Altered Integrity of Perisylvian Language Pathways in Schizophrenia: Relationship to Auditory Hallucinations

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Background: Functional neuroimaging supports the hypothesis that auditory verbal hallucinations (AVH) in schizophrenia result from altered functional connectivity between perisylvian language regions, although the extent to which AVH are also associated with an altered tract anatomy is less clear.

Methods: Twenty-eight patients with schizophrenia subdivided into 17 subjects with a history of AVH and 11 without a history of hallucinations and 59 age- and IQ-matched healthy controls were recruited. The number of streamlines, fractional anisotropy (FA), and mean diffusivity were measured along the length of the arcuate fasciculus and its medial and lateral components.

Results: Patients with schizophrenia had bilateral reduction of FA relative to controls in the arcuate fasciculi ($p < .001$). Virtual dissection of the subcomponents of the arcuate fasciculi revealed that these reductions were specific to connections between posterior temporal and anterior regions in the inferior frontal and parietal lobe. Also, compared with controls, the reduction in FA of these tracts was highest, and bilateral, in patients with AVH, but in patients without AVH, this reduction was reported only on the left.

Conclusions: These findings point toward a supraregional network model of AVH in schizophrenia. They support the hypothesis that there may be selective vulnerability of specific anatomical connections to posterior temporal regions in schizophrenia and that extensive bilateral damage is associated with a greater vulnerability to AVH. If confirmed by further studies, these findings may advance our understanding of the anatomical factors that are protective against AVH and predictive of a treatment response.

Key Words: Arcuate fasciculus, auditory verbal hallucinations, diffusion tensor imaging, language, schizophrenia, tractography, white matter

The hypothesis that psychotic symptoms result from dysconnectivity between different cortical areas can be traced back to early 19th century associationist theories of brain function (1,2). More recently the development of brain imaging and electrophysiological techniques has enabled neuroscientists to study dysconnectivity in vivo in patients with psychotic symptoms (3,4). To date these studies have primarily focussed on auditory verbal hallucinations (AVH) in patients with schizophrenia.

Positron emission tomography (5), functional magnetic resonance imaging (MRI) (6–9), and electroencephalography (10) studies have reported that schizophrenia is associated with abnormal interactions between frontal, parietal, and temporal brain regions during tasks that engage language processing. These abnormalities are especially marked in patients with vulnerability towards experiencing AVH, particularly when these patients are performing cognitive tasks that require the generation and/or appraisal of inner or overt speech (11). The perisylvian language areas implicated in these studies have also been found to be activated when patients are actually experiencing AVH (12–14). Hence, there is increasing evidence that patients with schizophrenia, particularly those who suffer from AVH, have abnormalities in the functional activation and interaction of perisylvian language regions. These perisylvian regions are interconnected by the arcuate fasciculus that, using diffusion tensor imaging (DTI) tractography, has recently been reported to be composed of three distinct segments (15). The direct long segment connects posterior temporal (i.e., Wernicke's territory) to inferior frontal (i.e., Broca's territory) cortex. This segment is larger on the left hemisphere compared with the right in the majority of the population, with males being more left lateralized than females (16). In addition to the long direct segment, two other shorter lateral segments indirectly connect the perisylvian language areas: 1) the anterior indirect segment connects the inferior parietal region (i.e., Geschwind's territory) to Broca's territory; and 2) the posterior indirect segment connects Wernicke's to Geschwind's territory. To date no one has investigated whether there are differences in the microstructural integrity of these three segments in patients with schizophrenia.

Previous studies have shown that DTI can identify changes in the microstructural integrity of white matter in schizophrenia. The majority of DTI studies in schizophrenia have used voxel-based methods (VBM) and region of interest (ROI) analyses (for recent reviews of DTI studies in schizophrenia, see [17,18]). Most of these studies have reported differences in diffusion-based indexes of white matter integrity (e.g., reduced fractional anisotropy [FA] or increased mean diffusivity [MD]) in many white matter regions, including the perisylvian regions containing the fibers of the arcuate fasciculus (19–26). Interestingly, only two studies have used DTI in relation to AVH and reported that vulnerability to hallucinations is associated with reduced FA in the medial voxels and increased FA in the lateral voxels of the regions containing the arcuate fasciculus (21,23). In particular, the first (21) showed statistically significant higher FA in the most lateral voxels of the arcuate region in patients with AVH compared with patient without AVH and controls, whereas the second (23) reported a relative increase of FA in patients with AVH compared with patients without AVH but not compared with controls. Finally, a further study (27) reported no differences in the

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Table 1. Subject Demographics

Variable	Patients with Schizophrenia ($n = 28$)	Healthy Controls ($n = 59$)	Group Comparisons
Age, years	34.83 (8.43)	31.3 (8.3)	$t = 1.97$, $p = .12$
Education, years	13.77 (2.28)	14.4 (3.2)	$t = .4$, $p = .702$
Premorbid IQ	107.25 (8.89)	107.4 (8.05)	$t = .066$, $p = .948$
Duration of Illness, years	9.47 (8.14)	—	—
Total SAPS Score	4.15 (2.64)	—	—
Total SANS Score	5.77 (3.49)	—	—
Sex, *n*			
Male	26	53	
Female	2	6	$\chi^2 = .01$, $p = .93$
Handedness	All right	All right	

Numbers are means with standard deviations. Group comparisons were by Student *t* test or χ^2 test. SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

diffusion indexes of the arcuate region in patients with schizophrenia compared with healthy controls.

The reasons for these discrepancies are probably partly due to differences in the inclusion criteria, leading to investigation of clinically heterogeneous groups and methodological limitations associated with VBM and ROI analyses of DTI data. These limitations include the influence of intersubject variability, operator-dependent biases on ROI placement, partial volume artefacts, and misregistration in regions of high and low anisotropy (28). However, perhaps the greatest limitation of VBM and ROI methods is the inability to dissect out individual tracts running within a specific pathway and quantify tract-specific microstructural integrity (28–35). This limitation is particularly significant for regions containing voxels crossed by fibers that belong to different tracts in which it is difficult to assign FA or MD differences to one of the many tracts coursing through this region.

Therefore, in this study we used DTI tractography to analyze, for the first time, the microstructural integrity of the three segments of the arcuate fasciculus in schizophrenia, particularly in relation to the vulnerability of patients to AVH. Based on previous studies, our main hypothesis was that all patients with schizophrenia would have reduced FA in the medial long direct segment connecting Broca's and Wernicke's territory. Our subsidiary hypothesis was that patients with AVH would have increased FA in the most lateral connections (i.e., anterior and posterior indirect segments).

Methods and Materials

Subject Recruitment and Clinical Assessment

We recruited 28 right-handed patients with schizophrenia from inpatient wards and outpatient clinics of the South London and Maudsley National Health Service Foundation Trust and 59 healthy controls. Premorbid intelligence quotient (IQ) was assessed with the National Adult Reading Test (36). For both groups, subjects were excluded if they had a premorbid IQ score of less than 80, history of head injury, severe neurological symptoms or speech or hearing difficulties; fulfilled current DSM-IV criteria for abuse or dependence of illicit drugs or alcohol; or had any contraindications to MRI scanning, including metal implants and claustrophobia. A diagnosis of schizophrenia was based on DSM-IV criteria (37). Patients with schizophrenia were assessed using the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) (38). Patients were matched for age, IQ, and gender with a sample of healthy volunteers (Table 1).

Patients were further subdivided into two groups according to the presence of history of AVH. Inclusion criteria for the group without AVH were the following: 1) a score of 0 for hallucinations in the SAPS; 2) no history of previous AVH as reported by the patient; and 3) no history of current or previous AVH as reported by the next of kin. Each patient's case notes were examined to corroborate the findings from this assessment. We excluded patients in whom there was any uncertainty about the presence or absence of AVH (either at the time of assessment or over the entire course of their illness prior to that point). Eleven patients denied previous or current AVH in their clinical histories, which was corroborated by case notes and collateral informants. Seventeen patients had a previous history of AVH; of these, seven described experiencing AVH at the time of scanning. There were no significant differences between these two subgroups in demographic characteristics (Table 2), including age, years of education, premorbid IQ, duration of illness, and medication status. The SAPS and SANS scores did not differ significantly between the patient groups. Approval was obtained from the Ethics Committee of the South London and Maudsley National Health Service Foundation Trust, and all subjects gave written informed consent.

DTI Data Acquisition

Data were acquired on a GE Signa 1.5 Tesla LX MRI system (General Electric, Milwaukee, Wisconsin) with 40 mT/m gradients, using a cardiac gated acquisition sequence fully optimized for diffusion tensor MRI of white matter, providing isotropic resolution (2.5 mm × 2.5 mm × 2.5 mm). Full details of the acquisition sequence are provided by Jones *et al.* (39). Following correction for the image distortions introduced by the application of the diffusion encoding gradients, the diffusion tensor was determined in each voxel following the method of Basser and colleagues (40,41). FA,

Table 2. Demographic Characteristics of Patients with Schizophrenia According to the Presence of Auditory Hallucinations

Variable	Patients without Hallucinations	Patients with Hallucinations	Group Comparisons
n	11	17	
Age, years	36.91 (9.65)	33.64 (7.21)	$F = 2.63$, $p = .083$
Education, years	13.28 (2.63)	14.37 (2.45)	$F = .375$, $p = .693$
Premorbid IQ	110.22 (6.5)	104.63 (10.07)	$F = 1.27$, $p = .292$
Duration of Illness, years	11.16 (9.63)	9.30 (7.51)	$t = .6$, $p = .556$
Total SAPS Score	3 (2.19)	5.5 (2.72)	$U = 13$, $p = .144$
Total SANS Score	5.83 (3.66)	5.71 (3.64)	$U = 20$, $p = .886$
Antipsychotic Medication			
Atypicals:typicals	5:3	15:2	$\chi^2 = .93$, $p = .335$
CPZ equivalents (mg)	507 (567)	318 (148)	$t = .8$, $p = .423$
Duration of treatment (months)	2.8 (3.3)	5.6 (4.5)	$t = -1.3$, $p = .213$
Gender			$\chi^2 = .588$, $p = .745$
Male	11	15	
Female	0	2	

Numbers are means with standard deviations. Group comparisons were by Student *t* test or χ^2 test. SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; CPZ, chlorpromazine.

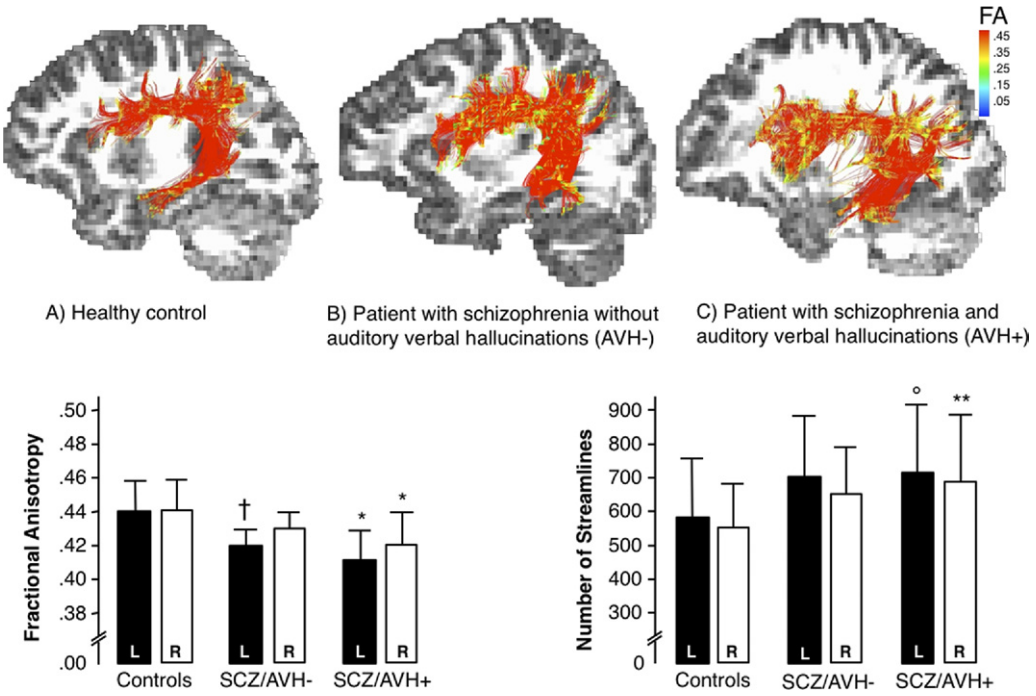

Figure 1. Tractography reconstruction of the arcuate fasciculus and tract-specific measurements of the fractional anisotropy (FA) and number of streamlines. Upper row, FA values mapped onto the tractography reconstruction of the arcuate fasciculus in a healthy control **(A)**, a patient with schizophrenia (SCZ) without auditory verbal hallucinations (AVH−) **(B)**, and a patient with schizophrenia and auditory verbal hallucinations (AVH+) **(C)**. *Differences are significant at $p < .001$ vs. healthy comparison group. †Differences are significant at $p = .042$ vs. healthy comparison group. **Differences are significant at $p = .029$ vs. healthy comparison group. °Differences are significant at $p = .006$ vs. healthy comparison group. L, left; R, right.

MD, and color-coded maps were generated for each individual. Half of the data sets were reflected about the midline before performing tractography to ensure blindness to side.

Tractography and Virtual Dissections

The software for reconstructing the trajectories of tracts from diffusion tensor data was written in the C programming language and based on the procedure originally described by Basser *et al.* (42). Details of the method have been previously published (15,39,43,44). We performed virtual dissections of the left and right arcuate fasciculus and its three segments connecting the frontal, parietal, and temporal regions (15) (Figures 1 and 2). All dissections were performed for each subject in the native space. A single ROI was defined on the FA map to encompass the streamlines of the arcuate fasciculus lateral to the corona radiata and medial to the cerebral cortex. The ROI was defined on axial slices as this projection facilitates the visualization of the borders between the streamlines of the arcuate and those of the corona radiata.

A two-ROI approach was used to analyze separately the medial and the lateral segments of the arcuate bundle. To dissect the medial streamlines of the arcuate fasciculus, two spatially separated regions were defined on the color-coded maps in the frontal and posterior temporal lobe. The frontal ROI was defined on a coronal slice anterior to the central sulcus. Here the voxels containing fibers of the arcuate fasciculus are colored in green, which indicate an anterior-posterior (or vice versa) orientation of the arcuate fibers through this region. The temporal ROI was defined on an axial slice through the posterior portion of the temporal stem, just below the supramarginal gyrus. Here the voxels containing the arcuate fasciculus are colored in blue, indicating a dorsal-ventral (and vice versa) orientation. All streamlines passing through both frontal and temporal regions were visualized and attributed to the long direct segment connecting Broca's and Wernicke's territories (45,46).

The same approach was repeated for the right hemisphere (15). To dissect the most lateral streamlines of the arcuate fasciculus, which consist of an anterior and posterior segment connecting classical language areas to the inferior parietal lobule, a third ROI was used. This third ROI was defined on a sagittal slice through the angular and supramarginal gyrus. All streamlines passing through inferior frontal region and the inferior parietal lobule were considered to belong to the anterior indirect segment and visualized in green, whereas all streamlines passing through the posterior temporal and the inferior parietal lobule were considered to belong to the posterior indirect segment and visualized in yellow (16). FA and MD were calculated at regular (0.5 mm) intervals along the defined tracts, and the means for each tract were computed (31). The number of streamlines was also calculated for each tract to obtain proxy measurements of tract volume. There was no statistically significant group × hemisphere interaction ($p = .525$) or group × hemisphere × ROI interaction ($p = .944$).

Statistical Analysis

Demographic differences between patients and healthy controls and between patients with and without AVH were analyzed using independent-samples Student *t* tests for normally distributed data and nonparametric tests (Mann-Whitney *U* test or χ^2) as appropriate. For the analysis of the arcuate fasciculus, an independent-samples Student *t* test was used, whereas for the three segments of the arcuate fasciculus, a multifactorial general linear model analysis (repeated measures) was used with location (three locations corresponding to the three segments) and side (left or right) as within-subjects factors and diagnosis as the between-subjects factor. The same analysis was repeated after dividing the patients into two

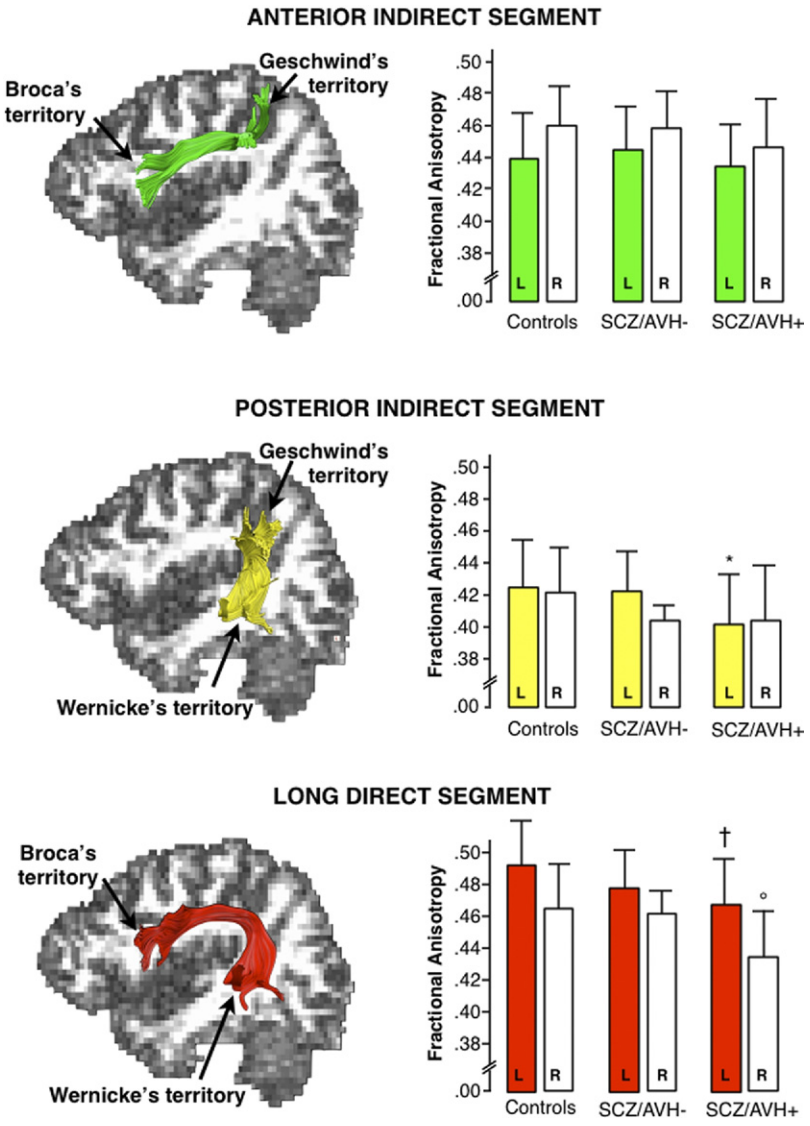

Figure 2. Differences between patients with schizophrenia (SCZ) without auditory verbal hallucinations (AVH−), patients with auditory verbal hallucinations (AVH+), and healthy controls in three segments of the arcuate fasciculus. *Differences are significant at $p = .011$ versus healthy controls. †Differences are significant at $p = .009$ versus healthy controls. °Differences are significant at $p = .008$ versus healthy controls. *P* values are corrected for multiple comparisons. L, left; R, right.

groups according to the presence or absence of a history of AVH. Differences were considered statistically significant after Bonferroni correction for multiple comparisons. Corrected *p* values are presented in Tables 3 and 4.

Results

Comparisons Between Patients with Schizophrenia and Controls

There was a significant increase in the number of streamlines in both the left ($p = .003$) and the right ($p < .001$) arcuate fasciculus in the schizophrenia group compared with controls. There was also a significant reduction of FA in both the left and right arcuate fasciculi in subjects with schizophrenia compared with controls ($p < .001$) (Table 3 and Figure 1). There were no between-group differences in the MD values (Table 3).

Repeated-measures analysis of measurements extracted from the single segments of the arcuate fasciculus revealed a significant group effect [$F(1,53) = 8.304$; $p = .006$], a group-by-tract interaction [Hotelling's Trace, $F(2,52) = 5.572$; $p = .006$], and a hemisphere-by-tract interaction [Hotelling's Trace, $F(2,52) = 28.887$; $p < .001$] for FA. The same analysis showed no significant group effect or interaction for the MD or the number of streamlines. These differences remained significant after covarying for age, IQ, and number of streamlines. Post-hoc comparisons of single tracts revealed a significant reduction of FA in the left and right direct long segments ($p = .003$ and $p = .015$, respectively) and in the left and right posterior indirect segments ($p = .026$ and $p = .006$, respectively) in patients with schizophrenia relative to controls. There were no significant differences in the anterior indirect segment (Table 3).

Comparisons Between Patients with Hallucinations and Patients Without a History of Hallucinations and Controls

Between-group differences were found in the number of streamlines in the left ($p = .01$) and right ($p = .003$) arcuate fasciculus and in the FA of the arcuate fasciculus bilaterally ($p < .001$) (Table 4). Post-hoc analyses revealed that patients with AVH had a greater number of streamlines than healthy controls in both the left ($p = .029$) and right ($p = .006$) arcuate fasciculus and lower FA in the left ($p < .001$) and right ($p < .001$) arcuate fasciculus. Patients without a history of hallucinations did not show significant differences in the number of streamlines in the arcuate fasciculi relative to controls. They had lower FA than controls in the left arcuate

Table 3. Tract-Specific Measurements of Number of Streamlines (NS), Fractional Anisotropy (FA), and Mean Diffusivity (MD)

	Healthy Controls	Subjects with Schizophrenia	Group comparisons *p* value
Arcuate Fasciculus			
NS (left)	582 ± 172	713 ± 205	.003
NS (right)	550 ± 136	673 ± 183	<.001
FA (left)	.44 ± .02	.42 ± .02	<.001
FA (right)	.44 ± .02	.43 ± .02	<.001
MD (left)	.71 ± .03	.71 ± .05	.949
MD (right)	.70 ± .03	.70 ± .04	.267
Anterior Segment			
NS (left)	62 ± 37	58 ± 35	.647
NS (right)	103 ± 46	78 ± 39	.013
FA (left)	.44 ± .03	.44 ± .03	.893
FA (right)	.45 ± .02	.45 ± .03	.144
MD (left)	.71 ± .03	.71 ± .04	.608
MD (right)	.70 ± .03	.69 ± .04	.141
Posterior Segment			
NS (left)	80 ± 44	65 ± 37	.125
NS (right)	72 ± 50	49 ± 31	.032
FA (left)	.42 ± .02	.40 ± .03	.026
FA (right)	.41 ± .02	.39 ± .02	.006
MD (left)	.73 ± .03	.72 ± .05	.247
MD (right)	.73 ± .02	.72 ± .04	.159
Long Segment			
NS (left)	45 ± 27	49 ±30	.545
NS (right)	19 ± 26	7 ±13	.006
FA (left)	.48 ± .02	.46 ± .02	.003
FA (right)	.46 ± .03	.44 ± .03	.015
MD (left)	.71 ± .03	.77 ± .04	.491
MD (right)	.70 ± .02	.69 ± .04	.389

Numbers are means ± standard deviations.

fasciculus ($p = .042$) but not in the right (Table 4 and Figure 2). There were no significant differences in the number of streamlines or FA between patients with and without AVH. There were no differences in the MD in the arcuate fasciculus between any of the groups (Table 4).

Assessment of the single segments of the arcuate fasciculi using a repeated-measures analysis of FA revealed a significant group effect [$F(2,52) = 4.67$; $p = .014$], a group-by-tract interaction [Hotelling's Trace, $F(4,100) = 2.84$; $p = .028$] and a hemisphere-by-tract interaction [Hotelling's Trace, $F(2,51) = 14.48$; $p < .001$]. These differences remained significant after covarying for age, IQ, and number of streamlines. There were no between-group differences in the number of streamlines and mean diffusivity values from the single segments (Table 4).

Post-hoc analyses revealed lower FA in patients with a history of AVH compared with controls in the left direct ($p = .009$) and posterior indirect ($p = .01$) segments and in the right direct segment ($p = .008$). There were no differences in FA between patients with and without AVH (Table 2 and Figure 2) and no differences in the MD and number of streamlines between the three groups (Table 4).

Discussion

Using DTI data, we performed virtual dissections of the perisylvian language pathways to study patients with schizophrenia and controls. We report bilaterally reduced FA in the arcuate fasciculi of patients with schizophrenia, relative to controls. These findings are consistent with earlier DTI studies. However, further dissection of the three segments of the arcuate fasciculi suggested that reduced FA was limited to the long direct segment and the posterior indirect segment, connecting frontotemporal and temporoparietal regions, respectively. Also, within the long direct and posterior indirect segments, FA was lowest and bilateral in patients with a history of AVH. In patients without a history of AVH, FA was intermediate (but still reduced) and only significant on the left side. In contrast, there were no group differences in the anterior indirect segment connecting frontoparietal regions.

The finding that schizophrenia may be associated with abnormalities in specific language pathways that selectively connect to posterior temporal regions has not to our knowledge been reported before. However, it is supported by previous VBM studies, which have reported reduced gray (47,48) and white matter volume in posterior temporal regions in schizophrenia (49). It is also supported by electrophysiological and functional imaging studies that have reported functional dysconnectivity of auditory temporal regions in schizophrenia (8,10,50-56).

Table 4. Tract-Specific Differences Between Controls, Subjects with Schizophrenia Without AVH, and Subjects with Schizophrenia and AVH

Tracts	Healthy Controls	Patients without Hallucinations	Patients with Hallucinations
Arcuate fasciculus			
NS (left)	582 ± 172	708 ± 174	717 ± 228[a]
NS (right)	550 ± 136	655 ± 158	684 ± 201[b]
FA (left)	.441 ± .020	.424 ± .015[c]	.416 ± .020[d]
FA (right)	.442 ± .022	.430 ± .015	.418 ± .024[d]
MD (left)	.714 ± .027	.711 ± .048	.714 ± .052
MD (right)	.709 ± .026	.706 ± .049	0.697 ± .043
Anterior segment			
NS (left)	62 ± 37	57 ± 42	59 ± 32
NS (right)	103 ± 46	79 ± 44	77 ± 37
FA (left)	.439 ± .028	.445 ± .026	.435 ± .026
FA (right)	.458 ± .024	.457 ± .021	.445 ± .029
MD (left)	.711 ± .028	.707 ± .047	.707 ± .043
MD (right)	.703 ± .029	.693 ± .047	.690 ± .037
Posterior Segment			
NS (left)	80 ± 44	66 ± 47	65 ± 31
NS (right)	72 ± 50	59 ± 34	42 ± 29
FA (left)	.418 ± .025	.416 ± .023[e]	.397 ± .029[f]
FA (right)	.416 ± .025	.399 ± .010	.399 ± .032
MD (left)	.729 ± .033	.714 ± .051	.722 ± .053
MD (right)	.730 ± .028	.719 ± .044	.719 ± .038
Long Segment			
NS (left)	45 ± 27	55 ± 32	44 ± 30
NS (right)	19 ± 26	7 ± 10	7 ± 15
FA (left)	.479 ± .026	.466 ± .021	.457 ± .026[g]
FA (right)	.464 ± .028	.461 ± .013[h]	.434 ± .027[i]
MD (left)	.710 ± .032	.711 ± .046	.700 ± .037
MD (right)	.706 ± .027	.701 ± .053	.696 ± .040

Numbers are means ± standard deviations.

AVH, auditory verbal hallucination; FA, fractional anisotropy; MD, mean diffusivity; NS, number of streamlines.

[a] $p = .029$ vs. healthy controls.
[b] $p = .006$ vs. healthy controls.
[c] $p < .042$ vs. healthy controls.
[d] $p < .001$ vs. healthy controls.
[e] $p = .076$ vs. schizophrenia with auditory hallucinations.
[f] $p = .011$ vs. healthy controls.
[g] $p = .009$ vs. healthy controls.
[h] $p = .06$ vs. schizophrenia with auditory hallucinations.
[i] $p = .008$ vs. healthy controls.

A further novel finding is the report of changes in the connections between posterior temporal regions (i.e., Wernicke's territory) and the inferior parietal lobe (i.e., Geschwind's territory). The exact role of the Geschwind's territory is still largely unknown. Recent functional neuroimaging studies have reported that temporoparietal connections form part of an extended network associated with specific language and memory functions that are abnormal in schizophrenia. These include comprehension of global coherence of narratives (57), processing concrete concepts (58), episodic memory retrieval of words (59), and verbal working memory (60).

Our findings also support the hypothesis that there may be selective vulnerability of specific anatomical connections in schizophrenia. This leads to questions about what might underpin the vulnerability of these specific tracts and ultimately to what factors might be protective. Previous histopathologic studies in schizophrenia suggest several possibilities. For example, reduced FA might reflect abnormalities of myelin and oligodendroglial architecture (61) and/or aberrantly located neurons in myelinated fiber bundles (62) that have been reported in patients with schizophrenia. Decreased FA has also been reported in demyelinating disorders that are associated with psychotic symptoms, including adrenoleukodystrophy (63,64), and in the white matter that may otherwise appear normal in conventional MRI (65). These studies therefore suggest several pathologic processes might be associated with findings of reduced FA in specific segments of the arcuate fasciculus, and additional studies are currently needed to understand these processes better.

In this study one hypothesis we tested, based on the findings of Hubl *et al.* (21), was that patients with a vulnerability to hallucinations would have increased FA in the lateral indirect segments and reduced FA in the medial long direct segment compared with control subjects. Consistent with this study, we reported reduced FA in the medial, long direct segment. However, we also reported reduced FA in the lateral posterior indirect segment. Hence, our study suggests that the defining factor of reduced FA in schizophrenia with AVH is the connection with the posterior temporal regions as opposed to the lateral versus medial segments predicted by Hubl *et al.* (21). One potential explanation for the discrepancy between the two studies, beyond possible differences in patient sampling or disease heterogeneity, is a difference in the methodologic approach applied. The tract-specific measurements method adopted by our study allowed us to quantify the microstructural integrity of a specific subpopulation of fibers. This represents a potential advantage over VBM group comparisons, which generate FA maps that can be affected by misregistration and partial volume artefacts. It could be argued that the method used in our study failed to sample the more lateral U-shaped fibers, which were previously reported to have increased FA using a VBM technique. Nevertheless, our findings are consistent with a recent study of schizophrenic patients with visual hallucinations, in which reduced FA was also reported in the inferior longitudinal fasciculus (66).

Another significant difference that we found between patients with and without AVH was the relative preservation of microstructural integrity of the right arcuate fasciculus in patients without AVH. This finding suggests that to experience AVH, abnormalities in white matter tracts need to be bilateral. This suggestion is supported by previous functional MRI studies, which have reported bilateral perisylvian activation during AVH in schizophrenia (14,67,68). One possible explanation of these findings is that increased bilateral activations result from reduced inhibition because of abnormal white matter integrity of callosal projections to these cortical regions (69,70). These abnormalities may, however, not be specific to AVH because a recent study reported that FA values in patients with schizophrenia were correlated with the severity of reality distortion (35).

The number of streamlines is usually considered to represent a surrogate measure of tract volume, and previous studies have reported for the arcuate fasciculus reduced number of streamlines (71) or no differences (31) in schizophrenia compared with controls. Therefore, an unexpected finding in our study was the higher number of streamlines in patients compared with controls. This finding was evident only in our analysis of the whole arcuate fasciculus following a single ROI approach and was not found in our two-ROI analysis of individual segments. In our opinion this finding is likely representative of a shortcoming of combining an FA threshold of .2 (i.e., as a stopping value for tracking) with a single-ROI approach (i.e., in which all voxels within a single ROI are used as starting seed points). If the FA within a single-ROI falls below this threshold, it could lead to an individual long streamline being incorrectly segmented and misregistered as two or more separate short streamlines. Therefore, in a patient group in which, on average, there are likely to be more regions containing voxels with low FA, this will lead to a greater number of short streamlines.

To test this hypothesis, we carried out a post-hoc analysis of the relationship between the FA and number of streamlines in patients with schizophrenia and found a statistically significant negative correlation between these measures in both left (–.404, $p < .001$) and right (–.398, $p = .003$) arcuate fasciculi. This shortcoming is avoided by applying a two-ROI approach in which a tract is registered only if the number of streamlines passes through both ROIs. This probably accounts for the absence of difference in the number of streamlines between patients and controls for the three segments of the arcuate that were dissected using a two-ROI approach. On a more general level, these findings highlight the limitation of using the streamline count as an indirect index of tract volume in brain disorders in which complex methodologic factors need to be accounted for in addition to biological explanations.

The issue associated with the stopping threshold represents a potential limitation of the DTI-based tract specific measurement approach we adopted in this study. However, this technique also has a number of strengths. In particular it permitted a supraregional approach to be taken that enabled us to test hypotheses about specific anatomical changes along single white matter tracts that otherwise appear normal on conventional MRI. This method of sampling FA along the entire length of the tracts of interest may be particularly well suited to the study of neurodevelopmental disorders such as autism (72,73) and schizophrenia (28,74) because changes may be more likely to occur along the course of the fibers, rather than be localized to circumscribed areas.

Further studies are now required to investigate whether selective white matter damage is limited to the perisylvian pathways or extend to other tracts (e.g., cingulum and uncinate fasciculus) in AVH. A recent study has, for example, reported white matter abnormalities in the cingulum correlated with negative symptoms. Also, future studies would benefit from having a larger sample of schizophrenia patients without AVH. Although our sample of nonhallucinators was larger, or comparable, with previous neuroimaging studies (21,75,76), the modest size of this subgroup may have reduced the power to detect differences relative to controls. This limitation was primarily due to difficulties associated with identifying schizophrenic patients without current and previous hallucinations. Finally, of particular interest is the possibility of using DTI tractography to predict response to transcranial magnetic stimulation (TMS) (77–80). To date most of the studies using TMS to treat AVH in schizophrenia have targeted almost exclusively the left temporoparietal cortex with mixed results. Our findings that bilateral

involvement of the perisylvian connections is associated with AVH in schizophrenia suggest that application of TMS to both the left and right temporoparietal cortex may be more effective in the treatment of AVH in schizophrenia.

In conclusion, we report specific diffusion differences in schizophrenia in perisylvian connections originating or projecting to the posterior temporal auditory regions. Furthermore, compared with control subjects, these findings were bilateral and more significant in patients with AVH and intermediate with right-sided preservation in patients without a history of AVH. These findings support the hypothesis that there may be selective vulnerability of specific anatomical connections in schizophrenia and that more extensive bilateral damage is associated with greater vulnerability to AVH.

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