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Reduced integrity of the left arcuate fasciculus is specifically associated with auditory verbal hallucinations in schizophrenia

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ABSTRACT

Background: Schizophrenia patients with auditory verbal hallucinations (AVH) have reduced structural integrity in the left arcuate fasciculus (AF_L) compared to healthy controls. However, it is neither known whether these changes are specific to AVH, as opposed to hallucinations or schizophrenia per se, nor how radial and/or axial diffusivity are altered. This study aimed to test the hypothesis that reductions to the structural integrity of the AF_L are specifically associated with AVH in schizophrenia.

Method: Diffusion tensor imaging scans and clinical data were obtained from the Australian Schizophrenia Research Bank for 39 schizophrenia patients with lifetime AVH (18 current, 21 remitted), 74 schizophrenia patients with no lifetime AVH (40 with lifetime hallucinations in other modalities, 34 no lifetime hallucinations) and 40 healthy controls.

Results: Fractional anisotropy was significantly reduced in the AF_L of patients with lifetime AVH compared to both healthy controls (Cohen's d = 1.24) and patients without lifetime AVH (d = .72), including compared to the specific subsets of patients without AVH who either had hallucinations in other modalities (d = .69) or no history of any hallucinations (d = .73). Radial, but not axial, diffusivity was significantly increased in patients with lifetime AVH compared to both healthy controls (d = .89) and patients without lifetime AVH (d = .39). Evidence was found for a non-linear relation between fractional anisotropy in the AF_L and state AVH.

Conclusion: Reduced integrity of the AF_L is specifically associated with AVH, as opposed to schizophrenia in general or hallucinations in other modalities. Increased radial diffusivity suggests dysmyelination or demyelination of the AF_L may play a role in AVH.

1. Introduction

Auditory verbal hallucinations (AVH) are proposed to result from altered connectivity between frontal and temporal left hemisphere language regions (Feinberg, 1978; Frith, 1992; Ford et al., 2007; Whitford et al., 2010). A key white matter tract linking these regions is the left arcuate fasciculus (AF_L), which connects the inferior frontal lobe, including Broca's area, to the posterior superior temporal lobe, including Wernicke's area (Catani et al., 2007). Diffusion tensor imaging (DTI) has examined whether structural alterations to the AF_L are associated with AVH. The most commonly employed measure in DTI is Fractional Anisotropy (FA), an index of the structural integrity of white matter fibres, with lower FA indicating reduced integrity.

A recent meta-analysis by Geoffroy et al. (2014) found reduced FA in the AF_L (henceforth FA-AF_L) of schizophrenia patients with AVH, compared to healthy controls. Because such comparisons cannot demonstrate specificity of changes to AVH, which could instead be due to schizophrenia per se, the authors recommended more studies comparing patients with and without AVH. The only two studies to do this (Catani et al., 2011, 28 first-episode psychosis patients with AVH, 18 without; Benetti et al., 2015, 17 chronic schizophrenia patients with AVH, 11 without) both failed to find significant differences. However, they only had sufficient power to detect large effect sizes, potentially causing Type II errors. For example, Benetti et al.'s data shows an FA-AF_L reduction in the AVH group of a medium effect size. The first aim of our study was to test the hypothesis that FA-AF_L is lower in patients with schizophrenia with AVH, compared to both patients with schizophrenia without AVH, and healthy controls, in a study powered to detect medium effect sizes.

A second recommendation of Geoffroy et al. (2014) was that DTI studies of AVH should report on radial diffusivity and axial diffusivity, as these are associated with specific biological changes. Increased radial diffusivity is associated with reduced myelination (Song et al., 2005), reduced axial diffusivity with axonal damage (Song et al., 2003), although caution is needed in such interpretations in the absence of post-mortem

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examination (Wheeler-Kingshott and Cercignani, 2009). Radial but not axial diffusivity has been found to be higher in schizophrenia patients with AVH compared to healthy controls (de Weijer et al., 2011), yet schizophrenia patients with AVH have also been found to have higher radial diffusivity than non-psychiatric patients with AVH, suggesting a lack of specificity to AVH (de Weijer et al., 2013). The second aim of our study was hence to test the hypothesis that schizophrenia patients with AVH have higher radial (but not axial) diffusivity than both patients without AVH, and healthy controls.

We also aimed to undertake more exploratory analyses. First, given the role of the AF_L in language (Catani et al., 2005), we hypothesised decreases in FA-AF_L in patients with AVH compared to patients with hallucinations restricted to other modalities (e.g., visual hallucinations). Second, as some previous studies have employed patients with both current and remitted AVH (e.g., Benetti et al., 2015), we aimed to test whether FA-AF_L changes associated with AVH reflected a state or trait phenomena. Finally, we aimed to undertake the first empirical test based on the proposal that if AVH represent the brain's attempt to incorporate disjointed neural activity then this integration may only be possible up to a certain level of temporal desynchronisation (Whitford et al., 2010). Whilst intermediate asynchronies could result in AVH, severe asynchronies may not be able to be incorporated into a coherent auditory experience, thus not giving rise to AVH, and mild asynchronies may integratable into the flow of normal experience (Whitford et al., 2010). We hence aimed to test the hypothesis that, within schizophrenia patients, changes in FA-AF_L relative to healthy controls would have a non-linear (quadratic) relationship to the probability of current AVH.

2. Method

2.1. Sample size

GPower v3.1.9 (Faul et al., 2007) indicated 102 patients were required to detect a medium effect size (Cohen's d = .50) when comparing patients with and without lifetime AVH ($\beta = .80$, one-tailed test, $\alpha = .05$). To allow testing of our exploratory hypotheses, we aimed for a ratio of two patients without lifetime AVH (one with hallucinations but not AVH, and one with no hallucinations in any modality) to each patient with lifetime AVH. Recalculating the necessary sample size using an allocation ratio of .5, indicated that an AVH group was required of 38 people, and a non-AVH group of 76 people.

2.2. Participants

Data on patients with DSM-IV schizophrenia diagnoses were obtained from the Australian Schizophrenia Research Bank (ASRB; Loughland et al., 2010). Clinical and diagnostic information had been obtained by trained research staff using the Diagnostic Interview for Psychosis (DIP; Castle et al., 2006). Exclusion criteria included an inability to converse fluently in English, organic brain disorder, brain injury with post-traumatic amnesia >24 h, intellectual disability (IQ < 70), current diagnosis of substance dependence, and electroconvulsive therapy received in the last 6 months.

Thirty-nine patients (SZ:AVH+) had a lifetime history of AVH, operationalized as a non-zero total score on lifetime ratings of DIP items #51 (Accusatory/abusive/persecutory voices), #52 (Running commentary) and #53 (Third person auditory hallucinations). Of these, 18 had current AVH (last occurrence < 1 month ago) and 21 had remitted AVH (last occurrence > 1 month ago). Seventy four patients (SZ:AVH−) were defined as having no lifetime history of AVH or non-verbal auditory hallucinations, as operationalized by a zero score on the lifetime rating of DIP items #50 (non-verbal auditory hallucinations), #51, #52 and #53. This group comprised of two subgroups; 34 patients with no lifetime history of any hallucinations (henceforth SZ:H−), operationalized by a zero score on the lifetime rating of DIP item #49 (hallucinations in any modality), and 40 patients with lifetime hallucinations but none in the auditory verbal modality (henceforth SZ:H+/AVH−), operationalized as a non-score on the lifetime rating of DIP item #49, but a zero score on the lifetime ratings of DIP items #51–53.

Duration of use of antipsychotic medication was taken from ASRB records, and was available for 107 of the 113 patients (Table 1). The upper limit of classification recorded by the ASRB was >8 years. This hence underestimated usage. The presence of delusions was defined as a non-zero score on the sum of present state (previous month) ratings on the delusions section of the DIP (items #58–64). Negative symptoms were assessed using lifetime ratings (current state not

Table 1
Descriptive statistics.

	SZ:AVH+(n = 39)	SZ:AVH−(n = 74)	Healthy controls (n = 40)	Group difference
Demographics				
Age/years (mean, SD)	39.36 (10.53)	39.05 (9.35)	39.03 (10.28)	$F(2,150) = .02$, $P = .99$
Gender (% male)	82%	81%	83%	$\chi^2(2) = .04$, $P = .98$
Handedness (% right)	92%	92%	93%	$\chi^2(2) = .02$, $P = .99$
IQ (mean, SD)	100.36 (16.41)	103.50 (14.50)	119.63 (8.77)	$F(2,150) = 23.63$, $P < .001$
Drugs				
Antipsychotic use/months (mean, SD)	48.28 (38.68)	48.16 (33.65)[b]	–	$t(105) = .02$, $P = .99$
Substance use (%)	72%	63%[c]	–	$\chi^2(1) = .87$, $P = .35$
Alcohol abuse/dependence (%)	32%[a]	46%[d]	–	$\chi^2(1) = 2.22$, $P = .14$
Psychopathology				
Duration of illness (years)	15.67 (8.98)	14.57 (8.80)	–	$t(111) = .63$, $P = .53$
Depression (mean, SD)	.31 (1.15)	.42 (1.52)	–	$t(111) = .40$, $P = .69$
Delusions (%)	38%	48%[c]	–	$\chi^2(1) = .93$, $P = .34$
Negative formal thought disorder (%)	29%[a]	37%[c]	–	$\chi^2(1) = .87$, $P = .65$
Catatonia (%)	11%[a]	8%[c]	–	$\chi^2(1) = .16$, $P = .69$
Scanner location (n)				
Melbourne	11	15	15	
Sydney	8	14	8	
Brisbane	14	36	8	$\chi^2(8) = 13.28$, $P = .10$
Perth	4	5	8	
Newcastle	2	4	1	

Note. SZ:AVH + = Schizophrenia with lifetime auditory verbal hallucinations. SZ:AVH− = Schizophrenia with no lifetime auditory verbal hallucinations. SD = standard deviation.
[a] n = 38 due to missing data.
[b] n = 68 due to missing data.
[c] n = 73 due to missing data.
[d] n = 69 due to missing data.

available) on DIP items #97 (negative formal thought disorder) and #88 (catatonia). Lifetime presence of substance use and alcohol abuse/dependence was assessed using DIP items #72 and #74 respectively. Depression was calculated as the sum of present state (previous month) ratings of DIP items #20–22, creating total scores (Cronbach's $\alpha = .75$) ranging from 0–9, with higher scores indicating greater levels of depression.

Forty healthy controls had been screened for a family history of, or treatment for, psychiatric illness, and did not have had a history of epilepsy, seizures, dementia, neurological illnesses, movement disorders, organic brain disorders, brain injury or head injury with post-traumatic amnesia >24 h.

2.3. Image acquisition

Diffusion-weighed images (DWIs) were acquired from identical 1.5T Siemens Avanto scanners (Siemens, Erlangen, Germany) from five different Australian locations. Imaging parameters were identical across scanners: 65 axial slices enabling whole-brain coverage were acquired in 64 diffusion directions with $b = 900$ s/mm^2. One baseline scan with $b = 0$ was also acquired. The scan parameters were: TR 8400 ms, TE 88 ms, FOV 25 cm, 104 × 104 matrix, 2.4 mm slice thickness without gap, producing isotropic 2.4 mm voxels. Total scanning time was approximately 9 min.

2.4. Extraction of the arcuate fasciculus

The AF_L was extracted from DT images using deterministic tractography (as per Whitford et al., 2011) and implemented in the Slicer-3 software package (version 4.2.0, nightly build, www.slicer.org). A cubic region of interest (i.e. a fiducial) of side 2.50 mm was manually placed in the dorsal longitudinal fibres of the AF_L. The voxels defined by this fiducial were used as seedpoints for deterministic (streamline) tractography, which followed the direction defined by the principal eigenvector. A step size of 1.00 mm was used, and tractography was terminated upon reaching a voxel of FA < 0.25 (the stopping criterion). Minimum/maximum path lengths were 20.00/800.00 mm, with an integration step length of 0.50 mm. The small number of voxels defined by the fiducial meant real-time feedback was available on the accuracy of the fiducial's location. Its spatial position was then adjusted until distinctive ventrally projecting, curved fibres of the AF_L became apparent. Once the fibres had been extracted, a binary label map was generated for each participant by labelling those voxels through which any fibres passed. Fig. 1 shows a sample AF_L. These u-shaped fibres represent what Catani et al. (2011) term the "long direct segment" of the AF_L, i.e., we were not assessing its anterior and posterior indirect segments.

FA was calculated for every voxel in each subject's label map. The mean FA of all voxels defined by the label map was calculated for each subject, and used in the statistical analysis. All tractography was performed by a single rater (L.O.), blind to participant group. Intra-rater reliability was assessed through the recalculation of FA for 10 participants using a different nightly build of Slicer. These recalculated values correlated significantly with the original values, $r = .95$, $P < .001$.

2.5. Statistical analysis

Group differences were tested using analysis of variance (ANOVA), with significant group effects being followed by 1000 bootstrapped sample t-tests. As recommended by Bender and Lange (2001), where confirmatory analyses were undertaken (i.e., confirming FA was lower in patients with AVH compared to healthy controls), Bonferroni corrections to alpha were used. Where t-tests were performed to test directional hypotheses, one-tailed tests were employed. For exploratory analyses, due to Type II errors being deemed more problematic than Type I errors, and due to the already reduced power of the subgroup analyses, we did not adjust significance levels for post-hoc tests (Perneger, 1998; Bender and Lange, 2001).

3. Results

The three study groups were matched on age, gender, and handedness (Table 1). There were no significant differences between the proportion of participants scanned at each location (Table 1). The two schizophrenia groups were matched on duration of antipsychotic usage, duration of illness, severity of illness (via symptom ratings) and alcohol and substance use (Table 1). When screening diffusivity data, outliers were defined as scores >3SD from the mean (Field, 2007), leading to the exclusion of axial diffusivity scores of three participants (two SZ:AVH−, one HC).

3.1. Primary analyses

Group means are presented in Table 2, and illustrated graphically in Fig. 2. ANOVA revealed an effect of group (SZ:AVH+, SZ:AVH−, HC) on FA-AF_L ($F_{2,150} = 13.33$, $P < .001$, partial $\eta^2 = .15$). Two planned t-tests (Bonferroni corrected alpha = .025) tested our specific directional hypothesis. The SZ:AVH+ group had significantly lower FA-AF_L than both the SZ:AVH− groups, P(one-tailed) < .001, d = .72, and the healthy control group, P(one-tailed) < .001, d = 1.24. Two further ANOVAs found an effect of group on radial ($F_{2,150} = 7.11$, $P = .001$, partial $\eta^2 = .09$), but not axial ($F_{2,147} = 2.10$, $P = .13$, partial $\eta^2 = .03$) diffusivity. Two planned t-tests (Bonferroni corrected alpha = .025) tested our specific directional hypothesis, finding that radial diffusivity was significantly higher in the SZ:AVH+ group than both the SZ:AVH−, P(one-tailed) = .024, d = .39, and healthy control group, P(one-tailed) < .001, d = .89. (See Fig. 3.)

3.2. Exploratory analyses

3.2.1. Specificity to AVH

ANOVA found an effect of group on FA-AF_L, after repeating the above analyses but splitting the SZ:AVH− group into its two sub-groups: SZ:H+/AVH− and SZ:H− ($F_{3,149} = 8.87$, $P < .001$, partial $\eta^2 = .15$; Table 2). Two planned t-tests tested our directional hypotheses, and found the SZ:AVH+ group had significantly lower FA-AF_L than both the SZ:H+/AVH− groups, P(one-tailed) = .002, d = .69, and the SZ:H− group, P(one-tailed) = .001, d = .73. ANOVA found an effect of group on radial diffusivity ($F_{3,149} = 4.87$, $P = .003$, partial $\eta^2 = .09$), with two planned t-tests finding that the SZ:AVH+ group had higher radial diffusivity than the SZ:H+/AVH− group, P(one-tailed) = .02, d = .46, but did not differ from the SZ:H− group, P(one-tailed) = .09, d = .31. ANOVA also found an effect of group on axial diffusivity ($F_{3,146} = 2.74$, $P = .05$, partial $\eta^2 = .05$), with two planned t-tests finding that SZ:AVH+ had lower axial diffusivity than the SZ:H− group, P(two-tailed) = .008, d = .65, but not the SZ:AVH−/H+ group, P(two-tailed) = .43, d = .17.

3.2.2. State and trait

ANOVA examined the effect of group on FA-AF_L, after splitting the SZ:AVH+ group into two sub-groups: SZ:AVH+(current) and SZ:AVH+(remitted), but retaining a single SZ:AVH− group (Table 2). There was an effect of group on FA-AF_L ($F_{3,149} = 9.85$, $P < .001$, partial $\eta^2 = .17$). Three planned t-tests found no difference between the SZ:AVH+(current) and SZ:AVH+(remitted) groups, P(two-tailed) = .08, d = .55, but found that both the SZ:AVH+(remitted) group, P(one-tailed) < .001, d = .90, and the SZ:AVH+(current) group, P(one-tailed) = .017, d = .49, had lower FA-AF_L than the SZ:AVH− group.

3.2.3. Non-linear relations

The difference between each patient's FA-AF_L and the mean FA-AF_L of healthy controls was calculated (henceforth ΔAF_L). Binary logistic

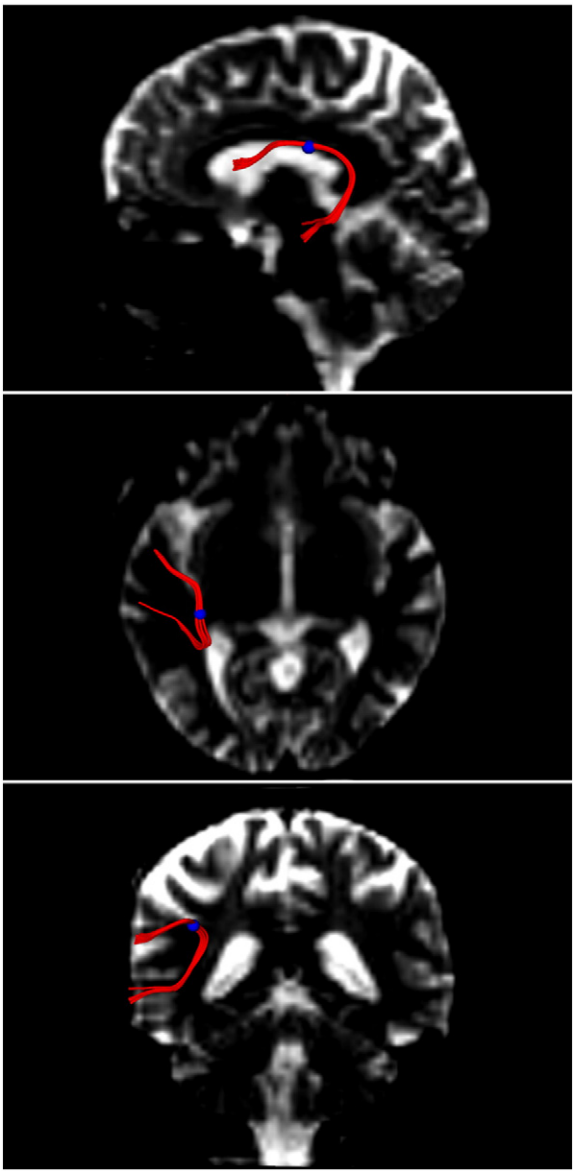

Fig. 1. Sample of tracing of the left arcuate fasciculus.

regression (1000 bootstrapped samples) was first performed, using patient data only (n = 113), with current experience of AVH as the dependent variable (current AVH = 1, no current or lifetime AVH = 0) and ΔAF_L as the independent variable. This model was not a significant predictor of the presence of AVH, $\chi^2(1) = .72$, $P = .40$, Nagelkerke $R^2 = .01$. Binary logistic regression was then performed with the addition of a quadratic term. ΔAF_L was mean centred, and used to create linear and quadratic terms as independent variables, i.e., $\left(\Delta AF_L - \overline{\Delta AF_L}\right)$ and $\left(\Delta AF_L - \overline{\Delta AF_L}\right)^2$. This model was a significant predictor of current AVH, $\chi^2(2) = 7.49$, $P = .024$, Nagelkerke $R^2 = .11$, with only $\left(\Delta AF_L - \overline{\Delta AF_L}\right)^2$ being a significant predictor, $P = .034$. To illustrate this, ΔAF_L scores were divided into six blocks of equal interval, and the proportion of patients with current AVH within each block was calculated. As Table 3 shows, patients with a 1–9% decrease in FA-AF_L, relative to the mean FA-AF_L of healthy controls, were most likely to currently experience AVH. Those with larger FA-AF_L decreases or smaller decreases/increases in FA-AF_L were less likely to have current AVH.

4. Discussion

DTI was used to examine if structural changes to the left arcuate fasciculus (AF_L) were specifically associated with AVH in patients with schizophrenia. Patients with lifetime AVH had significantly lower fractional anisotropy in this tract (FA-AF_L) than patients without lifetime experience of AVH, with this difference representing a large effect size. Patients with lifetime AVH had significantly higher radial (but not reduced axial) diffusivity in the AF_L than patients without lifetime experience of AVH. Although this could indicate that dysmyelination or demyelination of this tract is associated with AVH (Song et al., 2005), post-mortem study would have been necessary to confirm this (Wheeler-Kingshott and Cercignani, 2009).

Exploratory sub-analyses found patients with lifetime AVH had significantly lower FA-AF_L than patients with hallucinations restricted to other modalities. This suggested specificity of FA-AF_L reductions to auditory verbal hallucinations, consistent with role of the AF_L in language (Catani et al., 2005). Inconsistent findings emerged from comparisons of radial diffusivity and axial diffusivity between patients with lifetime AVH and the two patient control groups (no history of hallucinations, hallucinations in non-auditory verbal modalities). However, in the case of radial diffusivity, non-significant increases in the lifetime AVH group compared to the two patient control groups were in the expected direction and were of a small–medium effect size, potentially suggesting a Type II error. Better powered study is required.

Exploratory analyses found that both patients with current and remitted AVH had lower FA-AF_L than patients without AVH. This suggested that remission of AVH is not associated with normalisation of FA-AF_L. A non-significant trend of medium effect size was found towards those with remitted AVH having lower FA-AF_L than those with current AVH. There was thus some evidence, in our underpowered analyses, that remitted AVH were associated with the lowest FA-AF_L, and that those with current AVH had FA-AF_L intermediate between remitted AVH patients and patients who had never experienced AVH. This is unexpected in a framework where AVH are understood to be linearly associated with decreased AF_L integrity. However, within non-linear frameworks (Whitford et al., 2010), this becomes interpretable. Specifically, AVH may be encouraged by intermediate levels of integrity reduction to the FA-AF_L, with greater or smaller reductions

Table 2
Means and standard deviations for fractional anisotropy and diffusivity measures.

Measure	Schizophrenia with lifetime AVH			Schizophrenia with no lifetime AVH			Healthy controls (n = 40)
	Total group (n = 39)	Current (n = 18)	Remitted (n = 21)	Total group (n = 74)	SZ:H+/AVH−(n = 40)	SZ:H−(n = 34)	
FA ($\times 10^2$)	50.26 (2.54)	50.99 (1.99)	49.64 (2.82)	52.19 (2.84)	52.09 (2.75)	52.30 (3.00)	53.28 (2.31)
RD ($\times 10^5$)	51.40 (2.85)	51.11 (2.58)	51.66 (3.11)	50.25 (3.00)	50.05 (2.98)	50.49 (3.06)	48.97 (2.60)
AD ($\times 10^4$)	11.74 (.41)	11.86 (.37)	11.64 (.41)	11.90 (.41)[a]	11.81 (.39)[b]	12.01 (.42)[b]	11.89 (.44)[b]

FA = Fractional anisotropy. RD = Radial diffusivity. AD = Axial diffusivity. AVH = Auditory verbal hallucination. SZ:H+/AVH− = Schizophrenia with lifetime hallucinations but none in the auditory verbal modality. SZ:H− = Schizophrenia with no lifetime hallucination.

[a] Two participants excluded as outliers (see text for definition of outlier).

[b] One participant excluded as an outlier.

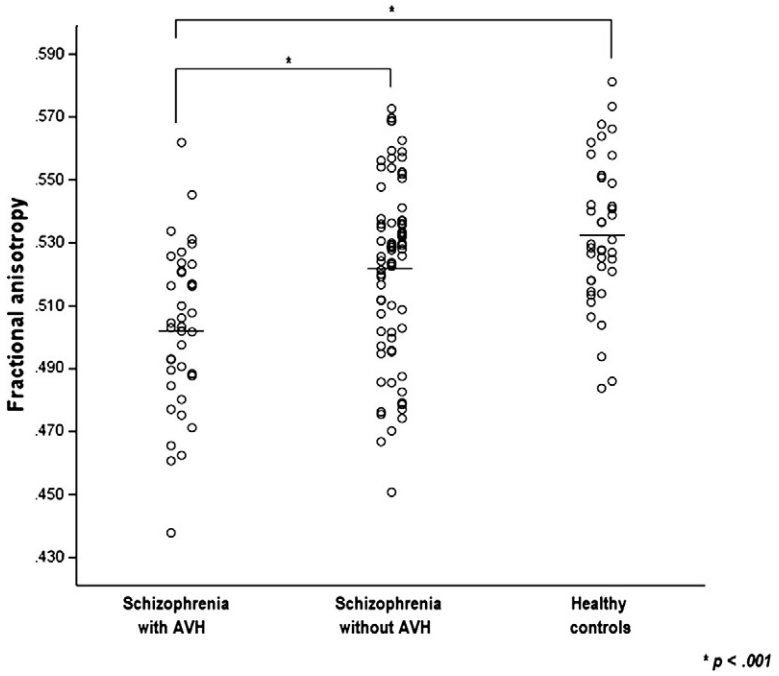

Fig. 2. Mean fractional anisotropy by group.

reducing the probability of AVH. Indeed, our preliminary finding of a non-linear relation between FA-AF_L alterations and current experiences of AVH, offered the first empirical evidence for this theory. Yet the finding that patients with remitted AVH did not have FA-AF_L comparable to patients without AVH, or healthy controls, is puzzling in the context of previous suggestions that atypical antipsychotics have their effects partly through improving myelin integrity (Ren et al., 2013; Ozcelik-Eroglu et al., 2014). Better powered studies, as well as the examination of longitudinal relations between FA-AF_L and AVH, are needed.

This study had a number of limitations. First, although data was available on duration of antipsychotic usage, dosage was not available and confounding by differences in medication exposure cannot be fully excluded. Second, recruiting such a precisely defined sample meant that it was necessary to use data from five sites. Whilst all scanners were built to identical specifications, the possibility that inhomogeneities between scanners could have affected DTI metrics cannot be eliminated. Third, our exploratory analyses were underpowered. Fourth, our lack of corrections to alpha, although increasing the power of our analyses, also increased the risk of Type I errors. Fifth, post-mortem studies of white matter pathways are needed, in addition to in vivo studies, to determine the histological correlates of altered anisotropy (Highley et al., 2002). Finally, we focussed specifically on intrahemispheric connectivity within the AF_L, but altered interhemispheric connectivity (cf. Crow, 1997, 2010) such as between left and right primary and secondary auditory cortices, may also play a role in AVH (Gavrilsecu et al., 2010). Future studies may wish to consider how both intra- and inter-hemispheric changes to structural and functional connectivity may individually and/or additively contribute to AVH formation.

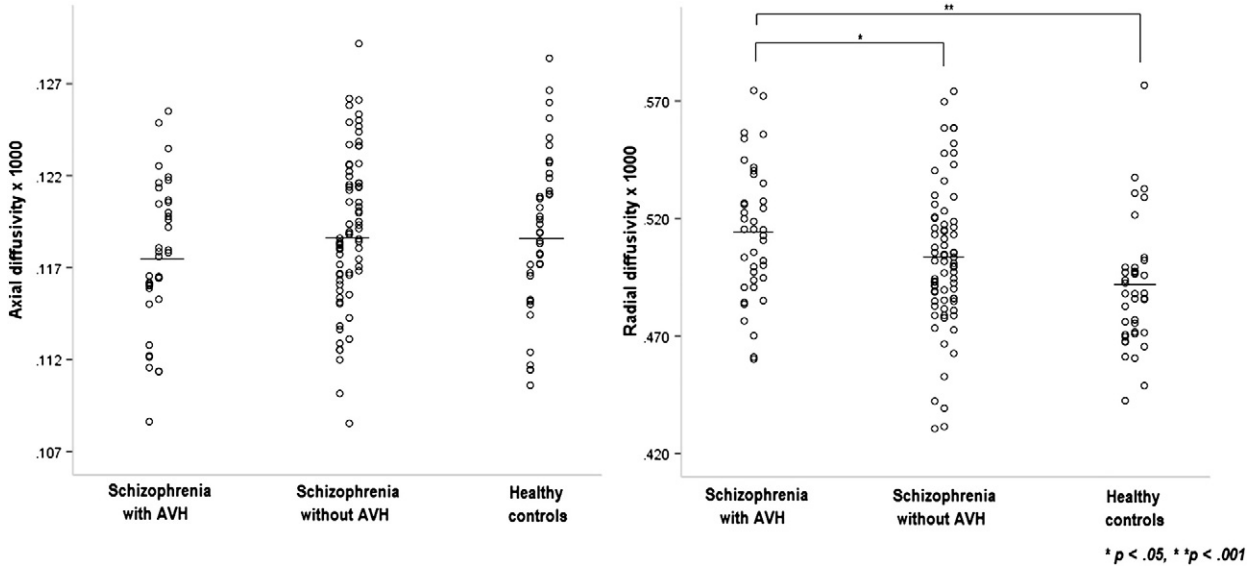

Fig. 3. Mean radial diffusivity and axial diffusivity by group.

Table 3
Probability of patients having current AVH by size/direction of structural integrity change relative to healthy controls.

	% Change in fractional anisotropy in the left arcuate fasciculus (FA-AF_L) relative to mean FA-AF_L of healthy controls					
	−17.8% to −13.6%	−13.5% to −9.4%	−9.3% to −5.1%	−5.0% to −0.9%	−0.8% to +3.3%	+3.4% to +7.6%
Number of patients	2	16	24	30	26	15
Percentage with current AVH	0%	13%	21%	27%	12%	0%

AVH = Auditory verbal hallucinations.

In conclusion, this study offers the first clear evidence of FA-AF_L reductions being specificity attributable to auditory verbal hallucinations, rather than hallucinations or schizophrenia per se. Although it also provides evidence consistent with these changes specifically reflecting reduced myelination of the AF_L, it remains unclear if such changes result from dysmyelination, a failure of myelination during development (Crow et al., 2007), or a process of demyelination similar to that found in multiple sclerosis. Both this question and the potential for a non-linear relation to exist between FA-AF_L and state AVH, require further study.

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Contributors

Simon McCarthy-Jones designed the study, obtained funding, undertook the literature search and statistical analysis, and wrote the first draught of the manuscript. Lena Oestreich undertook the DTI analyses, under the supervision of Thomas Whitford who was also involved in obtaining funding. The Australian Schizophrenia Research Bank collected the data. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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