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Hyperconnectivity in perisylvian language pathways in schizophrenia with auditory verbal hallucinations: A multi-site diffusion MRI study

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ABSTRACT

Auditory verbal hallucinations (AVH) are one of the cardinal symptoms of schizophrenia, and are proposed to be associated with altered integrity of the left perisylvian language pathways. There is considerable heterogeneity in the pattern of white matter abnormalities across previous studies. We investigated the white matter integrity of the perisylvian language pathways in schizophrenia patients with AVH based on a relatively large sample dataset from four different sites. 113 schizophrenia patients with AVH, 96 patients without AVH (nAVH), and 269 healthy controls (HC) underwent diffusion-weighted imaging. Between-group comparisons were performed on the fractional anisotropy (FA) values of the anterior, posterior, and long segment fasciculi within the perisylvian language network. Analysis of covariance among the 3 groups revealed the long segment of the left perisylvian language pathways was significantly different in FA value. Post hoc analysis showed that compared with the HC group, the AVH group had significantly higher FA measurements in the left long segment. The nAVH group showed intermediate FA values for this segment compared to the AVH and HC group but did not differ significantly from either group. Furthermore, the prospective meta-analyses also revealed that FA value of the left long segment was significantly higher in the AVH group compared to the HC group. Our findings suggest the hyperconnectivity pattern of the left perisylvian language pathways in the presence of AVH in schizophrenia and support the self-monitoring of inner speech model.

1. Introduction

Auditory verbal hallucinations (AVH) are one of the most potentially debilitating symptoms of schizophrenia (Andreasen and Flaum, 1991; Leff et al., 1992; Mondino et al., 2016). However, the exact pathophysiology and underlying neurobiology of this condition remain elusive. Over the past 3 decades, developments in MRI have enabled researchers to acquire a rudimentary understanding of the brain regions and networks that are involved in this symptom (Alderson-Day et al., 2016; Allen et al., 2012; Bohlken et al., 2017). To date, a majority of neuroimaging studies have suggested that AVHs are associated with abnormalities in the structural connectivities between the frontal and temporal language regions (Curcic-Blake et al., 2017). The pathways within the perisylvian language network are frequently implicated in

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the etiology of AVH. The major white matter tract that interconnects the perisylvian language regions is the arcuate fasciculus (AF), which can be subdivided into three segments (Catani et al., 2005). Beyond the classical arcuate pathway (the long segment), which connects Wernicke's territory to Broca's territory, there are two other shorter tracts, the anterior and the posterior segments (Catani et al., 2005).

To date, studies of structural connection using DTI have revealed different abnormal patterns for the AF in schizophrenia patients with AVH compared with schizophrenia patients without a history of AVH (nAVH) or with healthy controls (HC). In the first DTI study that made comparisons between AVH patients, nAVH patients, and HC, an increased FA value in the AF was reported in the patients with AVH compared with control subjects (Hubl et al., 2004). Another two DTI studies reported compatible results, in that the propensity to experience auditory hallucinations was associated with a relatively increased FA in the superior longitudinal fasciculi (SLF) (Seok et al., 2007; Shergill et al., 2007). Moreover, several DTI studies using voxel-based analysis or tract-based spatial statistics (TBSS) reported that the only region of increased FA value in schizophrenia patients in comparison with HC was the AF and that the severity of hallucination was positively correlated with the FA values in the AF (Knochel et al., 2012; Rotarska-Jagiela et al., 2009). However, there are also DTI-based studies that reported decreased FA rather than increased FA of the AF in AVH patients (Catani et al., 2011; Curcic-Blake et al., 2015; de Weijer et al., 2011; McCarthy-Jones et al., 2015). A recent multimodal investigation (Benetti et al., 2015) found that the AVH group showed an intermediate, non-significant value in the FA of the long segment of the AF compared to the nAVH group and the HC. Therefore, currently, the previous DTI studies have provided insufficient neuroimaging evidence to integrate a coherent abnormal pattern (hypo- or hyperconnectivity) of the perisylvian language pathways in schizophrenia patients with AVH. One of the primary reasons that can probably explain the discrepancies in these results is the limited number of samples (number of patients with AVH <40) in the vast majority of existing DTI studies (Curcic-Blake et al., 2017).

Therefore, the aim of the current study was to investigate the microstructural integrity of the perisylvian language pathways in schizophrenia patients with and without AVH using a relative large number of independently evaluated samples from the Chinese Han population collected at four sites. We used an region of interest (ROI)-based analysis in which the regions were defined by automated segmentation based on a white matter atlas. To assess the replicability and consistency across our four sites, a prospective meta-analysis was performed on the three pathways. Based on the results of previous DTI studies, we hypothesized that the white matter integrity of the perisylvian language pathways was altered in the schizophrenia patients with AVH.

2. Materials and methods

2.1. Participants

A total of 209 schizophrenia patients were recruited from four different hospitals in China: Peking University Sixth Hospital (PKU6), Beijing Huilongguan Hospital (HLG), Xijing Hospital (XJ), and Henan Mental Hospital (HM). All the patients from each site were assessed using the Structured Clinical Interview for DSM disorders (SCID) and diagnosed by experienced psychiatrists as meeting the criteria for schizophrenia per the Diagnostic and Statistical Manual for Mental Disorders 4th Edition text revision (DSM-IV-TR). The psychotic symptoms of the patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). A group of 269 healthy controls was recruited by advertisement from the local community near each site. All the participants were within the 18–45 age range and Chinese Han in origin. The exclusion criteria for all the participants included a history of neurological disorder, substance abuse or dependence, pregnancy, prior electroconvulsive therapy, or head injury resulting in loss of consciousness. Every effort was made at each site to match the controls to the patients in terms of age, gender, and handedness. All the subjects gave written informed consent and this study was approved by the local research ethics committee at each site.

The patients who scored 4 or more on the hallucination assessment (P3) of the PANSS and reported AVHs at least once a day for the past four weeks before the time of scanning were assigned to the AVH group. The patients who scored 2 or less on the item P3 of the PANSS were assigned to the nAVH group. We excluded patients with a P3 score of 3 in this study. Finally, 103 patients with AVH and 96 patients without AVH were included. To further characterize the AVH group in terms of the AVH severity, we evaluated the AVH patients using the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003).

2.2. Data acquisition and preprocessing

Diffusion-weighted images and 3D T1-weighted structural MRI data were acquired on either a 3.0 T Siemens TrioTim Scanner at three sites (PKU6, HLG, and XJ) or a 3.0 T Siemens Verio Scanner (HM) with an 8-channel SENSE head coil. The DTI data were acquired using a single-shot spin-echo echo-planar imaging sequence. The main acquisition parameters for the DTI included: field-of-view (FOV) = 256 mm × 256 mm, matrix size = 128 × 128, slices = 50, voxel size = 2 mm × 2 mm × 3 mm and without a slice gap, repetition time (TR) = 7000 (8400 for HM) ms, echo time (TE) = 92 (91 for XJ and HM) ms, flip angle = 90°. For each subject, a total of 65 volumes were acquired, 1 volume without diffusion weighting ($b = 0$ s/mm^2) and 64 volumes with diffusion weighting ($b = 1000$ s/mm^2) along 64 noncollinear diffusion gradient directions. The 3D T1-weighted image for each subject was obtained using a magnetization prepared rapid gradient echo (MPRAGE) sequence. The imaging parameters for 3D T1-weighted image included: FOV = 256 mm × 256 mm, matrix size = 256 × 256, 192 sagittal slices, voxel size = 1 mm × 1 mm × 1 mm, TR = 2530 ms, TE = 3.44 (2.43 for HM and 3.5 for XJ) ms, flip angle = 7°.

To preprocess the DTI data, we performed a correction for distortions induced by eddy currents and head motion. All the diffusion-weighted images were aligned to the non-diffusion-weighted image (the first b0 volume) using the *eddy_correct* function in FSL 5.0 (Jenkinson et al., 2012). For each subject the b-matrix was reoriented to provide a more accurate estimate of tensor orientations using *fdt_rotate_bvec* in FSL (Leemans and Jones, 2009). The MRI data for each individual were visually inspected by two specialists to make sure there were no apparent artifacts arising from the acquisition or data processing procedures. After the above corrections and reorientation, the FA map was estimated using the FSL FDT tool. The 3D T1-weighted image was segmented using the voxel-based morphometry tool included in the SPM8 package (http://www.fil.ion.ucl.ac.uk/spm) to generate the brain image in T1 space (brain_T1).

2.3. FA measurements of the perisylvian language pathways

The neuroimaging atlas of the perisylvian language pathways used in this study was created by Catani et al. (2005). The procedure of warping the three segments from the atlas to the individual native DTI space is as follows: First, we employed linear and then non-linear methods to register the native FA map to the individual brain_T1 image in T1 space using the registration tool *flirt* (Jenkinson et al., 2002) and *fnirt* in FSL, respectively. Second, we also used *flirt* and *fnirt* to linearly and then non-linearly register the individual brain_T1 image to the standard anatomical reference (00average_brain.nii) in the atlas. Next, we inverted the two derived transformations from DTI space to T1 space and from T1 space to atlas space. Finally, the two inverted transformations were applied to warp each pathway of the perisylvian language network from atlas space to native DTI space. To reduce the chances of including voxels outside the perisylvian language pathways, we selected the three tract segment masks by thresholding the probabilistic atlas at 50%.

The white matter mask in DTI space was applied in the subsequent calculations to ensure that each included voxel was in the white matter. The median FA values for each tract segment were computed for each subject. We employed the median values of the diffusion properties rather than the arithmetic mean because previous studies showed that the median was more robust to noise, registration, and segmentation errors (Shi et al., 2013).

2.4. Statistical analysis and meta-analysis

The statistical analysis was performed in SPSS (version 19.0, IBM Comp. & SPSS Inc., 2010). Demographic differences between the three groups were examined with one-way analysis of variance and chi-square tests. The clinical parameters of the nAVH patients and the AVH patients were analyzed for differences using independent-samples Student *t*-tests and chi-square tests (Cui et al., 2018). For the combined dataset pooled from the four sites, as well as for each site independently, a general linear model analysis was performed for each segment with median FA as the dependent variable and group as the independent variable. To correct for multiple comparisons, a Bonferroni-corrected threshold of $P < 0.008$ (i.e. 0.05/3 segments/2 hemispheres) was used. Subsequent comparisons between the three groups were performed in the segment with a significant main effect of group using post hoc two sample *t*-tests with a Bonferroni-corrected threshold of $P < 0.016$ (i.e. 0.05/3 groups). In each analysis, age and gender were included as nuisance covariates. In addition, site was also defined as a covariate in the analyses that used the combined dataset.

To assess the extent of replication and consistency across our four sites, we used a prospective meta-analytic method (van Erp et al., 2016) for all segments. The meta-analysis was conducted using the metafor package in R (Viechtbauer, 2010). First, a linear regression analysis (R's linear model function *lm*()) was performed to predict the mean FA value(s) of the selected segment of each group for each site. The linear regression analysis included age and gender as nuisance covariates. Then the meta-analysis pooled Cohen's *d* group sizes, for selected segment, using a random-effects model (metafor package, re() function), which can protect against dominating effects of the largest samples in the meta-analysis.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the subjects from the four sites are presented in Table 1. The detailed demographic and clinical characteristics for each site are in Table S1a–d in the Supplementary materials. There were no significant differences in age or gender between the three groups in the combined dataset and in each of the four sites. Education differed significantly between the groups at the XJ and HM sites, but not at the HLG or PKU6 sites. Post hoc tests revealed that the education level of the HC group was higher than that of the patients with and without AVH at the XJ and HM sites. All the subjects at all four sites in our study were right-handed. In terms of clinical characteristics, there were no significant differences between the patients without AVH and patients with AVH in the duration of illness, PANSS total (excluding P3) score, PANSS negative score, PANSS general score, or medication dosage in the combined dataset and in each of the four sites.

3.2. FA measurements of the perisylvian language pathways for the combined dataset

In the analyses of the combined dataset collected from the four sites, a significant group difference in the FA measurement of the long segment of the left perisylvian language pathways was observed ($F = 5.786$, $P = 0.003$) using our Bonferroni-corrected threshold of $P < 0.008$ (Table 2). Follow-up post hoc analyses revealed a significant increase in the FA value for the left long segment in the AVH group compared to the HC group (Fig. 1). The nAVH group showed intermediate FA values for this segment compared to the AVH group and the HC group but did not differ significantly from either group. There were no significant between-group differences in the FA values of the anterior segment or the posterior segment of the left perisylvian language network (Table 2). In the right perisylvian language network, none of the three segments showed significant between-group differences as presented in Table 2.

3.3. FA measurements of the perisylvian language pathways for each site

Independent analyses of the FA measurements extracted from each single segment of the perisylvian language network revealed a significant group difference in the left long segment from the PKU6 site data ($F = 3.352$, $P = 0.037$, uncorrected) but it was not significant using our Bonferroni-corrected threshold of $P \le 0.008$. Post hoc analyses indicated a significantly higher FA value in the left long segment in the AVH group compared to the HC group ($P = 0.033$, adjusted value, Bonferroni-corrected; Fig. 2). The FA measurements for the left long segment did not differ significantly between groups in the data from the HLG, XJ, and HM sites. The AVH group consistently showed the highest FA value and the nAVH group showed an intermediate FA value for the left long segment in the comparison between the three

Table 1
Demographic and clinical characteristics of the participants.

	HC ($n = 269$)	nAVH ($n = 96$)	AVH ($n = 113$)	Statistics
Age (years)	27.04 (5.82)	26.95 (5.43)	26.77 (5.86)	$F = 0.085$, $P = 0.918$
Gender (male/female)	136:133	54:42	56:57	$\chi^2 = 1.122$, $P = 0.567$
Handedness (right/left)	269:0	96:0	113:0	NA
Education (years)[a]	13.65 (3.42)	11.89 (3.88)	12.39 (3.64)	$F = 10.593$, $P < 0.001$
Duration of illness (months)	NA	46.70 (42.92)	45.89 (49.04)	$t = 0.126$, $P = 0.900$
CPZ-eq at scan (mg/d)[b]	NA	411.84 (212.43)	435.82 (184.19)	$t = 0.716$, $P = 0.475$
PANSS hallucination (P3)	NA	1.29 (0.46)	5.08 (0.77)	$t = -42.311$, $P < 0.001$
PANSS total	NA	78.50 (7.91)	81.33 (8.70)	$t = -2.441$, $P = 0.016$
PANSS total (excluding P3)	NA	77.21 (7.86)	76.25 (8.70)	$t = 0.832$, $P = 0.407$
PANSS positive	NA	21.44 (3.45)	25.36 (4.14)	$t = -7.368$, $P < 0.001$
PANSS negative	NA	18.92 (5.37)	18.63 (5.11)	$t = -0.397$, $P = 0.692$
PANSS general	NA	38.15 (5.39)	37.34 (5.21)	$t = 1.102$, $P = 0.272$
AHRS	NA	NA	24.30 (7.071)	NA

HC, healthy controls; nAVH, schizophrenia patients without auditory verbal hallucinations; AVH, schizophrenia patients with auditory verbal hallucinations; CPZ-eq, chlorpromazine equivalents; PANSS, Positive and Negative Syndrome Scale; AHRS, Auditory Hallucinations Rating Scale.
Means and standard deviations are reported unless otherwise specified.

[a] Post hoc tests revealed significantly fewer years of education for both patient groups than for the healthy controls.

[b] Data were not available for 8 AVH and 6 nAVH patients at Xijing Hospital, and schizophrenia patients at Beijing Huilongguan Hospital were medication free.

Table 2
FA differences between the HC, nAVH, and AVH groups for perisylvian language pathways in the combined dataset.

	HC	nAVH	AVH	Statistics *P* value
Left hemisphere				
Anterior segment	0.413 ± 0.030	0.417 ± 0.030	0.416 ± 0.031	0.544
Long segment	0.459 ± 0.032	0.465 ± 0.033	0.471 ± 0.033	0.003*
Posterior segment	0.510 ± 0.034	0.508 ± 0.034	0.516 ± 0.035	0.188
Right hemisphere				
Anterior segment	0.419 ± 0.030	0.423 ± 0.030	0.426 ± 0.030	0.070
Long segment	0.378 ± 0.077	0.392 ± 0.077	0.393 ± 0.078	0.110
Posterior segment	0.495 ± 0.039	0.488 ± 0.039	0.490 ± 0.039	0.290

Means and standard deviations are reported unless otherwise specified. HC, healthy controls; nAVH, schizophrenia patients without auditory verbal hallucinations; AVH, schizophrenia patients with auditory verbal hallucinations.

* Difference is significant with a Bonferroni-corrected threshold of $P < 0.008$.

groups in all four sites (HC < nAVH < AVH, Fig. 2). There were no significant between-group differences in the FA values for the anterior segment or the posterior segment of the left perisylvian language network in the data from any of the four sites. In the right perisylvian language network, none of the three segments showed significant between-group differences in any of the four sites.

3.4. Meta-analyses

In the meta-analyses, the AVH group showed significantly higher FA values extracted from the long segment of the left perisylvian language network compared with the HC group (Cohen's $d = 0.38$, $P = 0.0013$, Table 3, Fig. 3). The left long segment did not reveal significant group differences in the group contrasts between AVH and nAVH or between nAVH and HC using our Bonferroni-corrected threshold of $P \leq 0.016$. As presented in Table 3, Group differences between the three group contrasts (AVH with HC, nAVH with HC, and AVH with nAVH) were not detected for the bilateral anterior segments, the right long segment or the bilateral posterior segments of the perisylvian language network.

4. Discussion

Using diffusion MRI scans from a relatively large cohort of schizophrenia patients with AVH (the largest such sample size published to date) recruited from four different sites, we investigated the microstructural integrity of the perisylvian language pathways in schizophrenia patients with AVH. In this analysis we found a significantly higher FA value for the long segment of the left perisylvian language network in the AVH group compared to the HC group. The nAVH group showed an intermediate value for this segment compared to the AVH group or the HC group but did not differ significantly from either group. In the replication analyses, we consistently found an increasing trend, HC group < nAVH group < AVH group, in the FA measurements for this segment. In addition, the prospective meta-analysis consistently revealed a

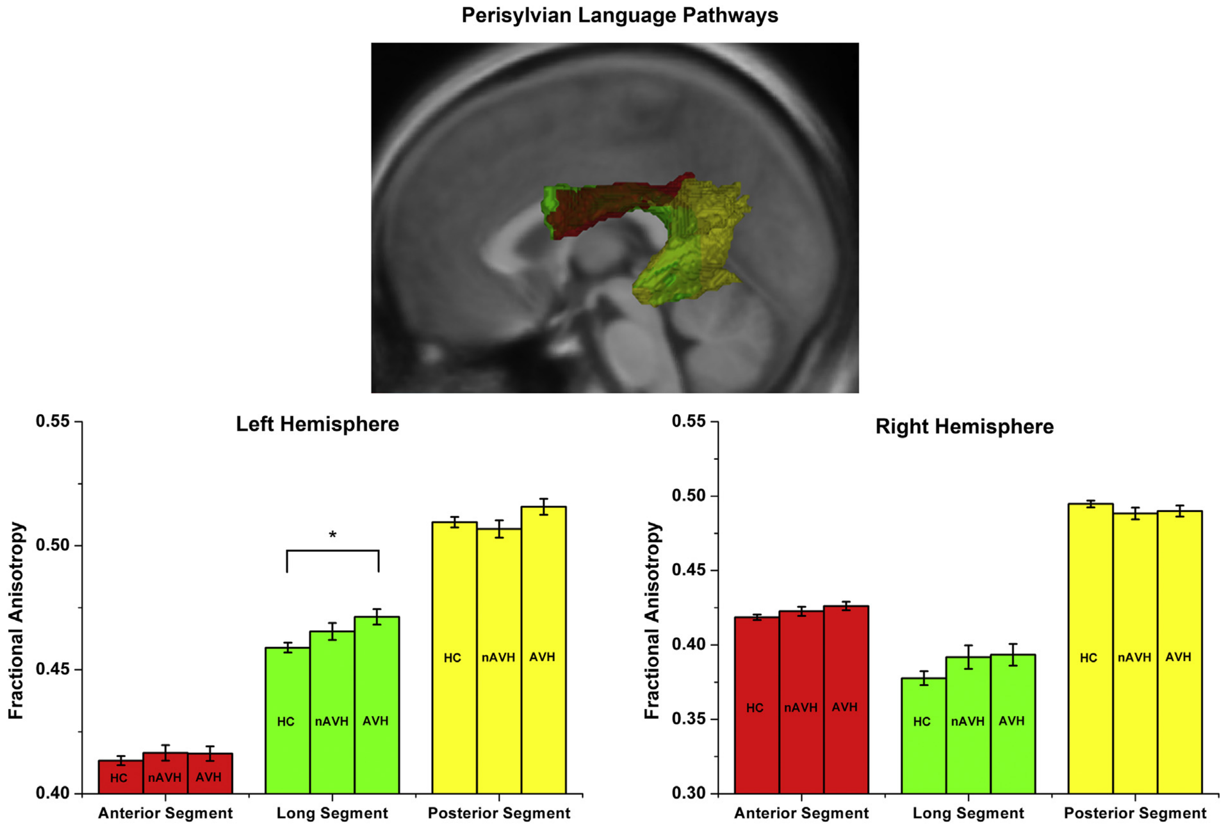

Fig. 1. Differences in FA value between healthy controls (HC), schizophrenia patients without auditory verbal hallucinations (nAVH), and schizophrenia patients with auditory verbal hallucinations (AVH) in the anterior, long, and posterior segments of the perisylvian language network for the combined dataset. The asterisk (*) indicates a statistically significant difference at $P < 0.05$ with Bonferroni correction for multiple comparisons. Error bars indicate standard errors.

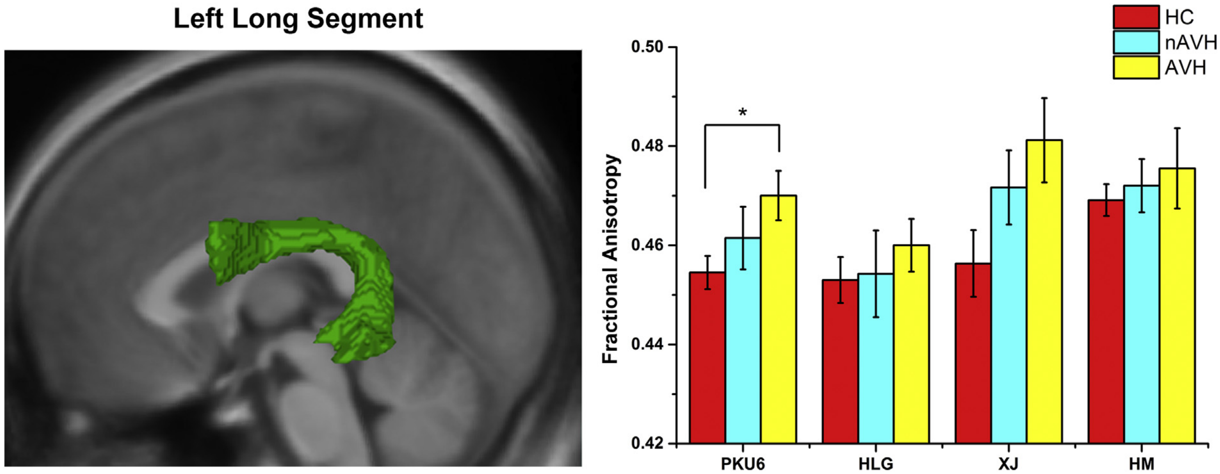

Fig. 2. Differences in FA value between healthy controls (HC), schizophrenia patients without auditory verbal hallucinations (nAVH), and schizophrenia patients with auditory verbal hallucinations (AVH) in the long segment of the left perisylvian language network for each site (PKU6, HLG, XJ and HM). The asterisk (*) indicates a statistically significant difference at $P < 0.05$ with Bonferroni correction for multiple comparisons. Error bars indicate standard errors.

significantly greater FA measurement for the AVH group compared to the HC group.

The primary finding of aberrant structural connectivity between Wernicke's region and Broca's region in patients with AVH supports the current influential hypothesis that AVHs are associated with altered connectivities in the language network (Curcic-Blake et al., 2017; Geoffroy et al., 2014; Jardri et al., 2011) and is consistent with current neurobiological models of dysconnectivity in schizophrenia. The FA measurement is commonly regarded as an index of microstructural integrity with a higher FA indicating hyperconnectivity and a lower FA indicating hypoconnectivity (Rotarska-Jagiela et al., 2009). The finding of hyperconnectivity of the left long segment in the patients with AVH, as indicated by a greater FA, is concordant with previous DTI findings (Hubl et al., 2004; Knochel et al., 2012; Psomiades et al., 2016; Rotarska-Jagiela et al., 2009; Seok et al., 2007). For instance, Hubl and her colleagues' DTI study showed that patients with AVH had greater directionality between language regions than healthy controls (Hubl et al., 2004). A similar difference pattern of white matter was reported in a multimodal MRI study, in which the white matter density of the ROI in the left SLF was greater in the hallucinating group than in the control group (Seok et al., 2007). In a recent TBSS study, schizophrenia patients had the highest FA value in the AF, followed by relatives and controls (Knochel et al., 2012).

It is tempting to speculate that the hyperconnectivity pattern of the left long segment that directly connects Broca's region and Wernicke's region could lead to elevated functional coupling between the frontal and temporal cortices, which are involved in the generation and perception of inner speech, and could, therefore, contribute to the abnormal hyperactivation of these regions found in functional MRI (fMRI) studies (Shergill et al., 2003). Structural connectivity in the brain is the basis for functional connectivity (Huang and Ding, 2016). In the following discussion, we will introduce further evidence from fMRI studies that support the finding of increased FA in the long segment. Hoffman and colleagues found that the functional connectivity between the Wernicke's region and the inferior frontal gyrus was significantly elevated in patients with AVH compared with nonhallucinating patients (Hoffman et al., 2011). A recent coordination-based meta-analysis, which used ten positron emission tomography or fMRI studies, found that patients experiencing AVHs demonstrated significantly increased activation likelihoods in multiple regions including the Broca's area and the superior temporal gyrus (Jardri et al., 2011).

Another replicable finding in our study was that the nAVH group showed an intermediate FA value in the long segment of the left perisylvian language pathways across all the analyses but did not differ significantly from either of the two groups (Bonferroni-corrected). An alternative interpretation for this replicated finding is that AVH of schizophrenia may increase the FA of the left AF whereas the other disease processes of schizophrenia may decrease the FA. There are several DTI studies that support this idea (Benetti et al., 2015; de Weijer et al., 2013; Hubl et al., 2004; Seok et al., 2007; Shergill et al., 2007). In an early DTI study in which patients were divided into three subgroups (currently hallucinating, previously hallucinated, and never hallucinated), the researchers found that the currently hallucinating group showed the highest FA in the SLF among the three groups and that the never hallucinated group showed the lowest FA (Shergill et al., 2007). In a multimodel investigation using diffusion MRI and fMRI, Benetti and colleagues found that both the structural and functional connectivity of the long segment within the left perisylvian language network

Table 3
Meta-analyses of the FA values of the perisylvian language network for the three contrasts.

	AVH - HC		nAVH - HC		AVH - nAVH	
	Cohen's *d*	*P* value	Cohen's *d*	*P* value	Cohen's *d*	*P* value
Left hemisphere						
Anterior segment	0.0945	0.5082	0.0772	0.5225	0.0204	0.8893
Long segment	0.3765	0.0013*	0.1763	0.1445	0.2084	0.1558
Posterior segment	0.1666	0.1516	−0.0653	0.6388	0.1412	0.3359
Right hemisphere						
Anterior segment	0.2810	0.1751	0.1442	0.2320	0.1835	0.2125
Long segment	0.2063	0.1381	0.1807	0.1343	0.0396	0.7873
Posterior segment	−0.1313	0.2580	−0.1621	0.1792	0.0223	0.8793

AVH, schizophrenia patients with auditory verbal hallucinations; HC, healthy controls; nAVH, schizophrenia patients without auditory verbal hallucinations.

* Difference is significant with Bonferroni correction.

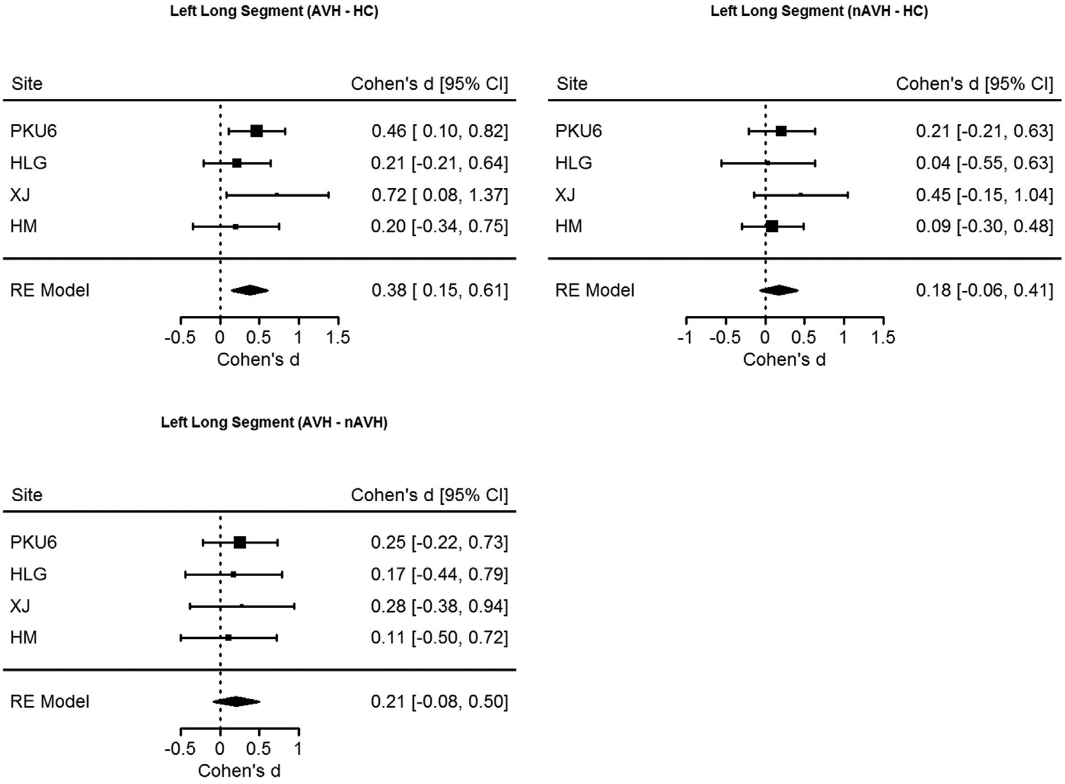

Fig. 3. The forest plots for the meta-analysis of the FA value extracted from the long segment of the left perisylvian language network for the three contrasts (AVH - HC, nAVH - HC and AVH - nAVH). The size of the box is directly related to the "weighting" of the site in the analyses. The overall estimate does not cross the line of "no-effect" for the AVH - HC contrast, which thus appears to be significant ($P < 0.05$). CI, confidence interval; RE, random-effects.

were higher in AVH than in nAVH patients, although the differences were not significant (Benetti et al., 2015).

The hyperconnectivity pattern of the long segment of the left perisylvian language pathways in patients with AVH is in concordance with the theory of use-dependent plasticity (Rotarska-Jagiela et al., 2009). Therefore, our finding may be interpreted to mean that as the connectivity strength between Wernicke's region and Broca's region strengthens, more inner speech is generated in patients with AVH. As a result, self-monitoring may fail to distinguish the excessive inner speech from external stimuli, leading to AVH (Stephan et al., 2009). In addition, the hypothesis about hyperconnectivity in AVH may be able to be explained by the dominant neurodevelopmental model of schizophrenia (Lewis and Levitt, 2002), which postulates that the illness is the end state of abnormal neurodevelopmental processes that started years before the illness onset (Rapoport et al., 2012). The normal path for brain neurodevelopment includes establishing and pruning of axonal connections and is determined by the combined effects of a complex network of genes and a wide range of environmental factors. However, the pruning of neuronal processes, which removes unused neuronal branches and connections in the immature nervous system to ensure the proper formation of functional circuitry (Low and Cheng, 2006), has been shown to be abnormal in schizophrenia (Garey et al., 1998). This can lead to the preservation of exuberant fibers, resulting in excessive structural connectivity between specific regions. As a consequence, the higher FA in the AF found in the present study can thus be expected to be observed in DTI studies.

Although the hyperconnectivity pattern of the left long segment in AVH is reasonable given previous MRI studies and can reasonably be interpreted in a neurodevelopmental context, some studies reported a decreased FA instead of an increased FA in the AF in individuals with AVHs compared with healthy controls (Catani et al., 2011; Curcic-Blake et al., 2015; McCarthy-Jones et al., 2015). The reasons for the discrepancy, beyond the high heterogeneity in schizophrenia, probably include differences in the analytical methods, different ethnic origins of the patients under investigation, and differences in the criteria used to make a categorical distinction between patients with and without AVH. Another important aspect, the limited sample size used in the vast majority of studies, should be considered (Allen et al., 2012; Curcic-Blake et al., 2017; Weiss and Heckers, 1999). Increasing attention has been paid to the problem of having small sample sizes with low statistical power in biomedical research (Button et al., 2013). The significant difference that our study found in the analysis using the combined dataset combined with the lack of a significant difference in the independent analyses for each site indicates the importance of sample size. However, one of the strengths of the present study is that we included a large sample of clinically well characterized schizophrenia patients with and without AVH, who matched on a number of demographic and clinical variables. To our knowledge, our study involved the highest number of schizophrenia patients with AVH and without AVH (103 and 96) to date of the AVH studies that used DTI. A further strength of our study is that high quality diffusion MRI data were collected using a common protocol across the 4 sites and that the analyses were performed for each site independently. Thus, these can be regarded as a series of replication studies. The relative large sample and the use of replicate studies can increase the statistical power and contribute to detecting potential differences between AVH and nAVH. The independent analyses from each site, using the limited samples, did not reveal significant differences with a Bonferroni correction. This points out the importance of having a sufficient sample in DTI studies of schizophrenia with AVH. Furthermore, the prospective meta-analysis, seemingly a somewhat circular analysis, revealed a robust and consistent abnormal pattern of AF to supplement our primary result.

There are several limitations of the present study that need to be considered. First, an ROI-based method can detect differences in a specific tract, but it cannot point out the specific position along the tract that is affected by AVH. A point-based analysis of the white matter tract, i.e. an automated fiber quantification (Yeatman et al., 2012), should be performed in future studies. Second, the medication histories for 14 of the patients at the XJ site were not available in the present study. Therefore, a confounding effect of medication exposure on the results of our study cannot be ruled out.

In conclusion, our investigation found that the schizophrenia patients with AVH expressed excessive integrity of the long segment within the left perisylvian language network compared to healthy controls and that the patients without AVH had an intermediate FA value for this segment relative to the AVH patients and healthy controls but did not differ significantly from either group. Our findings not only provide reliable support for the hypothesis that structural hyperconnectivity between Wernicke's region and Broca's region may represent a neuroanatomical signature in AVH of schizophrenia but also partially confirm the influential pathophysiological models of AVH based on a potential failure in the process of recognizing self-generated inner speech.

Conflict of interest

All authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Sangma Xie: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Bing Liu:** Conceptualization, Investigation, Writing - review & editing. **Jiaojian Wang:** Conceptualization, Investigation, Writing - review & editing. **Yuan Zhou:** Methodology, Writing - review & editing. **Yue Cui:** Methodology, Writing - review & editing. **Ming Song:** Data curation. **Yunchun Chen:** Data curation. **Peng Li:** Data curation. **Lin Lu:** Data curation. **Luxian Lv:** Data curation. **Huaning Wang:** Data curation. **Hao Yan:** Data curation. **Jun Yan:** Data curation. **Hongxing Zhang:** Data curation. **Dai Zhang:** Data curation. **Tianzi Jiang:** Conceptualization, Funding acquisition, Investigation, Project administration, Writing - review & editing.

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Appendix A. Supplementary data

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