C)	20	27.0 ± 6.0					
	Female (C)	30	27.2 ± 6.4					
	Male (P)	5	21.6 ± 3.5	13.8 ± 3.1	11.2 ± 1.9	28.8 ± 8.4	≤1 years	Medicated
	Female (P)	8	26.0 ± 8.8	17.2 ± 5.7	13.0 ± 5.85	33.6 ± 9.2	≤1 years	
4# Taiwan (chronic)	Male (C)	19	31.0 ± 7.2					
	Female (C)	32	32.3 ± 8.7					
	Male (P)	29	33.8 ± 8.7	10.7 ± 3.4	13.9 ± 5.3	26.0 ± 8.5	8.1 ± 6.2	Medicated
	Female (P)	23	33.1 ± 10.5	13.1 ± 5.5	13.3 ± 7.3	28.5 ± 10.7	6.3 ± 7.0	
5# Nottingham (chronic)	Male (C)	23	31.5 ± 8.0					
	Female (C)	9	34.0 ± 9.7					
	Male (P)	22	33 ± 9					Medicated
	Female (P)	5	33.8 ± 12.8					

Note: C, control; P, patients; FE, first episode.

National Research Ethics Committee, Derbyshire, UK, respectively, for the above 5 datasets. All subjects underwent resting-state functional MRI scanning for 5–7 minutes. All individuals were asked to remain still, think of nothing while remain awake, with eyes open in subjects of datasets 1#, 2#, and 4#, and eyes closed in datasets 3# and 5#. The imaging acquisition protocols for 5 datasets are provided in the supplementary data acquisition.

### Data Preprocessing

All fMRI data were preprocessed by Statistical Parametric Mapping package (SPM8, Wellcome Department for Imaging Neuroscience). The first 10 image volumes of each subject were discarded to allow the fMRI signal to reach a steady state. After slice time correction, the image was realigned and normalized to a standard template (Montreal Neurological Institute) and resampled to  $3 \times 3 \times 3$  mm<sup>3</sup>, and subsequently smoothed with an isotropic Gaussian kernel (FWHM 8 mm).

All fMRI time-series underwent band-pass temporal filtering (0.01–0.08 Hz), nuisance signal removal from ventricles, deep white matter, global mean signal (GMS) and 6 rigid-body motion correction parameters. Considering the concern about the possible influence of excessive movement, we performed the following procedures for motion

correction. We first apply 3-dimensional motion correction by aligning each functional volume to the mean image of all volumes and then implemented a careful data scrubbing (see [supplemental method S1](#) for detail). The mean frame-wise displacement (Jenkinson) was computed with a threshold for displacement of 0.5. One preceding and 2 succeeding time points were also deleted. Subjects with >10% displaced frames were excluded due to the high-level of movement. Finally, the mean displacements after scrubbing were used as a covariate in *t*-tests between control and patient groups. After this, 90 regional time series were extracted by averaging voxel time series within each anatomically defined region (by the Automated-Anatomical-Labeling template<sup>27</sup>). A discussion of global-signal removal can also be found in [supplemental method S1](#).

### Statistical Analysis

**Whole-Brain Functional-Connectivity Analysis** Pearson cross-correlations between all pairs of regional BOLD signals were calculated to reflect the functional connectivity between regional pairs. The whole-brain functional network (90 × 90 network with 4005 edges) was then constructed. For each of the 4005 connection, a 2-sample, 2-tailed *t*-test was performed to identify whether differences between controls and patients were significant for each functional

connectivity link in each dataset, with age, sex, root mean square displacements of head movement, and dosage (if the dataset contains both medicated and drug-naïve patients) being regressed out, and Bonferroni correction applied for multiple statistical comparisons ( $P$ -threshold = .05/4005).

**Sex Effect** To investigate how sex affects alterations in functional connectivity, we compared schizophrenia patients with matched controls of the same sex. That is, we compared male patients with matched male controls, and female patients with matched female controls, to identify sex-specific changes. We also differentiated between first-episode and chronic patients, and analyzed whole brain functional connectivity for each site. The  $P$ -value for each change in functional connectivity was then derived by meta-analysis.

**Meta-Analysis** To combine results from different imaging centers with patients of the same sex and stage, we used the Leptá–Stouffer  $z$ -score method that has been widely used in multi-site gene<sup>28</sup> and MRI data analysis.<sup>29,30</sup> The  $P$ -value of each functional connectivity result from 2-sample  $t$ -tests in each center was converted to the corresponding  $z$  score as in equation:  $z_i = \Phi^{-1}(1 - p_i)$ , where  $\Phi$  is the standard normal cumulative distribution function and  $i$  represent the  $i$  site. A combined  $z$  score for a functional connectivity was then obtained using the Liptak–Stouffer formula:

$$Z = \frac{\sum_{i=1}^k w_i z_i}{\sqrt{\sum_{i=1}^k w_i^2}}$$

which has a standard normal distribution under the null hypothesis; where  $w_i$  is the square root of the  $i$ th dataset. Finally, The  $Z$  is transformed into its corresponding  $P$ -value and a Bonferroni procedure was used to correct for multiple comparisons ( $P$ -threshold = .05/4005).

For first-episode schizophrenia, we integrated results from datasets 1# (first-episode patients), 2# (first-episode patients), and 4# (first-episode patients) for each sex, respectively; For chronic schizophrenia, we integrated datasets 2# (chronic patients), 3# (chronic patients), 4# (chronic patients), and 5# (chronic patients) also for each sex. Note that 2# and 4# contain patients of both first episode and chronic stage. After meta-analysis, we obtained functional connectivity links that are significantly changed in schizophrenia patients compared with matched controls (ie,  $P < .05/4005$ ).

**Patterns of Laterality of Functional Connectivity Changes** After identifying functional connectivity links that are significantly changed in schizophrenia patients through meta-analysis, we then counted the number of altered functional connectivity and relevant brain regions (nodes) in each hemisphere.

The difference between our laterality investigation and traditional laterality studies is that the literatures<sup>12</sup>

usually calculated the laterality index of a pair of symmetric structure in each subject first and then performed group-level analysis. While in our work, we first identified significant group-level functional connectivity changes, and then examined their laterality patterns.

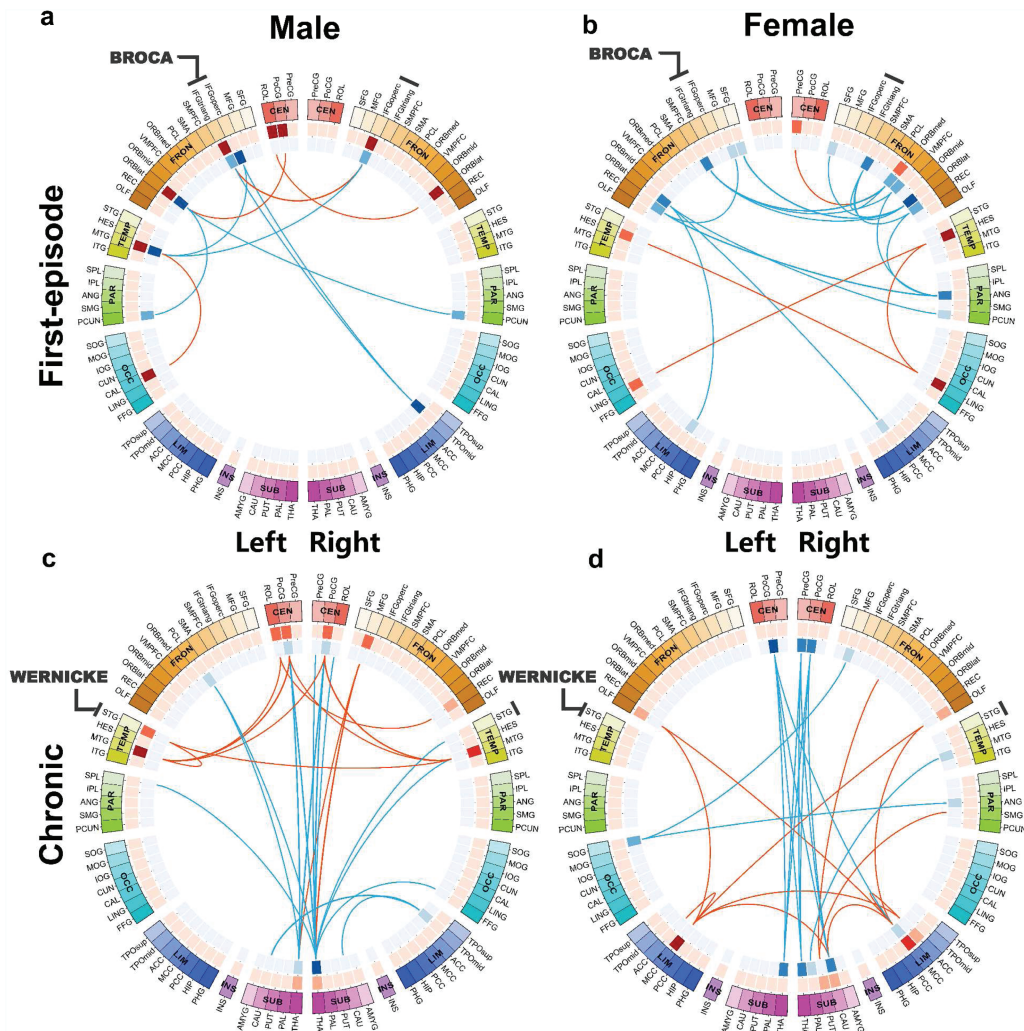
To attach statistical significance to this statistics, we used 60%-sample permutation approach, ie, we randomly pick 60% of the sample in both the patient and control group. After obtained the significantly changed functional connectivity by integrating results for each relevant dataset through meta-analysis, we count the number of nodes pertinent to the altered functional connectivity in each hemisphere ( $N_l$  and  $N_r$ , representing the number of affected nodes in left and right hemisphere). We permute for 1000 times, and get the distribution of  $N_l$  and  $N_r$ . We then evaluate the statistical significance of the following: (1)  $N_l$  and  $N_r$  are significantly larger than 0; (2)  $N_l - N_r$  significantly different from 0 ( $N_l - N_r > 0$  indicated left-laterality, while  $N_l - N_r < 0$  indicated right-laterality).

**Correlation With Symptom Scores** Pearson correlations between symptom score and altered functional connectivity were calculated. Meta-analysis was used to combine data from each illness stage. For the first-episode, the results were obtained integrating datasets 1#, 2#, and 4#, and for the chronic stage, by integrating datasets 2#, 3#, 4#, and 5#.

## Results

### *Lateralization of Functional Connectivity Changes in First-Episode Schizophrenia*

In the first-episode in male patients functional change (number of brain regions, or nodes affected) was more frequent in the left (8 nodes) than right hemisphere (4 nodes), with 60%-sample permutation test showing that  $N_l - N_r$  significantly larger than 0 ( $P < .001$ ,  $N_l$  and  $N_r$  represent the number of affected nodes in left and right brain hemisphere, respectively). While in female patients it was more frequent in the right (12 nodes) than left (8 nodes), with 60%-sample permutation test showing  $N_l - N_r$  significantly smaller than 0 ( $P = .002$ ). Notably males had changes in connectivity to the components of Broca's area (Brodmann areas 44, the triangular inferior frontal gyrus, and Brodmann areas 45, the opercular inferior frontal gyrus) in the left hemisphere in 5 of 10 of their deviant connections whereas females had no such connections (figures 1a, 1b and 2, table 2, supplementary table S1; Fisher's exact test  $P < .05$ ). Alterations were more widely spread in female patients than in males, including structures on the medial (bilateral superior) and orbital (inferior and superior) frontal and lateral surfaces (the lingual and Heschl's gyri—both affected bilaterally in first episode female patients; figures 1a, 1b and 2, table 2, supplementary table S1). Notably, the orbital part of inferior frontal gyrus is the only node to be changed



**Fig. 1.** Sex-specific functional connectivity changes for first-episode (a and b) and chronic (c and d) schizophrenia patients. Meta-analysis is performed combining 3 first-episode datasets (1#, 2#, and 4#) for each sex, and by comparing male patients with matched male controls (a) and comparing female patients with matched female controls (b). Similarly, for chronic schizophrenia. Meta-analysis is performed combining 4 chronic datasets (2#, 3#, 4#, and 5#) for each sex (c for male patients and d for females). The color of the 3 circles (from outside to inside) denotes the 90 different automatic anatomical labeling (AAL) regions (the first circle); the number of increased links (the second circle, deep red means a region has more increased links); the number of decreased links (the third circle, deep blue means a region has more decreased links). Here, the increased/decreased links means the functional connectivity in patients is larger/smaller compared to controls. Broca's area (inferior frontal gyrus, triangular and opercular part) and Wernicke's area (superior temporal gyrus) are both marked in the figure.

in disease in both hemispheres in both males and females at the time of the first episode ([supplementary table S1](#)).

*Lateralization of Functional Connectivity Changes in Chronic Schizophrenia*

In the chronic stage, functional alterations for patients of both sexes extended posteriorly ([figures 1c, 1d](#) and [2, supplementary table S2](#)). Both sexes demonstrate significant change in thalamo-cortical connections, with 5 such connections (bilateral thalamus to bilateral postcentral gyrus and right thalamus to right precentral gyrus; [figures 1c, 1d](#) and [2, supplementary table S2](#)) altered in common to patients of both sexes.

As the focus of aberrant connectivity moves posteriorly in both sexes, with the females preceding the males, males who were left-lateralized in the first episode (L: R ratio 8:4 for number of affected nodes) now become right-lateralized (L:R ratio 8:11) in the chronic stage, with 60%-sample permutation test showing  $N_l - N_r$  significantly smaller than 0 ( $P = .006$ ). Female patients still demonstrate a right-laterality in chronic stage, with L: R = 6:14 (60%-sample permutation test showing  $N_l - N_r$  significantly smaller than 0 ( $P < .001$ )).

[Figures 1c](#) and [d](#) also illustrates a possible sex difference with respect to sensory modality. In males, there is evidence of changed function in the temporal lobe (the

**Table 2.** The Number of Affected Nodes/Connections in First-Episode Patients (a) and in Chronic Patients (b) in Both Hemispheres and for Both Sexes

Hemisphere	Males		Females	
	Left	Right	Left	Right
<b>a. First-episode</b>				
Total nodes affected	8	4	8	12
Total connections	10	6	11	17
Intra-hemispheric	4	0	2	8
Paired nodes	3 pairs		7 pairs	
	Precuneus		SFG dorsolateral	
	IFG opercular		IFG orbital	
	IFG triangular		SFG medial	
			Rectus	
			Posterior cingulate	
			Lingual gyrus	
			Heschl gyrus	
Broca's area	Left	Right	Left	Right
Total nodes	2	1	0	0
	IFG opercular	IFG opercular		
	IFG triangular			
Total connections	4	2	0	0
<b>b. Chronic</b>				
Total nodes	8	11	6	14
Total connections	15	19	14	21
Intra-hemispheric	5	9	3	10
Paired nodes	5 pairs		5 pairs	
	Rolandic operculum		Olfactory cortex	
	Postcentral gyrus caudate		Anterior cingulate	
	Thalamus		Middle cingulate	
	Middle temporal gyrus		Post-central gyrus	
			Thalamus	
Wernicke's area	Left	Right	Left	Right
Total nodes	1	1	0	0
Total connections	2	1	0	0

*Note:* The statistical significance of the number of affected nodes: under 60%-sample permutation, for all cases in table 2,  $N_l$  and  $N_r$  (represent the number of affected nodes in left and right brain hemisphere, respectively) are significantly larger than 0. For first-episode male patients/matched controls,  $N_l - N_r$  is significantly larger than 0 ( $P < .001$ ), ie, left lateralized; for first-episode female patients/matched controls,  $N_l - N_r$  is significantly smaller than 0 ( $P = .002$ ), ie, right lateralized. For chronic male and female patients,  $N_l - N_r$  are both significantly smaller than 0 ( $P = .006$  and  $P < .001$ , respectively), indicating right lateralization of altered functional connectivity. Total nodes, number of affected structures; total connections, number of connections between nodes; intrahemispheric connections, both affected ends in the same hemisphere; paired nodes, the same node affected in both hemispheres.

superior temporal gyrus on the left and middle gyrus on both sides) in association with the precentral gyrus bilaterally. In females, there is an indication of changed function bilaterally in olfactory pathways in association with the anterior and dorsal cingulate gyrus and the precentral gyrus on both sides.

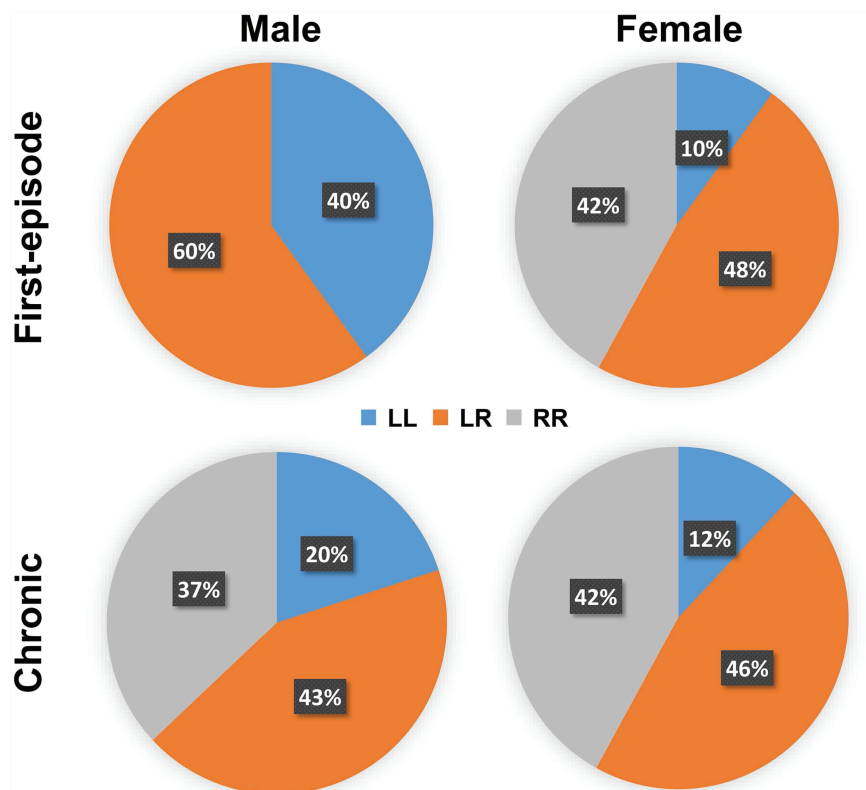
#### *Sex-Specific Laterality Patterns of Functional Connectivity Change*

In first-episode patients, there is a striking difference between the sexes in selectivity of the affected connections by hemisphere. In males, none of the affected connections are confined to the right hemisphere (RR in figure 2). For female patients, half of the connections (9 out of 19) are associated with the right hemisphere, and only 2 out of 19 connections—of the

orbital frontal gyrus—are between structures both located in the left hemisphere (LL), figure 2. In the chronic stage, both male and female patients show right laterality in functional connectivity changes, with female patients showing a higher level of right-laterality, figures 1 and 2.

#### *Group by Sex Effect to the Laterality Pattern of Altered Functional Connectivity*

To determine if there are group by sex effect to the laterality pattern observed, we performed a group by sex ANOVA analysis for the altered functional connectivity links we identified for both the first-episode and chronic schizophrenia patients. The links with significant sex by group effect ( $P < .05$ ) were marked in Table S1 (in italic). A reexamination of their laterality patterns for the 4



**Fig. 2.** Percentage of significantly altered functional connectivity that belong to inter-hemispheric (LR) or intra-hemispheric (left to left: LL; right to right: RR) connections for both sexes in first-episode and chronic schizophrenia patients.

groups (first-episode male patients, first-episode female patients, chronic male patients, and chronic female patients) still demonstrate the same laterality patterns as we identified previously.

#### *Correlation With Symptom Scores*

In first-episode males, functional connectivity between left inferior triangular and right inferior opercular frontal gyri was correlated with delusions (Table S3a). In females, connectivity between the posterior cingulate gyrus and the left inferior orbital frontal gyrus correlated with hostility and poor impulse control (Table S3b). In the chronic state, there were significant clinical correlations involving the thalamus in males (with suspiciousness and anxiety; Table S4a) and in females (including hostility and excitement; Table S4b). At the level of the cortex, the significant connectivity with symptom score was largely with the right hemisphere, but in males with right middle frontal or temporal gyri, whereas in females almost exclusively with right pre- and postcentral gyri.

Some negative findings should be noted. There was little evidence of disturbed connectivity with the insula, amygdala, or hippocampus, subcortical structures in which abnormality in schizophrenia is often invoked. The findings in general relate to functions of the cortex rather than to subcortical structures (apart from the thalamus as noted above).

#### **Discussion**

Whatever the origin of the deviation in connectivity in psychosis the factor of sex must be taken into account. With the same diagnosis, females in the first episode had more widespread functional connectivity changes than males and these were more likely to be in the right hemisphere. In males, the changes were less numerous, predominantly left-sided and targeted to Broca's area. In transition to the chronic condition, the focus of pathology in both sexes shifted from the anterior to the posterior half of the brain, but in males from the left to the right hemisphere, with the focus of aberrant connection moving toward the females from whom they were earlier largely separated by the mid-line. Of particular note, the males who in the first episode had connectivity changes strongly lateralized to the left hemisphere (Left: Right 8:4) in the chronic state had changes lateralized to the right (Left: Right 8:11). The deficit can be characterized as a decrease or loss of lateralization. Symptoms follow the hemispheric pattern of aberrant connectivity. In the first episode, significant change in functional connectivity at the cortical level was predominantly in the left hemisphere particularly in females, see Table S3. In the chronic state such correlations were all but one located in the right hemisphere and associated, respectively, with the mid-temporal and mid-frontal gyri in males and pre- and postcentral gyri in females, Table S4.

### *Sex Difference in Laterality of Functional Connectivity Changes in Schizophrenia*

“Given that schizophrenic illnesses are generally associated with earlier onset and worse outcome in males the more widespread distribution of aberrant connectivity in females requires explanation. One possibility is that (1) cortical complexity goes on developing in an antero-posterior direction into the third and fourth decades of life; (2) a sex difference (with some anterior components greater in males and posterior components greater in females) reflects earlier, faster lateralization in females; who avoid aberrant connections in the frontal lobes that males, developing more slowly, encounter at a younger age with subsequent greater risk of negative symptoms, eg, poverty of speech.”<sup>31</sup>

Whereas language is often regarded as a left hemisphere function a body of evidence<sup>32</sup> is consistent with the concept that it involves both hemispheres. Separate components are located in either hemisphere,<sup>25,33</sup> aligned along the antero-posterior sensory-motor axis to confer a 4 quadrant structure on the human brain.<sup>34</sup> Phonological components, both motor and sensory and grammar are located in the left hemisphere and semantic components to a greater extent in the right. Language deficits in schizophrenia are more severe in males than females<sup>35</sup> and increase in severity from phonology to semantics to grammar (syntax). In contrast, in ill females grammar is least affected.

Sex differences in brain structure have been little studied in psychosis. Only one of 11 meta-analyses<sup>36</sup> of magnetic resonance imaging voxel-based morphometry (VBM) took sex systematically into account but this study did so with singular effect. In schizophrenia and bipolar illness, Bora et al<sup>37</sup> found that when all studies were included without respect to sex (ie, with the expected excess of early onsets of schizophrenia in males included) there was loss of substance in the insula and anterior cingulate gyrus on both sides together with loss in the region of the hippocampus and para-hippocampal gyrus on the left side. When studies were selected for equality of the sex ratio the pattern of findings was notably different. In schizophrenia, the losses were in the insula and lateral sulcus on the left side and the anterior cingulate gyrus on the right. In bipolar disorder, the losses were in the insula/lateral sulcus on the right and the anterior cingulate on the left. Thus with respect to structure as well as function schizophrenia and bipolar disorder are related to each other on a continuum of laterality, and the continuum interacts with sex.

### *The Role of Cerebral Dominance in Language and Schizophrenia*

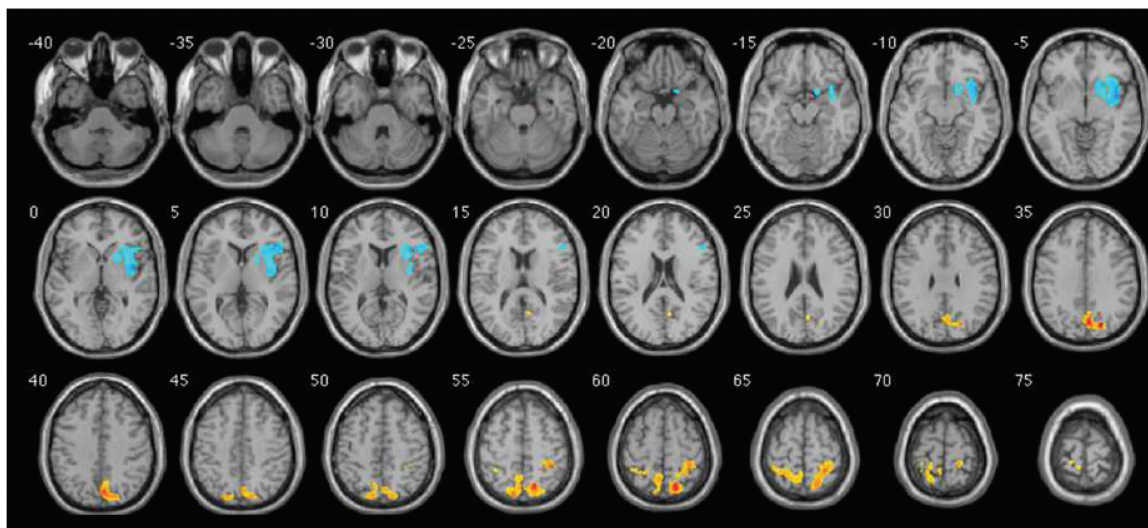
Where and what is the cerebral dominance gene? On the basis of genome-wide association studies (GWAS), it is claimed that predisposition to psychosis is highly

polygenic and that the genes are predominantly autosomal.<sup>38</sup> The present findings indicate that an interaction between sex and laterality of major effect has yet to be accounted for. Following Broca, it has been argued that a gene for cerebral dominance was pivotal to the evolution of *Homo sapiens*<sup>39,40</sup> but the search for a genetic correlate of handedness<sup>41–43</sup> or schizophrenia<sup>41,44,45</sup> by linkage has yielded inconsistent findings, as also have association studies of handedness.<sup>46</sup> The difficulty is exemplified by a micro-array study in which the expression of 3000 genes was assessed at 11 pairs of corresponding sites in the 2 hemispheres in 15 pre- and postnatal epochs of development.<sup>47</sup> No consistent asymmetry of expression was observed for any gene at any site or developmental stage.

The answer probably lies in observations on sex chromosome aneuploidies.<sup>48</sup> Turner’s syndrome individuals with only one X (XO) have spatial deficits (right hemisphere’s deficit), while Klinefelter’s syndrome (XXY) and XXX individuals with an extra X, and XYY individuals, with an extra Y each have language problems (left hemisphere). Thus, it is possible that loss of a sex chromosome (X or Y) impairs the development of the right hemisphere, whereas the presence of an extra X or Y impairs left hemisphere. The hypothesis was proposed that cerebral dominance is carried by a gene pair with homology between X and Y chromosomes.<sup>49</sup> In an MRI comparison, frontal lobe deficits in gray matter were found in the XYY syndrome individuals exclusively on the right side (figure 3),<sup>50</sup> suggesting that a gene with an influence on anatomical asymmetry is located on the Y chromosome.

These findings direct attention to the Y and its interaction with the X chromosomes in cerebral dominance and also, our observations indicate, in schizophrenia. Whereas the gene-pair in pseudo-autosomal region 1 (PAR1—within which recombination between X and Y sequences maintains strict sequence homology) is shown to be relevant<sup>51–53</sup> such a gene would not explain sex differences. An XY homologous gene-pair with the Y homologue within the nonrecombining region<sup>49,54</sup> can explain such a difference (as in the absence of recombination the X and Y gene sequences will diverge over evolutionary time) and may explain the genetic predisposition to psychosis.<sup>55,56</sup> Finally, it is likely that a solution to both problems lies in the origin of the species<sup>57,58</sup>: a “species identifier” is created from the pattern of genes on the X chromosome that is protected from inactivation in male meiosis and thus is active on the inactive X in females. This pattern is being formed by the combination of X and Y chromosome changes specified above, and stabilized in the XY body in male meiosis by the speciation gene PRDM9.<sup>59</sup> This gene has the capacity to change the motif that localizes sites of recombination across the genome. The theory incorporates the notion of a saltation (a jump or discontinuity) between successive species,<sup>56</sup> and depends on the generation of a single sexual dimorphism as the distinctive core of each species.





**Fig. 3.** Distribution of gray matter deficits (blue) in XYY individuals, from Legrance et al.,<sup>50</sup> with kind permission from the authors. Orange indicates gain of tissue.

### Strengths and Weaknesses

Some strengths and shortcomings have to be borne in mind. The strength is that we have used the largest dataset yet to report sex-specific functional changes in schizophrenia, and a meta-analytic approach that integrates results from multiple sites. Traditional validation tests whether an observation survives a type I error in multiple datasets. Meta-analysis is more appropriate here as it assesses the effect-size distribution rather than individual observations across arbitrary thresholds. A limitation, however, is that while most first-episode patients are drug-naïve and the result from first-episode populations is minimally confounded by medication, chronic patients are mostly medicated at the time of assessment. We assessed the possible influence of medication by examining medication dose of patients and altered functional connectivity strength differences between medicated and drug-naïve patients. For first-episode patients (in dataset 2#), we find no functional connection showing significant correlation with medication dosage. For the chronic stage schizophrenia (dataset 3#), only one connection shows a weak correlation ( $P = 0.0506$ , uncorrected) between medication dose of female patients and functional connectivity strength, see [Table S5](#), indicating the influence of medication is limited. It is also beneficial to adopt an individual-based parcellation scheme<sup>60,61</sup> for our analysis, considering the individual variability.<sup>60</sup> Finally, our hypothesis of the underlying genetic mechanism related to the X and Y chromosomes needs to be scrutinized with further genetic data, which remains to be our future work.

### Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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