Psychiatry Research: Neuroimaging 224 (2014) 303–310

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Reduced structural integrity and functional lateralization of the dorsal language pathway correlate with hallucinations in schizophrenia: A combined diffusion spectrum imaging and functional magnetic resonance imaging study

Chen-Hao Wu [a,b,1], Tzung-Jeng Hwang [c,d,1], Pin-Jane Chen [e], Tai-Li Chou [d,e,*], Yung-Chin Hsu [b], Chih-Min Liu [c,d], Hsiao-Lan Wang [b], Chung-Ming Chen [a], Mau-Sun Hua [e], Hai-Gwo Hwu [c,d], Wen-Yih Isaac Tseng [a,b,d,f,**]

[a] Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan
[b] Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, Taipei, Taiwan
[c] Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan
[d] Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan
[e] Department of Psychology, National Taiwan University, Taipei, Taiwan
[f] Department of Medical Imaging, National Taiwan University Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 25 November 2013
Received in revised form
15 June 2014
Accepted 15 August 2014
Available online 3 September 2014

Keywords:
Schizophrenia
Auditory verbal hallucinations
Language network
Diffusion spectrum imaging
Functional MRI

ABSTRACT

Recent studies suggest that structural and functional alterations of the language network are associated with auditory verbal hallucinations (AVHs) in schizophrenia. However, the ways in which the underlying structure and function of the network are altered and how these alterations are related to each other remain unclear. To elucidate this, we used diffusion spectrum imaging (DSI) to reconstruct the dorsal and ventral pathways and employed functional magnetic resonance imaging (fMRI) in a semantic task to obtain information about the functional activation in the corresponding regions in 18 patients with schizophrenia and 18 matched controls. The results demonstrated decreased structural integrity in the left ventral, right ventral and right dorsal tracts, and decreased functional lateralization of the dorsal pathway in schizophrenia. There was a positive correlation between the microstructural integrity of the right dorsal pathway and the functional lateralization of the dorsal pathway in patients with schizophrenia. Additionally, both functional lateralization of the dorsal pathway and microstructural integrity of the right dorsal pathway were negatively correlated with the scores of the delusion/hallucination symptom dimension. Our results suggest that impaired structural integrity of the right dorsal pathway is related to the reduction of functional lateralization of the dorsal pathway, and these alterations may aggravate AVHs in schizophrenia.

1. Introduction

Auditory verbal hallucinations (AVHs) are one of the main diagnostic features in schizophrenia (de Weijer et al., 2013). Earlier neuroimaging studies of schizophrenia found structural and functional alterations of the language network (Allen et al., 2008; Glahn et al., 2008; Li et al., 2009), and the alterations of the language network were found to associate with AVHs (Allen et al., 2008, 2012; Benetti et al., 2013).

Lesion studies of the 19th century and modern neuroimaging studies have identified specialized brain regions for language processing, namely, Broca's area (left Brodmann's area (BA) 44 and 45) for speech production (Broca, 1861), Wernicke's area (left BA 22) for speech comprehension (Wernicke, 1874), and the arcuate fasciculus for information transfer between these two regions (Catani et al., 2005; Glasser and Rilling, 2008; Li et al., 2009). Previous diffusion tensor imaging (DTI) studies investigating the perisylvian language pathways in schizophrenia have shown that schizophrenic patients exhibit reduced fractional anisotropy (FA) in the bilateral arcuate fasciculi and that these decreases in FA are associated with AVHs (Catani et al., 2011;

* Corresponding author at: Department of Psychology, National Taiwan University, No. 1, Section 4, Roosevelt Road, Taipei 106, Taiwan. Fax: +886 2 23631463.
** Corresponding author at: Center for Optoelectronic Biomedicine, National Taiwan University College of Medicine, No. 1, Section 1, Jen-Ai Road, Taipei 10051, Taiwan. Fax: +886 2 23926922.
E-mail addresses: tlchou25@ntu.edu.tw (T.-L. Chou), wytseng@ntu.edu.tw (W.-Y. Isaac Tseng).
[1] These authors contributed equally to this study.

http://dx.doi.org/10.1016/j.pscychresns.2014.08.010
0925-4927/

de Weijer et al., 2013; van den Heuvel and Fornito, 2014). Increasing evidence provided by functional magnetic resonance imaging (fMRI) studies suggests that schizophrenia is associated with a reduction in the typical pattern of left-greater-than-right lateralization of language processing (Sommer et al., 2001; Kubicki et al., 2003; Weiss et al., 2006; Razafimandimby et al., 2007). Sommer et al. (2001) reported that decreased functional lateralization in schizophrenia was associated with the severity of AVHs.

Recently, a dual stream model was proposed for language processing (Hickok and Poeppel, 2004; Borowsky et al., 2006). In addition to the arcuate fasciculus, which serves as the dorsal pathway that maps sound to articulation (Hickok and Poeppel, 2007; Rilling et al., 2008), a ventral pathway has been proposed to be responsible for mapping sound to meaning (Saur et al., 2008, 2010). Using probabilistic diffusion tractography and fMRI, Saur et al. (2008) were able to demonstrate the fiber pathways of the dorsal and ventral streams and their functional significance. The ventral pathway is mainly composed of the inferior fronto-occipital fasciculus, which interconnects the orbital part of the inferior frontal gyrus (BA47) and middle temporal gyrus (BA 21) (Hickok and Poeppel, 2004; Seghier et al., 2011; Weiller et al., 2011). Using stochastic tractography, Kubicki et al. (2011) found that patients with schizophrenia demonstrated decreased microstructural integrity in the ventral language pathway.

Although alterations of the structure and function in the language network have been extensively studied in schizophrenia (Allen et al., 2008; Whalley et al., 2012; Benetti et al., 2013), the structural components underlying the network's relationship to reduced functional lateralization has not yet been defined. Knowledge about the involvement of the ventral pathway in schizophrenia is not advanced, especially compared with that concerning the dorsal pathway. By studying both the structure and function of the dual stream model, we may obtain a more complete understanding of how these aspects are altered in schizophrenia and how the observed alterations relate to each other.

Thus, the present study aimed to investigate the structural and functional alterations of the dual stream language network and their associations with AVHs. We used diffusion spectrum imaging (DSI) to reconstruct the dorsal and ventral pathways and measured the microstructural integrity for each of these pathways. Furthermore, we used fMRI in a semantic task to obtain information about functional activation in corresponding regions of the dorsal and ventral pathways. Structural asymmetry and functional lateralization were computed from the DSI and fMRI results, respectively. Specifically, we attempted to define the structural counterpart of the altered functional lateralization in schizophrenia.

2. Methods

2.1. Participants

Participants comprised 18 right-handed adults with schizophrenia and 18 healthy adult controls. Handedness was measured with the Edinburgh Handedness Inventory (Oldfield, 1971). All participants met the following inclusion criteria: (1) score above 80 on the verbal scale of the Wechsler Adult Intelligence Scale (WAIS-III), (2) native Mandarin-Chinese speakers, and (3) normal or corrected-to-normal vision. Patients were recruited from the outpatient clinics of the Department of Psychiatry at the National Taiwan University Hospital. Patients met with the following criteria: (1) DSM-IV diagnosis of schizophrenia, (2) no lifetime history of substance use problems within the past 6 months, (3) no neurological disorders such as epilepsy or stroke, and (4) no major systemic physical illness.

Patients were assessed using the Positive and Negative Syndrome Scale (PANSS). The PANSS raters received training annually with acceptable reliability (intraclass correlations ranged from 0.66 to 0.89 for the PANSS items). The healthy controls were also interviewed to ensure the absence of a history of psychiatric disorders or major medical illnesses. The Research Ethics Committee of the hospital approved the study, and all subjects provided their informed consent before participation.

2.2. MRI data acquisition

Participants were scanned on a 3-Tesla MRI scanner (Trio, Siemens, Erlangen, Germany) with a 32-channel phased array head coil. Head movement was restricted with expandable foam cushions. The slice orientation of all of the axial images was parallel to the anterior-commissure/posterior-commissure line.

2.2.1. Structural MRI

High-resolution T1-weighted images were acquired using a magnetization-prepared 3D gradient echo sequence: repetition time (TR)=1560 ms; echo time (TE)=3.68 ms; flip angle=15°; matrix size=256 × 256; field of view (FOV)=256 × 256 × 192 mm^3; and slice thickness=1 mm. Axial T2-weighted images were also acquired using a fast spin echo sequence with 34 contiguous slices that covered the entire brain: TR=5920 ms; TE=102 ms; flip angle=150°; matrix size=256 × 256; FOV=248 × 248 mm^2; and slice thickness=3 mm.

2.2.2. Diffusion spectrum imaging

Diffusion-weighted images (DWIs) were acquired using a spin-echo diffusion echoplanar imaging (EPI) sequence with a twice-refocused balanced echo (Reese et al., 2003). The DWI volumes were acquired by applying diffusion-sensitive gradients of different strengths and directional combinations at isotropic grid points within the diffusion-encoding space (*q*-space) (Wedeen et al., 2005). A total of 102 DWI volumes within a half sphere of the *q*-space were acquired, where the maximum diffusion sensitivity value (*b*-value) corresponding to the radius of the sphere was 4000 s/mm^2. The acquisition scheme was a modified version (a half sphere rather than a full sphere) of the optimal *q*-space sampling method, DSI 203, as previously described (Kuo et al., 2008). Other acquisition parameters included the following: TR=9600 ms; TE=130 ms; matrix size=80 × 80; FOV=200 × 200 mm^2; and slice thickness=2.5 mm without gap. The scan time for each DSI acquisition was approximately 16.5 min.

2.2.3. Functional MRI

A meaning judgment task was used to explore the dual pathways (Lo et al., 2013). Two Chinese characters were visually presented sequentially. Participants were asked to determine whether the characters were related in meaning. The trials lasted for 4500 ms and consisted of a solid square (500 ms) followed by the first character (800 ms), a 200-ms blank interval, and the second character (3000 ms). The participants were instructed to respond during the presentation of the second character. The participants were instructed to quickly and accurately press the “yes” button to semantically related pairs and the “no” button to semantically unrelated pairs. The trial also included 24 baseline events, in which participants were instructed to press a button when a solid square (1300 ms) at the center of the visual field turned into a hollow square (3000 ms) following a blank interval (200 ms). The stimulus characteristics were the same as those described by Chou et al. (2009).

An event-related design was used for the fMRI study. Functional images were acquired via a gradient-echo EPI sequence to detect a blood oxygenation level-dependent signal. The scanning parameters were as follows: TR=2000 ms; TE=24 ms; flip angle=90°; matrix size=64 × 64; FOV=256 × 256 mm; slice thickness=3 mm; and number of slices=34. Each participant performed two functional runs; each functional run consisted of 136 image volumes that lasted for approximately 4.7 min. The task was administered in a pseudo-random order to each participant, in which the order of trials was optimized for the event-related design (Burock et al., 1998).

2.2.4. DSI data reconstruction

After acquisition of the DSI data, the diffusion probability density function (PDF) was obtained based on the Fourier relationship between the PDF and *q*-space signal (Callaghan et al., 1991). The orientation distribution function (ODF) was computed by obtaining the second moment of the PDF along each of the 362 radial directions (6-fold tessellated icosahedron). To quantify the microstructural integrity of the white matter in the dorsal and ventral language pathways, a generalized fractional anisotropy (GFA), which is the DSI index equivalent to the DTI index FA (Gorczewski et al., 2009; Fritzsche et al., 2010), was computed for each voxel using the following formula: (standard deviation of the ODF)/(root mean square of the ODF) (Tuch, 2004). To determine the fiber directions in each voxel, an iterative approach was used to decompose the ODF into several constituent Gaussian ODFs (Yeh et al., 2011). The resulting fiber direction field was used for tractography.

2.2.5. Tractography procedure

To minimize the variation of region of interest (ROI) placement in the individual DSIs, ROIs for constructing a specific tract bundle were defined and adjusted only once in a DSI template. The procedure of defining ROIs to perform tractography in each individual's DSI data is summarized as follows: (1) ROIs in Montreal Neurological Institute (MNI) space were selected using MARINA software; (2) the ROIs were transformed from MNI space to a template space (Hsu et al., 2012a); (3) the ROIs in the template space were adjusted to reconstruct the four fiber tracks; (4) the adjusted ROIs were transformed from the template space to the

native DSI space; and (5) the fiber tracts were reconstructed in the native DSI space without further adjustment of the ROIs.

We used MARINA software (Bender Institute of Neuroimaging, University of Giessen, Germany) to define the cortical regions in MNI space. The ROIs for reconstruction of the dorsal and ventral pathways were selected in the same regions as those used by Saur et al. (2008). For the dorsal pathway, the bilateral superior temporal gyri and opercular part of the inferior frontal gyri were selected as the ROIs (Fig. 1a). For the ventral pathway, the ROIs were located in the bilateral middle temporal gyri and orbital part of inferior frontal gyri (Fig. 1d). These ROIs in MNI space were transformed to the DSI template space using Statistical Parametric Mapping-8 (SPM8) software. The shape of the ROI in the DSI template space was adjusted to a sphere with a radius of 5 voxels, where the center of the sphere was the same as the centroid of the ROI before adjustment. The size and location of the ROIs were further adjusted until the reconstructed tracts were consistent with those shown in the atlas of Mori and van Zijl (2002) (Fig. 1b, c, e, f). After adjustment of the ROIs in the template space, the ROIs were transformed to the individual native DSI space. The transformation relationship between the individual DSI and template DSI was estimated using the LDDMM-DSI method with the same parameters previously used (Hsu et al., 2012b).

After ROIs in the native DSI space had been obtained, deterministic tractography was performed using in-house software (DSI Studio: http://dsi-studio.labsolver.org). For the dorsal and ventral pathways, the angular thresholds were established at 80° and 60°, respectively. In addition, the track lengths of the dorsal and ventral pathways were set between 80 mm and 120 mm and between 120 mm and 180 mm, respectively. Moreover, the tract number for each targeted tract bundle was set to 500.

2.3. Data analysis

2.3.1. Tract integrity analysis

A tract-specific analysis method, known as the mean path algorithm, was used to select the GFA values at voxels that were traversed by the fiber tracts (Chiang et al., 2007). In the present study, we selected the GFA values for the dorsal and ventral pathways separately and then calculated the mean GFA values of each pathway. The details of the tract-specific analysis have been previously described (Lo et al., 2011).

2.3.2. fMRI data analysis

Data analysis was performed using SPM8 software. The functional images were corrected for differences in the slice-acquisition time to the middle volume and were realigned to the first volume in the scanning session using affine transformations. None of the participants demonstrated more than 3 mm of movement within any plane. Co-registered images were normalized to the MNI average template. Statistical analyses were calculated on the smoothed data (10-mm isotropic Gaussian kernel) with a high pass filter (with a 128-s cut-off period) to remove low frequency artifacts.

Data from each of the participants were analyzed based on a general linear model using an event-related analysis procedure. Character pairs were treated as individual events for the analysis and modeled using a canonical HRF (Hemodynamic Response Function). There were three event types: related, unrelated, and baseline. The parameter estimates from contrast analyses of the canonical HRF in the single subject models were entered into a random-effects analysis using one-sample *t*-tests across all of the participants to determine whether activation during a contrast was significant.

The fMRI image analysis focused on the neural activity for the contrast of the related versus baseline conditions in patients and healthy controls separately. Based on the results of the within-group contrasts, we used a two-sample *t*-test to compare the neural activity in the ROIs between patients and healthy controls. For within-group contrasts, there were corrected and uncorrected *P*-values for the analyses because we wanted to show the results for all ROIs. For between-group contrasts, all of the reported areas of activation were significant using $P < 0.05$ FWE (family-wise error) corrected with a sphere radius of 8 mm centered on peak coordinates of three ROIs from a meta-analysis (Wu et al., 2012), including right inferior frontal gyrus [56, 24, 22], left inferior frontal gyrus [−44, 34, 2] and right middle temporal gyrus [58,–44, 0]. Moreover, we extracted the β-values from the peak voxels of the ROIs to quantify the amount of activation occurring in the dorsal and ventral regions of the language network during the meaning judgment task. The ROIs were the same as those used in the diffusion tractography (Fig. 2).

2.3.3. Lateralization indices

The lateralization index (LI) of the microstructural integrity (GFA was used as a measure of structural integrity) and LI of the functional activation (β-value was used as a measure of activation) were calculated using the following formula: LI = (left measure − right measure)/(left measure + right measure) (Powell et al., 2006).

2.3.4. Statistical analysis

Data normality was verified using the Kolmogorov–Smirnov test, and descriptive analysis results were expressed as the mean and standard deviation. The statistical analysis was performed in the following four steps: (1) between-group comparisons of β and GFA values were performed using an analysis of variance (ANOVA) and post hoc comparisons with Fisher's Least Significant Difference (LSD); (2) between-group comparisons of functional LI and structural LI were performed using an ANOVA and post hoc comparisons; (3) the β or GFA values and LI that exhibited significant between-group differences in the two preceding steps were chosen for multiple linear regression analysis in which the chosen functional/structural LI was the dependent variable and the chosen GFA/β values were the explanatory variables; (4) a Pearson correlation was applied to the LI and GFA/β values that were significantly correlated in the multiple linear regression analysis to measure their associations with the dimension scores of delusion/hallucination.

The dimension scores of delusion/hallucination were based on the four symptom dimensions that were empirically derived from the PANSS (Hwu et al., 2002). In addition, Spearman's rank correlation was used to analyze the

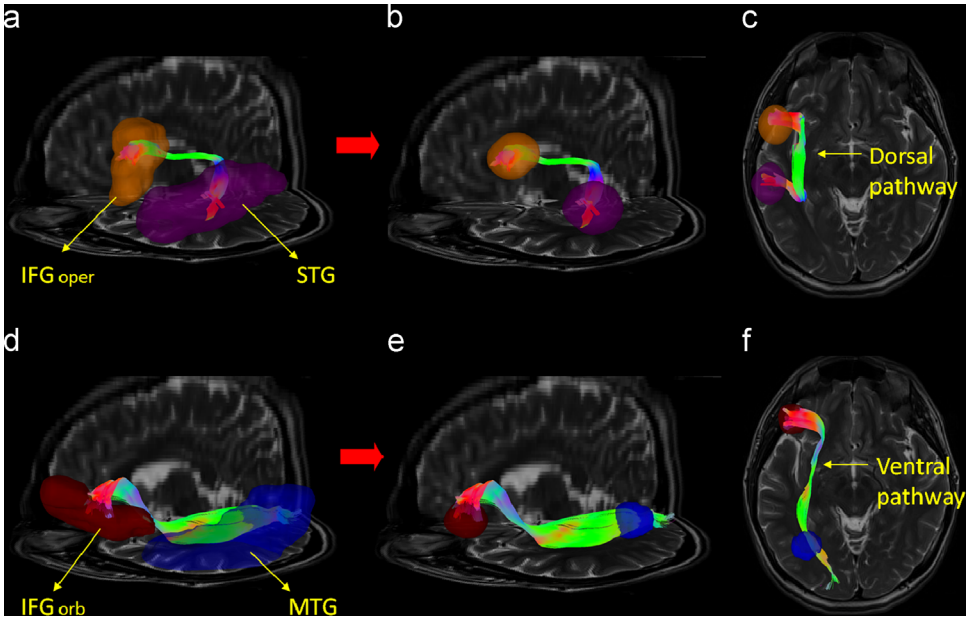

Fig. 1. Three-dimensional tractography renderings visualizing the spatial orientation of the dorsal and ventral pathways (a), (b) sagittal and (c) axial views of the DSI tractography between the IFG oper and STG of the dorsal pathway. (d) and (e) Sagittal and (f) axial view of the DSI tractography between the IFG orb and MTG of the ventral pathway. The ROIs of the IFG oper (orange), STG (purple), IFG orb (brown) and MTG (blue) were chosen and modified into a spherical shape. IFG oper, the opercular part of the inferior frontal gyrus; STG, superior temporal gyrus; IFG orb, the orbital part of the inferior frontal gyrus; MTG, middle temporal gyrus.

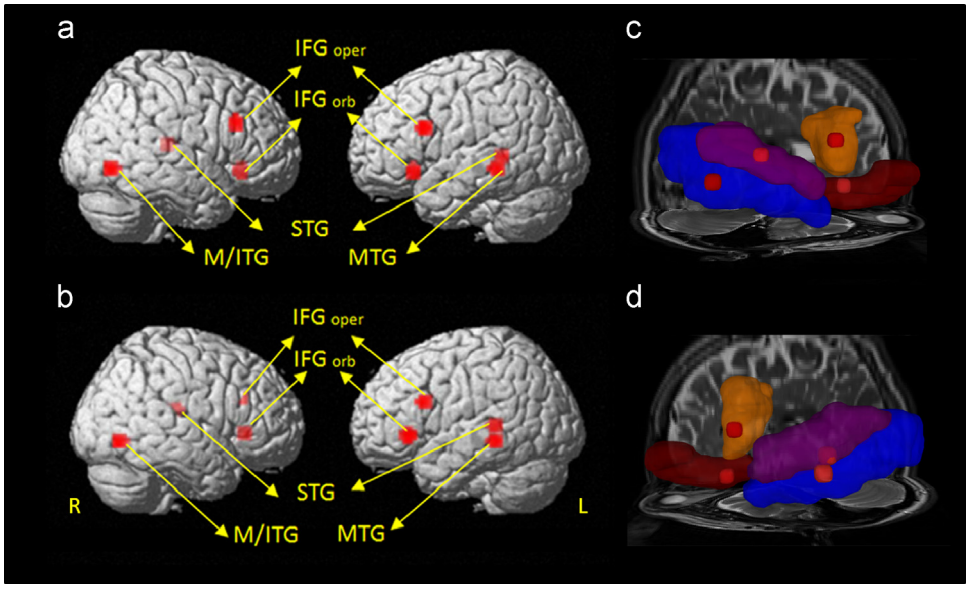

Fig. 2. Functional activation maps of dorsal and ventral pathways in patients with schizophrenia (a), and in healthy controls (b). The regions of interest (ROIs) used in the diffusion tractography for the right dorsal and ventral pathways (c), and for the left dorsal and ventral pathways (d). The peak activation regions (red spheres) of the fMRI are located within the ROIs of the IFG oper (orange), STG (purple), IFG orb (brown) and MTG (blue). L, left hemisphere; R, right hemisphere; IFG oper, the opercular part of the inferior frontal gyrus; IFG orb, the orbital part of the inferior frontal gyrus; MTG, middle temporal gyrus; M/ITG, middle/inferior temporal gyrus; STG, superior temporal gyrus.

associations between the structural and functional LI with the AVHs based on the PANSS item P3.

Statistical comparisons were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL). The significance level for these statistical analyses was defined as $P < 0.05$.

3. Results

3.1. Demographic features and clinical symptoms

The patient and control groups were age-, sex- and handedness-matched (Table 1). Patients were clinically stable with a mean total PANSS score below 60. Of the 18 patients, 11 did not report any AVHs, three reported very mild AVHs (PANSS P3 = 3) and four reported significant AVHs (P3 = 4–6; one patient also endorsed visual hallucinations). Mild AVHs usually consisted of the experience of a voice commenting on the patient, low in volume, brief in duration and associated with no emotional reaction. Significant AVHs included voice commenting and/or conversing with content of a persecutory or controlling nature, higher in volume, longer in duration and associated with emotional reactions. Most of the patients (83%) were treated with atypical antipsychotic agents, including three patients who were taking clozapine. On the basis of a recent proposal by Andreasen et al. (2010), the mean chlorpromazine-equivalent dose of the 18 patients was 314 mg/day (range 79–960 mg/day).

3.2. fMRI measures

The accuracy rate for the related condition was 90% ± 12 in patients and 91% ± 11 in controls. An independent samples *t*-test yielded no significant group difference, $t = -0.45$, $P > 0.05$. The response time for the related condition was 1024 ms ± 144 in patients and 875 ms ± 230 in controls. An independent samples *t*-test revealed a significant difference, $t = 2.32$, $P < 0.05$, where the control group was faster than the patient group.

For the contrast between the related versus baseline conditions, both groups produced greater activation in bilateral inferior frontal gyri (IFG, BA 45/47), bilateral middle/inferior temporal gyri (MTG, BA 21) and bilateral superior temporal gyri (STG, BA 22/41) (Table 2). For the between-groups analysis, patients exhibited greater activation in right IFG (BA 45) and right MTG (BA 21), whereas healthy controls showed greater activation in left IFG (BA 45) (Table 2). In addition, we extracted the β-values of the peak voxels in the ROIs of the dorsal and ventral regions in each group. The total β-values of activation (mean ± SD) in the ROIs of each hemisphere were provided for both groups (Table 3). Patients demonstrated higher β-values at a borderline level of significance in the right dorsal region. The variation of β-values was consistent with findings reported by Kuperberg et al. (2007), partly due to the use of large brain regions as ROIs.

Table 1
Demographic and clinical characteristics of patients with schizophrenia and healthy control subjects.

	Schizophrenia	Control	
	(*N* = 18)	(*N* = 18)	*P*
Sex (male/female)	8/10	8/10	
Age (years)	30.77 (6.14)	29.61 (6.69)	0.589
Handedness (% right)	100	100	
FIQ	97.20 (15.61)	106.17 (10.88)	0.066
Duration of illness (years)	8.61 (4.36)	–	
PANSS positive score	13.27 (5.26)	–	
PANSS negative score	14.83 (5.81)	–	
PANSS general score	26.72 (9.59)	–	
Antipsychotics		–	
Atypical (*n*)	15	–	
Traditional (*n*)	3	–	
Chlorpromazine equivalent (mg)	314 (204)	—	

Note: the means and standard deviations (in parentheses) are provided; FIQ, full scale intelligence quotient; PANSS, Positive and Negative Syndrome Scale.

3.3. DSI and fMRI measures

Table 3 summarizes the DSI microstructural integrity measures (GFA values) and fMRI measures (β-values) in the ventral and

Table 2
Brain regions of activation for the contrast of the related versus baseline conditions.

Brain regions	H	BA	Voxels	*Z* test	MNI coordinates		
					x	*y*	*z*
Patient group							
Inferior frontal gyrus (opercular)	L	45	244	4.64[a]	−51	14	22
	R	45	24	2.76[b]	51	26	25
Inferior frontal gyrus (orbital)	L	47	776	5.19[a]	−48	29	−5
	R	47	7	2.50[b]	30	29	−11
Middle temporal gyrus	L	21	257	4.63[a]	−51	−40	−5
Middle/Inferior temporal gyrus	R	21	20	3.61[a]	45	−73	−2
Superior temporal gyrus	L	22	9	2.22 [c]	−51	−28	1
	R	41/22	–	1.53[c]	36	−31	10
Control group							
Inferior frontal gyrus (opercular)	L	45	246	4.92[a]	−39	14	22
	R	45	–	0.76[c]	63	14	28
Inferior frontal gyrus (orbital)	L	47	981	5.79[a]	−45	26	7
	R	47	267	1.77[c]	30	29	−8
Middle temporal gyrus	L	21	145	4.03[a]	−60	−43	−8
Middle/Inferior temporal gyrus	R	21	8	3.43[a]	42	−73	−2
Superior temporal gyrus	L	22	52	2.48[c]	−45	−37	4
	R	22	–	0.16[c]	46	−31	10
Patient > Control[d]							
Middle temporal gyrus	R	21	53	3.00	60	−43	−5
Inferior frontal gyrus	R	45	29	2.82	51	23	28
Control > Patient							
Inferior frontal gyrus[d]	L	45	71	3.02	−45	35	7

Note: H, hemisphere; L, left; R, right; BA, Brodmann's area; Coordinates of activation peak(s) within a region based on a *z* test are given in the MNI stereotactic space (*x*, *y*, *z*); Voxels, number of voxels in cluster.

[a] $P < 0.05$ FDR (false discovery rate) corrected with the use of anatomical ROIs.
[b] $P < 0.01$ uncorrected.
[c] *P*-value uncorrected.
[d] $P < 0.05$ FEW (family-wise error) corrected with the use of ROIs from a meta-analysis (Wu et al., 2012).

Table 3
Mean generalized fractional anisotropy (GFA) of fiber tracts and total β-values of the fMRI semantic task.

Measure	Schizophrenia Mean ± S.D.	Control Mean ± S.D.	Schizophrenia vs. Control *P*
Mean GFA of fiber tracts			
Left ventral pathway	0.240 ± 0.029	0.277 ± 0.020	< 0.001*
Right ventral pathway	0.237 ± 0.024	0.262 ± 0.029	0.004*
Left dorsal pathway	0.251 ± 0.021	0.268 ± 0.017	0.060
Right dorsal pathway	0.233 ± 0.023	0.255 ± 0.023	0.006*
Total β-values of the fMRI			
Left ventral (IFG orb+MTG)	4.498 ± 2.533	2.578 ± 0.329	0.616
Right ventral (IFG orb+MTG)	4.753 ± 3.724	2.793 ± 0.74	0.868
Left dorsal (IFG oper+STG)	5.141 ± 2.849	4.454 ± 1.582	0.866
Right dorsal (IFG oper+STG)	1.636 ± 2.802	0.051 ± 0.677	0.395

Note: S.D.=standard deviation; IFG oper, the opercular part of the inferior frontal gyrus; STG, superior temporal gyrus; IFG orb, the orbital part of the inferior frontal gyrus; MTG, middle temporal gyrus.

* Significant difference between groups using the Least Significant Difference (LSD) post hoc analysis, $P < 0.05$.

dorsal pathways for both groups. The ANOVA showed that both the GFA ($F=7.249$, $P<0.001$) and β-values ($F=6.007$, $P<0.001$) were significantly different between groups. Fisher's LSD post hoc comparisons yielded a significant decrease in the GFA values of three fiber tracts in patients, namely the left ventral, right ventral and right dorsal tracts ($P<0.05$). Post hoc comparisons failed to yield significant differences in β-values. In addition, GFA values and β-values did not demonstrate correlations with age, duration of illness, and clinical status.

3.4. Structural and functional lateralization indices

The ANOVA revealed that functional LI demonstrated significant differences between groups ($F=8.007$, $P<0.001$), while the structural LI did not ($F=2.334$, $P=0.082$). The post hoc analysis revealed a decrease in functional LI of the dorsal pathway in patients ($P=0.028$).

3.5. Associations between lateralization indices and structural/functional counterparts

The GFA values of the three fiber tracts (i.e., the left ventral, right ventral and right dorsal tracts) and functional LI of the dorsal region were chosen for multiple linear regression analysis. The functional LI of the dorsal region was the dependent variable and the GFA values of the three fiber tracts were the explanatory variables. The results indicated that among the three fiber tracts, only the right dorsal tract had significant explanatory power with respect to functional LI of the dorsal pathway, partial correlation coefficient $r=0.531$, $P=0.034$ (Fig. 3). None of the data points were considered to be outliers; Mahalanobis distance < critical value of 16.27 (range: 0.206–6.070) and Cook's distance < 1 (range: 0.000–0.734). In addition, there was no significant correlation between the structural and functional measures in the control group.

3.6. Associations of delusion/hallucination with dorsal functional LI and right dorsal GFA

Given the significant correlation between the functional LI of the dorsal pathway and the right dorsal GFA, we further explored the

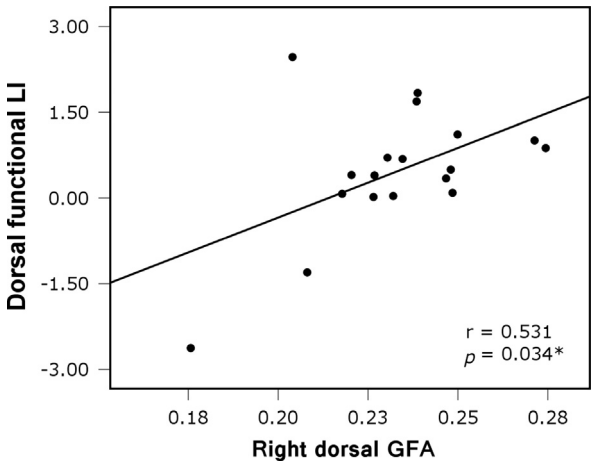

Fig. 3. Partial correlation between the dorsal functional LI and right dorsal GFA in patients with schizophrenia. LI, lateralization index; GFA, generalized fractional anisotropy; r=partial correlation coefficient; *denotes $P<0.05$.

relationship between the dimension scores of delusion/hallucination and these aspects. The delusion/hallucination scores were negatively correlated with the functional LI of the dorsal pathway ($r=-0.487$, $P=0.048$) and the right dorsal GFA ($r=-0.509$, $P=0.031$). Moreover, functional LI of the dorsal pathway ($r=-0.510$, $P=0.037$) and structural LI of the dorsal pathway ($r=0.470$, $P=0.049$) were significantly associated with the AVHs.

4. Discussion

A major significant finding of this study was a positive correlation between the microstructural integrity of the right dorsal pathway and functional lateralization of the dorsal pathway in patients with schizophrenia. When correlated with clinical symptoms, both microstructural integrity of the right dorsal pathway and functional lateralization of the dorsal pathway were negatively correlated with the delusion/hallucination dimension scores. To the best of our knowledge, this study is the first that elucidates the structural counterparts of altered functional lateralization of the language network in schizophrenia and their associations with AVH in this condition.

This study demonstrated that the reduced microstructural integrity of the right dorsal pathway was the structural counterpart of reduced functional lateralization of the dorsal pathway in patients with schizophrenia (Fig. 3). To discuss the implication of this finding, we suggest reference to an earlier study by Vernooij et al. (2007), who studied the relationship between language structure and function in healthy subjects. They demonstrated that the relative fiber density, which is an alternative measure of microstructural integrity, of the right arcuate fasciculus was negatively correlated with the corresponding functional lateralization. Their result indicates that the microstructural integrity of the right dorsal pathway is associated with functional lateralization of the dorsal pathway. In healthy subjects, the right dorsal pathway tends to exhibit reduced microstructural integrity to achieve leftward functional lateralization. However, in patients with schizophrenia, the microstructural integrity of the right dorsal pathway is reduced *a priori*, and we speculate that further decreases may inversely act to reduce leftward functional lateralization. This hypothesis is supported in part by a prior study (Vandervliet et al., 2008), which reported a neurological patient with acutely developed aphasia following a right hemispheric stroke. The patient exhibited increased functional activation in the ipsilateral gyri following remission of global aphasia. This report suggests that when the right dorsal pathway is disrupted, an increase in ipsilateral functional activation follows; it is possible that this is a mechanism to compensate for language impairment by reducing functional lateralization.

As previously described, statistical analyses revealed a positive correlation between functional lateralization of the dorsal pathway and microstructural integrity of the right dorsal pathway in patients with schizophrenia. This finding prompted an investigation of correlations between these two measures with the dimension scores of delusion/hallucination. Our results showed that both functional lateralization of the dorsal pathway and microstructural integrity of the right dorsal pathway were negatively correlated with the scores of the delusion/hallucination symptom dimension. This is consistent with our findings that the severity of AVHs alone was negatively correlated with functional lateralization of the dorsal pathway and positively correlated with structural asymmetry of the dorsal pathway. Our results indicate that functional lateralization of the dorsal pathway and structural integrity of the right dorsal pathway may serve as a functional correlate and a structural correlate of AVHs observed in schizophrenia, respectively. Considering the tight coupling of these two measures (Fig. 3), we hypothesized that as the microstructural integrity of the right dorsal pathway becomes more impaired, functional lateralization of the dorsal pathway will be more drastically reduced. It follows that as the alterations of these two measures become more severe, they may aggravate the AVHs.

We used DSI to assess the microstructural integrity of the fiber tracts along the dorsal and ventral streams of the language network. The key advantage of using DSI is that this technique is capable of resolving intravoxel crossing fibers (Wedeen et al., 2008) and some studies have reported that GFA is highly correlated with FA (Gorczewski et al., 2009; Fritzsche et al., 2010). In the present study, the structural measures demonstrated generally decreased structural integrity of the bilateral dorsal and ventral pathways in schizophrenia (Table 3). This finding was consistent with previous DTI studies using region-based or voxel-based measurements, which reported reduced FA in the bilateral arcuate fasciculi (Phillips et al., 2009; Catani et al., 2011; de Weijer et al., 2011), higher MD in the bilateral inferior fronto-occipital fasciculi (Clark et al., 2011), and reduced integrity of the ventral pathway (Kubicki et al., 2011).

Prior research has demonstrated that the dorsal pathway is involved in semantic processing. Rossell et al. (2001) used fMRI to examine neural activity during semantic priming with short and long stimulus onset asynchrony (SOA). They found that the right superior temporal gyrus (STG) was activated in semantically related conditions across different SOAs (Rossell et al., 2001). Furthermore, greater activation in the left superior temporal gyrus may reflect hyperactivation of semantic representations in patients with schizophrenia (Kubicki et al., 2003). These findings regarding dorsal activation during semantic processing are consistent with our results. Compared with healthy controls, the schizophrenia patients exhibited increased activation in fronto-temporal regions (Table 2); this difference is consistent with findings reported by Kuperberg et al. (2007) and Chen et al. (2013). The increased activation may possibly be due to an aberrant semantic network or difficulty in accessing semantic representations. Moreover, the reduction of functional lateralization of the dorsal pathway in patients was also consistent with previous studies (Weiss et al., 2006; van Veelen et al., 2011). The earlier reports showed that reduced functional lateralization was most prominent in the inferior frontal gyrus and superior temporal gyrus. These gyri are brain regions that are part of the dorsal pathway, as was confirmed in the present study.

We found a positive correlation between structural integrity of the right dorsal pathway and functional lateralization of the dorsal

pathway in patients with schizophrenia, but no correlations in the ventral pathways. Currently, there are different models of anatomical pathways involved in semantic processing (Catani et al., 2005; Glasser and Rilling, 2008). Compared with other models, the dual stream model proposes a ventral pathway that is anatomically different from a distinct dorsal pathway; this is analogous to dual processing pathways in the visual and auditory systems. Mandonnet et al. (2007) corroborated the existence of similar localization of ventral language pathway using intraoperative direct electrostimulation. Recent studies further clarified that the ventral stream is formed by three anatomical tracts, inferior fronto-occipital fasciculus as the direction connection between prefrontal and occipital lobes, and inferior longitudinal fasciculus and middle longitudinal fasciculus as indirect connections (Duffau et al., 2013). In the present study, we found decreased GFA in the bilateral ventral pathways in schizophrenia. However, the GFA values were not associated with the functional LI. Further study of the ventral pathway is warranted to clarify its clinical significance in schizophrenia.

The present study is not without limitations. First, this study focused on right-handed subjects whose handedness was determined by the Edinburgh Handedness Inventory. We did not analyze the effect of the degree of handedness or the direction of hand preference, which may have potentially affected the relationship between structural asymmetry and functional lateralization (Propper et al., 2010). To date, one study (Razafimandimby et al., 2011) has evaluated left-handed patients with schizophrenia and found that decreased lateralization of language production was more strongly related to handedness compared with schizophrenia in general. Second, the present study did not consider the potential effect of gender differences on language lateralization in schizophrenia. Although several studies have demonstrated that reduced language lateralization in women is not likely to underlie gender differences observed in schizophrenia (Sommer et al., 2003), an association of the cortical volume of the right temporal region with language dysfunction has been reported in female schizophrenia patients (Walder et al., 2007). To further understand the effects of handedness and gender, a large cohort is needed that contains both genders, comprising individuals of a wide range of handedness. Such a cohort would be useful to analyze the alterations of language lateralization related to handedness and gender. In addition, further studies are required to investigate the relation between AVHs and language lateralization in other patients with psychotic disorders as well as non-psychotic individuals. For example, recent studies on a group of non-psychotic individuals with AVHs did not find reduced language lateralization (Diederen et al., 2010) and decreased FA in the arcuate fasciculus (de Weijer et al., 2013). Third, although we propose a key role of the right dorsal pathway in reducing functional lateralization of the dorsal pathway in patients with schizophrenia, the correlation analysis used in this study cannot provide a definitive causal relationship between structure and function of the language network. Finally, the sample size of this study was relatively moderate, even though it was determined based on our previous structural imaging studies for individuals with psychiatric disorders (Lo et al., 2011, 2013). In fact, we have analyzed DSI data using a new tract-specific analysis method in another group of 31 schizophrenic patients and observed consistent results. The right arcuate fasciculus showed reduced GFA (patients vs. controls: 0.269 ± 0.021 vs. 0.286 ± 0.020, $P=0.004$) and significant association with delusion/hallucination scores ($r=-0.380$, $P=0.046$) (Wu et al., 2014).

In conclusion, the present study is the first to elucidate the structural counterpart of altered functional lateralization of the language network in schizophrenia. We found a positive correlation between the structural integrity of the right dorsal pathway and functional lateralization of the dorsal pathway in patients with schizophrenia. Both of these measures were negatively correlated with the severity of the patients' AVHs. Our results suggest that impaired structural integrity of the right dorsal pathway is related to reduced functional lateralization of the dorsal pathway and that these alterations may aggravate AVHs in schizophrenia.

Acknowledgments

This work was supported by the National Science Council, Taiwan (NSC100-3112-B-002-016, NHRI-EX101-10145NI, and NSC101-2410-H-002-093-MY2), and in part by the Department of Medical Imaging and Advanced Biomedical MRI Laboratory, the National Taiwan University Hospital, Taipei, Taiwan. We thank all of the subjects for their participation in this study.

References

Allen, P., Laroi, F., McGuire, P.K., Aleman, A., 2008. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. Neuroscience and Biobehavioral Reviews 32, 175–191.

Allen, P., Modinos, G., Hubl, D., Shields, G., Cachia, A., Jardri, R., Thomas, P., Woodward, T., Shotbolt, P., Plaze, M., Hoffman, R., 2012. Neuroimaging auditory hallucinations in schizophrenia: from neuroanatomy to neurochemistry and beyond. Schizophrenia Bulletin 38, 695–703.

Andreasen, N.C., Pressler, M., Nopoulos, P., Miller, D., Ho, B.C., 2010. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. Biological Psychiatry 67, 255–262.

Benetti, S., Pettersson-Yeo, W., Allen, P., Catani, M., Williams, S., Barsaglini, A., Kambeitz-Ilankovic, L.M., McGuire, P., Mechelli, A., 2013. Auditory verbal hallucinations and brain dysconnectivity in the perisylvian language network: a multimodal investigation. Schizophrenia Bulletin (epub ahead of print, 22 December).

Borowsky, R., Cummine, J., Owen, W.J., Friesen, C.K., Shih, F., Sarty, G.E., 2006. FMRI of ventral and dorsal processing streams in basic reading processes: insular sensitivity to phonology. Brain Topography 18, 233–239.

Broca, P., 1861. Remarques sur le siege de la faculté du langage articulé. Bulletin de la Societé Anatomique de Paris 6, 343–345.

Burock, M.A., Buckner, R.L., Woldorff, M.G., Rosen, B.R., Dale, A.M., 1998. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. NeuroReport 9, 3735–3739.

Callaghan, P.T., Coy, A., MacGowan, D., Packer, K.J., Zelaya, F.O., 1991. Diffraction-like effects in NMR diffusion studies of fluids in porous solids. Nature 351, 467–469.

Catani, M., Craig, M.C., Forkel, S.J., Kanaan, R., Picchioni, M., Toulopoulou, T., Shergill, S., Williams, S., Murphy, D.G., McGuire, P., 2011. Altered integrity of perisylvian language pathways in schizophrenia: relationship to auditory hallucinations. Biological Psychiatry 70, 1143–1150.

Catani, M., Jones, D.K., ffytche, D.H., 2005. Perisylvian language networks of the human brain. Annals of Neurology 57, 8–16.

Chen, P.J., Fan, L.Y., Hwang, T.J., Hwu, H.G., Liu, C.M., Chou, T.L., 2013. The deficits on a cortical-subcortical loop of meaning processing in schizophrenia. Neuroreport 24, 147–151.

Chiang, W.Y., Wang, H.L., Huang, S.C., Yeh, F.C., Tseng, W.Y.I., 2007. Tract-specific analysis of human white matter: mean-path based method. In: Proceedings of the16th Triennial Conference for the International Society of Magnetic Resonance, Kenting, Taiwan, October 14–19.

Chou, T.-L., Chen, C.-W., Wu, M.-Y., Booth, J.R., 2009. The role of inferior frontal gyrus and inferior parietal lobule in semantic processing of Chinese characters. Experimental Brain Research 198, 465–475.

Clark, K.A., Nuechterlein, K.H., Asarnow, R.F., Hamilton, L.S., Phillips, O.R., Hageman, N.S., Woods, R.P., Alger, J.R., Toga, A.W., Narr, K.L., 2011. Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. Journal of Psychiatric Research 45, 980–988.

de Weijer, A.D., Mandl, R.C., Diederen, K.M., Neggers, S.F., Kahn, R.S., Hulshoff Pol, H.E., Sommer, I.E., 2011. Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations. Schizophrenia Research 130, 68–77.

de Weijer, A.D., Neggers, S.F., Diederen, K.M., Mandl, R.C., Kahn, R.S., Hulshoff Pol, H.E., Sommer, I.E., 2013. Aberrations in the arcuate fasciculus are associated with auditory verbal hallucinations in psychotic and in non-psychotic individuals. Human Brain Mapping 34, 626–634.

Diederen, K.M., De Weijer, A.D., Daalman, K., Blom, J.D., Neggers, S.F., Kahn, R.S., Sommer, I.E., 2010. Decreased language lateralization is characteristic of psychosis, not auditory hallucinations. Brain 133, 3734–3744.

Duffau, H., Herbet, G., Moritz-Gasser, S., 2013. Toward a pluri-component, multimodal, and dynamic organization of the ventral semantic stream in humans: lessons from stimulation mapping in awake patients. Frontiers in Systems Neuroscience 7, 44.

Fritzsche, K.H., Laun, F.B., Meinzer, H.P., Stieltjes, B., 2010. Opportunities and pitfalls in the quantification of fiber integrity: what can we gain from Q-ball imaging? NeuroImage 51, 242–251.

Glahn, D.C., Laird, A.R., Ellison-Wright, I., Thelen, S.M., Robinson, J.L., Lancaster, J.L., Bullmore, E., Fox, P.T., 2008. Meta-analysis of gray matter anomalies in

schizophrenia: application of anatomic likelihood estimation and network analysis. Biological Psychiatry 64, 774–781.
Glasser, M.F., Rilling, J.K., 2008. DTI tractography of the human brain's language pathways. Cerebral Cortex 18, 2471–2482.
Gorczewski, K., Mang, S., Klose, U., 2009. Reproducibility and consistency of evaluation techniques for HARDI data. Magma 22, 63–70.
Hickok, G., Poeppel, D., 2004. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 92, 67–99.
Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nature Reviews Neuroscience 8, 393–402.
Hsu, Y.C., Hsu, C.H., Tseng, W.Y., 2012a. A large deformation diffeomorphic metric mapping solution for diffusion spectrum imaging datasets. NeuroImage 63, 818–834.
Hsu, Y.C., Hsu, C.H., Tseng, W.Y., 2012b. Template estimation for a group of DSI datasets using LDDMM. In: Proceedings of the 20th Annual Meeting of International Society for Magnetic Resonance in Medicine, Melbourne, Australia, May 5–11.
Hwu, H.G., Chen, C.H., Hwang, T.J., Liu, C.M., Cheng, J.J., Lin, S.K., Liu, S.K., Chi, Y.Y., Ou-Young, C.W., Lin, H.N., Chen, W.J., 2002. Symptom patterns and subgrouping of schizophrenic patients: significance of negative symptoms assessed on admission. Schizophrenia Research 56, 105–119.
Kubicki, M., Alvarado, J.L., Westin, C.F., Tate, D.F., Markant, D., Terry, D.P., Whitford, T.J., De Siebenthal, J., Bouix, S., McCarley, R.W., Kikinis, R., Shenton, M.E., 2011. Stochastic tractography study of inferior frontal gyrus anatomical connectivity in schizophrenia. NeuroImage 55, 1657–1664.
Kubicki, M., McCarley, R.W., Nestor, P.G., Huh, T., Kikinis, R., Shenton, M.E., Wible, C.G., 2003. An fMRI study of semantic processing in men with schizophrenia. NeuroImage 20, 1923–1933.
Kuo, L.W., Chen, J.H., Wedeen, V.J., Tseng, W.Y., 2008. Optimization of diffusion spectrum imaging and q-ball imaging on clinical MRI system. NeuroImage 41, 7–18.
Kuperberg, G.R., Deckersbach, T., Holt, D.J., Goff, D., West, W.C., 2007. Increased temporal and prefrontal activity in response to semantic associations in schizophrenia. Archives of General Psychiatry 64, 138–151.
Li, X., Branch, C.A., DeLisi, L.E., 2009. Language pathway abnormalities in schizophrenia: a review of fMRI and other imaging studies. Current Opinion in Psychiatry 22, 131–139.
Lo, Y.C., Chou, T.L., Fan, L.Y., Gau, S.S., Chiu, Y.N., Tseng, W.Y., 2013. Altered structure-function relations of semantic processing in youths with high-functioning autism: a combined diffusion and functional MRI study. Autism research: official journal of the International Society for Autism Research 6, 561–570.
Lo, Y.C., Soong, W.T., Gau, S.S., Wu, Y.Y., Lai, M.C., Yeh, F.C., Chiang, W.Y., Kuo, L.W., Jaw, F.S., Tseng, W.Y., 2011. The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion spectrum imaging tractography. Psychiatry Research: Neuroimaging 192, 60–66.
Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., Duffau, H., 2007. Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. Brain 130, 623–629.
Mori, S., van Zijl, P.C., 2002. Fiber tracking: principles and strategies – a technical review. NMR in Biomedicine 15, 468–480.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9, 97–113.
Phillips, O.R., Nuechterlein, K.H., Clark, K.A., Hamilton, L.S., Asarnow, R.F., Hageman, N.S., Toga, A.W., Narr, K.L., 2009. Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia. Schizophrenia Research 107, 30–38.
Powell, H.W., Parker, G.J., Alexander, D.C., Symms, M.R., Boulby, P.A., Wheeler-Kingshott, C.A., Barker, G.J., Noppeney, U., Koepp, M.J., Duncan, J.S., 2006. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. NeuroImage 32, 388–399.
Propper, R.E., O'Donnell, L.J., Whalen, S., Tie, Y., Norton, I.H., Suarez, R.O., Zollei, L., Radmanesh, A., Golby, A.J., 2010. A combined fMRI and DTI examination of functional language lateralization and arcuate fasciculus structure: effects of degree versus direction of hand preference. Brain and Cognition 73, 85–92.
Razafimandimby, A., Maiza, O., Herve, P.Y., Lecardeur, L., Delamillieure, P., Brazo, P., Mazoyer, B., Tzourio-Mazoyer, N., Dollfus, S., 2007. Stability of functional language lateralization over time in schizophrenia patients. Schizophrenia Research 94, 197–206.
Razafimandimby, A., Tzourio-Mazoyer, N., Mazoyer, B., Maiza, O., Dollfus, S., 2011. Language lateralization in left-handed patients with schizophrenia. Neuropsychologia 49, 313–319.
Reese, T.G., Heid, O., Weisskoff, R.M., Wedeen, V.J., 2003. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. Magnetic Resonance in Medicine 49, 177–182.
Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., Behrens, T.E., 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nature Neuroscience 11, 426–428.
Rossell, S.L., Bullmore, E.T., Williams, S.C., David, A.S., 2001. Brain activation during automatic and controlled processing of semantic relations: a priming experiment using lexical-decision. Neuropsychologia 39, 1167–1176.
Saur, D., Kreher, B.W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M.S., Umarova, R., Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., Weiller, C., 2008. Ventral and dorsal pathways for language. Proceedings of the National Academy of Sciences of the United States of America 105, 18035–18040.
Saur, D., Schelter, B., Schnell, S., Kratochvil, D., Kupper, H., Kellmeyer, P., Kummerer, D., Kloppel, S., Glauche, V., Lange, R., Mader, W., Feess, D., Timmer, J., Weiller, C., 2010. Combining functional and anatomical connectivity reveals brain networks for auditory language comprehension. NeuroImage 49, 3187–3197.
Seghier, M.L., Josse, G., Leff, A.P., Price, C.J., 2011. Lateralization is predicted by reduced coupling from the left to right prefrontal cortex during semantic decisions on written words. Cerebral Cortex 21, 1519–1531.
Sommer, I.E., Ramsey, N.F., Kahn, R.S., 2001. Language lateralization in schizophrenia, an fMRI study. Schizophrenia Research 52, 57–67.
Sommer, I.E., Ramsey, N.F., Mandl, R.C., Kahn, R.S., 2003. Language lateralization in female patients with schizophrenia: an fMRI study. Schizophrenia Research 60, 183–190.
Tuch, D.S., 2004. Q-ball imaging. Magnetic Resonance in Medicine 52, 1358–1372.
van den Heuvel, M.P., Fornito, A., 2014. Brain networks in schizophrenia. Neuropsychology Review 24, 32–48.
van Veelen, N.M., Vink, M., Ramsey, N.F., Sommer, I.E., van Buuren, M., Hoogendam, J.M., Kahn, R.S., 2011. Reduced language lateralization in first-episode medication-naive schizophrenia. Schizophrenia Rresearch 127, 195–201.
Vandervliet, E.J., Verhoeven, J., Engelborghs, S., De Deyn, P.P., Parizel, P.M., Marien, P., 2008. FMRI findings in an aphasic patient with reversed cerebral dominance for language. Acta Neurologica Belgica 108, 161–166.
Vernooij, M.W., Smits, M., Wielopolski, P.A., Houston, G.C., Krestin, G.P., van der Lugt, A., 2007. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. NeuroImage 35, 1064–1076.
Walder, D.J., Seidman, L.J., Makris, N., Tsuang, M.T., Kennedy, D.N., Goldstein, J.M., 2007. Neuroanatomic substrates of sex differences in language dysfunction in schizophrenia: a pilot study. Schizophrenia Research 90, 295–301.
Wedeen, V.J., Hagmann, P., Tseng, W.Y., Reese, T.G., Weisskoff, R.M., 2005. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magnetic Resonance in Medicine 54, 1377–1386.
Wedeen, V.J., Wang, R.P., Schmahmann, J.D., Benner, T., Tseng, W.Y., Dai, G., Pandya, D.N., Hagmann, P., D'Arceuil, H., de Crespigny, A.J., 2008. Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. NeuroImage 41, 1267–1277.
Weiller, C., Bormann, T., Saur, D., Musso, M., Rijntjes, M., 2011. How the ventral pathway got lost: and what its recovery might mean. Brain and Language 118, 29–39.
Weiss, E.M., Hofer, A., Golaszewski, S., Siedentopf, C., Felber, S., Fleischhacker, W.W., 2006. Language lateralization in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. Psychiatry Research: Neuroimaging 146, 185–190.
Wernicke, C., 1874. Der Aphasische Symptomenkomplex: Eine Psychologische Studie auf Anatomischer Basis. Cohn und Welgert, Breslau.
Whalley, H.C., Papmeyer, M., Sprooten, E., Lawrie, S.M., Sussmann, J.E., McIntosh, A.M., 2012. Review of functional magnetic resonance imaging studies comparing bipolar disorder and schizophrenia. Bipolar Disorders 14, 411–431.
Wu, C.H., Chen, Y.J., Hsu, Y.C., Lo, Y.C., Hwang, T.J., Hwu, H.G., Chen, C.M., Tseng, W.Y., 2014. Altered white matter tract integrity as a potential endophenotype of schizophrenia: a sibling study using automatic tract-specific analysis of the whole brain. In: Proceedings of the 22th Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM), Milan, Italy, May 10–16, (Program number: 3459).
Wu, C.Y., Ho, M.H., Chen, S.H., 2012. A meta-analysis of fMRI studies on Chinese orthographic, phonological, and semantic processing. NeuroImage 63, 381–391.
Yeh, F.C., Wedeen, V.J., Tseng, W.Y., 2011. Estimation of fiber orientation and spin density distribution by diffusion deconvolution. NeuroImage 55, 1054–1062.