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ORIGINAL RESEARCH

Decreased integrity of the fronto-temporal fibers of the left inferior occipito-frontal fasciculus associated with auditory verbal hallucinations in schizophrenia

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Abstract Auditory verbal hallucinations (AVH) have been proposed to result from altered connectivity between frontal speech production regions and temporal speech perception regions. Whilst the dorsal language pathway, serviced by the arcuate fasciculus, has been extensively studied in relation to AVH, the ventral language pathway, serviced by the inferior occipito-frontal fasciculus (IOFF) has been rarely studied in relation to AVH. This study examined whether structural changes in anatomically defined subregions of the IOFF were associated with AVH in patients with schizophrenia. Diffusion tensor imaging scans and clinical data were obtained from the Australian Schizophrenia Research Bank for 113 schizophrenia patients, of whom 39 had lifetime experience of AVH (18 had current AVH, 21 had remitted AVH), 74 had no lifetime experience of AVH, and 40 healthy controls. Schizophrenia patients with a lifetime experience of AVH exhibited reduced fractional anisotropy (FA) in the fronto-temporal fibers of the left IOFF compared to both healthy controls and schizophrenia patients without AVH. In contrast, structural abnormalities in the temporal and occipital regions of the IOFF were observed bilaterally in both patient groups, relative to the healthy controls. These results suggest that while changes in the structural integrity of the bilateral IOFF are associated with schizophrenia per se, integrity reductions in the fronto-temporal fibers of the left IOFF may be *specifically* associated with AVH.

Keywords Language · Fractional anisotropy · Hearing voices · Psychosis · Tractography · Diffusion tensor imaging (DTI)

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Auditory verbal hallucinations (AVH) refer to the experience of hearing voices, in the absence of external stimuli, in a state of wakefulness. AVH are commonly associated with schizophrenia, with around two-thirds of patients reporting such experiences (Nayani and David 1996). It has been proposed that some AVH may be caused by reduced structural integrity in the white matter fiber tracts that extend from frontal to temporal regions, potentially leading to temporal asynchronies in the corollary discharges travelling along these fiber bundles (Whitford et al. 2012). According to this account, the activation of superior temporal lobe structures is consequently insufficiently suppressed during self-generated mentation (Ford and Mathalon 2004), causing misattributions of self-generated inner speech to external sources in the form of AVH (Feinberg 1978).

The white matter fiber tract that has been most heavily implicated in the etiology of AVH is the arcuate fasciculus. This tract connects Broca's area (i.e. a speech production area) with Wernicke's area (i.e. a speech perception area; Bernal and Ardila 2009), and as such has been proposed as a potential route for corollary discharges evoked by self-generated mentation (Whitford et al. 2011). A meta-analysis has found evidence of reduced structural integrity of the left arcuate fasciculus in patients with schizophrenia with AVH, compared to healthy controls (Geoffroy et al. 2014). Furthermore, a recent study by our group found that schizophrenia patients with a

history of AVH had reduced structural integrity of the left arcuate compared to schizophrenia patients without any history of AVH, suggesting that these changes may be specific to AVH as opposed to schizophrenia per se (McCarthy-Jones et al. 2015).

Whilst the arcuate fasciculus has been the primary white matter tract studied in connection to AVH in schizophrenia, it is not the only fasciculus involved in the fronto-temporal language system. Hickok and Poeppel (2004) suggested a dual stream model of speech processing. From the superior temporal gyrus (which is involved in early cortical stages of speech perception) the system branches into two processing streams. The dorsal stream projects to the posterior frontal lobe via the inferior parietal region, and is believed to be involved in auditory-motor integration by mapping acoustic speech sounds to articulatory representations (Saur et al. 2008; Hickok and Poeppel 2004). Due to its location and function, the arcuate fasciculus has been proposed as the primary white matter fasciculus in the dorsal stream (Duffau 2008). The dorsal stream is connected to the left-lateralized motor speech area and is hence thought to be lateralized to the left hemisphere (Hickok 2000).

In contrast, the ventral stream projects to the inferior and middle temporal cortex, which is believed to be involved in converting basic auditory information into meaningful concepts (Hickok and Poeppel 2004). The inferior occipito-frontal fasciculus (IOFF) has been suggested to represent the primary white matter fasciculus in the ventral stream (Duffau 2008; Almairac et al. 2014). In contrast to the dorsal stream, which is strongly lateralized to the left-hemisphere (Catani et al. 2007), auditory processing in the ventral stream is believed to be more bilaterally distributed (Hickok 2000).

Electrostimulation of the IOFF induces semantic paraphasia (i.e. substitution of one word for another, based on a meaningful relation between them), which indicates the importance of the IOFF in semantic language processing (Duffau et al. 2005). In contrast, electrostimulation of the arcuate fasciculus induces phonemic paraphasia (i.e. substitution of one word with a non-word due to phonemic confusion of one phoneme with a similar sounding phoneme), highlighting the role of the arcuate fasciculus in speech production (Duffau et al. 2002). Functional MRI studies also support a dual processing model in the auditory system. A study by Saur et al. (2008) found that while repetition of aurally presented non-words produced activity in the left temporal and frontal regions, which are connected via the arcuate fasciculus, a higher-level language comprehension task involving listening to meaningful versus nonsense sentences led to increased activity in the inferior and middle temporal regions and the ventro-lateral prefrontal cortex, which are connected via the IOFF.

Given the accumulating evidence for a dual processing model in the auditory system, the question arises as to whether changes to the fronto-temporal language network associated with AVH are limited to the arcuate fasciculus, or whether alterations to the integrity of the IOFF may also be involved in the etiology of these symptoms. To our knowledge, only one previous study has examined the association between AVH and the structural integrity of the IOFF. Ćurčić-Blake et al. (2015) used a tract-based spatial statistics (TBSS) approach and found that schizophrenia patients with current AVH (n = 17) had significantly lower fractional anisotropy (FA) in the anterior part of the left IOFF than a combined group of patients (n = 14) who either had remitted AVH or who had never experienced AVH. Furthermore, a negative correlation was observed between FA in the left IOFF and the severity of patients' AVH.

The present study aimed to extend the findings of Ćurčić-Blake et al. (2015) by using a tractography-based approach to extract the IOFF. The advantage of using tractography is that it enables the fasciculus-of-interest to be reliably extracted in native space and thereby avoids the complications associated with warping images of different sizes and geometries to a common template. The IOFF is one of the longest associative fiber bundles in the brain, which connects occipital, temporal and frontal lobes (Forkel et al. 2014). Investigating fiber integrity over the entire tract may therefore not be optimal for detecting local white matter differences. To enable the detection of localized white matter changes, the present study segmented the IOFF into several subregions. The structural integrity of these IOFF subregions were compared between schizophrenia patients with a history of AVH, schizophrenia patients without a history of AVH, and healthy controls. An additional analysis investigated whether IOFF integrity was associated with state AVH by dividing the patient group with AVH into patients with current AVH and those with remitted AVH. The structural integrity of the IOFF was assessed with a battery of diffusion metrics, namely FA, axial diffusivity (associated with axonal integrity; Song et al. 2003) and radial diffusivity (associated with myelin integrity; Song et al. 2003). It was hypothesized that schizophrenia patients with lifetime experience of AVH would show significantly reduced FA in the frontal and temporal regions of the IOFF compared to both schizophrenia patients without lifetime experience of AVH, and healthy controls. It was further hypothesized that patients with current AVH would show significantly reduced FA in the frontal and temporal regions of the IOFF, compared to patients with AVH that were currently in remission.

Method

Participants

Data was obtained from the Australian Schizophrenia Research Bank (ASRB). A comprehensive outline of the data

collection process for the ASRB is provided elsewhere (Loughland et al. 2010). A total of 153 participants were included in this study, consisting of 40 healthy controls and 113 participants who had been diagnosed with schizophrenia based on DSM-IV criteria (APA 1987). Research staff from the ASRB, who were trained in the conduction of the Diagnostic Interview for Psychosis (DIP; Castle et al. 2006), collected diagnostic and clinical information from all patients. Exclusion criteria for this study were organic brain disorders such as Huntington's disease, brain injury with more than 24 h post-traumatic amnesia, intellectual disability (defined as a total IQ score of less than 70), movement disorders, non-fluency in English, a history of electroconvulsive therapy within the last 6 months and a present diagnosis of substance dependence. Analyses of the integrity of the arcuate fasciculus from the current dataset have previously been reported (McCarthy-Jones et al. 2015).

Participants diagnosed with schizophrenia were divided into subgroups based on their scores on different items of the DIP. The subgroup of schizophrenia patients with lifetime experience of AVH was defined based on an overall score greater than zero on the lifetime ratings of DIP item number 51, identifying accusatory, abusive and persecutory voices, item number 52, determining running commentary and item number 53, identifying third person auditory hallucinations (SZ:AVH+; $n = 39$). For the purposes of examining associations between IOFF integrity and state AVH, patients with lifetime experiences of AVH were further split into those with current AVH (experienced in the past month, henceforth SZ:AVH+$_{current}$; $n = 18$) and those with remitted AVH (last experienced >1 month ago, henceforth SZ:AVH+$_{remitted}$; $n = 21$). The third subgroup (SZ:AVH-) comprised 74 schizophrenia patients without a lifetime history of AVH or non-verbal auditory hallucinations, which was operationalized as a score of zero on the DIP item numbers 50 (non-verbal auditory hallucinations), 51, 52 and 53.

The clinical and demographic profiles of the patient groups are outlined in Table 1. Present state (experienced in the past month) delusional ideation was assessed using the seven delusion items (#58–64) on the DIP. Depression was measured using the sum of lifetime ratings of the DIP item numbers 20 (dysphoria), 21 (loss of pleasure) and 22 (thoughts of suicide). Duration of antipsychotic medication usage was recorded for 107 out of the total 113 schizophrenia patients. The upper limit of treatment with antipsychotic medication recorded by the ASRB was a period of longer than 8 years. Lifetime history of alcohol or substance abuse was assessed using DIP item number 74 (lifetime diagnosis of alcohol abuse/dependence) and item number 78 (lifetime diagnosis of drug abuse/dependence). Negative symptoms were assessed using the sum of DIP item numbers 88 (catatonia), 90 (restricted affect), 91 (blunted affect) and 97 (negative formal thought disorder).

The demographic profile of the healthy control group is outlined in Table 1. Healthy control participants were screened for the following exclusion criteria: a history of epilepsy, seizures, neurological illnesses, dementia, organic brain disorders, movement disorders, brain injury or head injury with more than 24 h post-traumatic amnesia, a personal history of any of the following disorders: schizophrenia, affective disorder with psychotic features, schizoaffective disorder, substance or alcohol induced psychosis, delusional disorder, organic brain disease or a general medical disease.

Data acquisition

The imaging parameters have been described previously (McCarthy-Jones et al. 2015). Diffusion-weighted MRI scans were acquired on five identical 1.5 T Siemens Avanto scanners located in Sydney, Newcastle, Melbourne, Perth and Brisbane. The imaging parameters for all scanners were identical across scanners: 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), 65 axial slices providing whole-brain coverage, 64 orthogonal diffusion directions with $b = 900$ s/mm^2 and one baseline image with $b = 0$. The total scanning time for this sequence was approximately 9 min.

Data processing (diffusion tensor tractography)

A streamline tractography method, using Slicer 3D software (version 4.2.0, www.slicer.org) was adopted for extracting the IOFF (Kubicki et al. 2013). As described in the study of Whitford et al. (2011), small cubic regions of interest dubbed fiducials (of side length 2.5 mm) were manually placed in the longitudinal fibers of each participant's left and right IOFF. Tractography proceeded in real-time and was performed by a single rater who was blind to participant diagnosis. For each participant, the position of the fiducial was manually readjusted until the distinctive fibers of the IOFF became apparent, based on the descriptions provided by Catani and Thiebaut de Schotten (2008). Fiber tracts were generated by applying a principal-eigenvector-tracking algorithm to the voxels defined by the individual fiducials. The step size was set at 1.00 mm and the tractography was terminated upon reaching a voxel of FA < 0.25 (stopping criterion). The minimum and maximum path lengths were set to 20 and 800 mm respectively. Once the fibers of the IOFF had been identified, a binary label map was generated for each participant, which was defined by the voxels through which any of the fibers passed. Fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) were calculated for every voxel in each participant's DTI, and averaged across the label map. The IOFF extracted from three representative participants are shown in Fig. 1.

Table 1 Demographics and clinical data on participants

Variable	SZ:AVH+$_{current}$ (n = 18)		SZ:AVH+$_{remitted}$ (n = 21)		SZ:AVH- (n = 74)		HC (n = 40)		Group difference
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Age (years)	37.22	10.47	41.19	10.48	39.05	9.35	39.03	10.28	$F(3149) = 0.53$, $p = 0.662$
Gender (male/female)	15/3		17/4		60/14		33/7		$F(3149) = 0.03$, $p = 0.995$
Handedness (right/left)	17/1		19/2		68/6		37/3		$F(3149) = 0.07$, $p = 0.974$
Scanner location (Melbourne/Sydney/ Brisbane/Perth/Newcastle)	4/4/8/2/0		7/4/6/2/2		15/14/36/5/4		15/8/8/8/1		$\chi^2(12) = 16.36$, $p = 0.175$
Delusions (% present)	67 %		14 %		48 %		–		$\chi^2(2) = 11.69$, $p = 0.003$
Depression	3.89	3.31	4.05	3.53	4.28	3.47	–		$F(2110) = 0.11$, $p = 0.893$
Negative symptoms	1.19	1.22	1.50	1.70	1.67	1.47	–		$F(2110) = 0.69$, $p = 0.504$
Duration of illness	14.06	9.23	17.05	8.75	14.57	8.80	–		$F(2110) = 0.69$, $p = 0.504$
Alcohol abuse	35 %		29 %		46 %		–		$\chi^2(2) = 3.94$, $p = 0.414$
Drug abuse	6 %		5 %		16 %		–		$\chi^2(2) = 2.90$, $p = 0.235$
Antipsychotics (months)	50.39	39.99	46.48	38.41	48.16	33.65			$F(2110) = 0.06$, $p = 0.943$

SZ:AVH+$_{current}$ AVH in the past month, *SZ:AVH+$_{remitted}$* AVH last experienced >1 month ago, *SZ:AVH-* no lifetime history of AVHs or non-verbal auditory hallucinations, *HC* healthy controls, *M* mean, *SD* standard deviation

The IOFF was segmented into four subregions (frontal, fronto-temporal, temporal and occipital), according to the landmark specifications of Mårtensson et al. (2013). The four subregions of the IOFF are illustrated in Fig. 2, which have been extracted from a representative participant. The frontal subregion (see Fig. 2, red) was defined as all IOFF fibers lying anterior to the coronal section in which the frontal and temporal branches of the external capsule joined. The occipital subregion (see Fig. 2, blue) was defined as all IOFF fibers lying posterior to the coronal section in which the splenium of the corpus callosum met the interhemispheric fissure. The fronto-temporal subregion (Fig. 2, yellow) was defined geometrically, as the fibers lying between the posterior border of the frontal subregion and a coronal section placed at one-third distance between the posterior edge of the frontal subregion and the anterior edge of the occipital subregion. Finally, the temporal subregion (Fig. 2, green) was defined geometrically as all fibers between the anterior edge of the occipital subregion and the posterior edge of the fronto-temporal subregion.

The statistical analysis was performed using SPSS (version 22, www.spss.com). Repeated measures analyses of variance (ANOVA) with *group* (3 levels: SZ:AVH+, SZ:AVH, HC) as the between-subjects factor and *subregion* (4 levels: frontal, fronto-temporal, temporal, occipital) and *hemisphere* (2 levels: left, right) as the within-subjects factors were performed for FA, RD and AD. Follow-up contrasts (Fisher's Least Significant Difference) were used to examine the underlying simple effects only in the case of a significant main effect of *group* or a significant *group*subregion* interaction, as these analyses were most germane to our specific hypotheses. All analyses were repeated as ANCOVAs, controlling for handedness, in order to account for any differences in hemispheric lateralization. To account for any effects that might be driven by scanner variability, all analyses were also repeated as ANCOVAs, controlling for scanner location.

Results

Demographic and clinical variables

The three groups (SZ:AVH+, SZ:AVH-, HC) did not differ in terms of age, handedness, gender and the scanner in which the images were acquired (McCarthy-Jones et al. 2015). The two groups of patients with schizophrenia did not differ in their rates of alcohol or substance abuse/dependence, delusions, their levels of negative symptoms, depression, duration of illness, or antipsychotic usage (McCarthy-Jones et al. 2015). The ANCOVAs controlling for handedness revealed the same pattern of results as the original ANOVAs, and are therefore not presented separately.

DTI variables

Fractional anisotropy (FA) The means and standard errors for mean fractional anisotropy of the four IOFF segments (frontal, fronto-temporal, temporal and occipital) for the left and right hemispheres for the three groups (SZ:AVH+, SZ:AVH-, HC) are presented in Fig. 3.

A repeated-measures ANOVA identified a significant main effect for *group* [$F(2150) = 9.192$, $p < .001$, $\eta_p^2 = .109$], a significant main effect for *subregion* [$F(3450) = 294.114$,

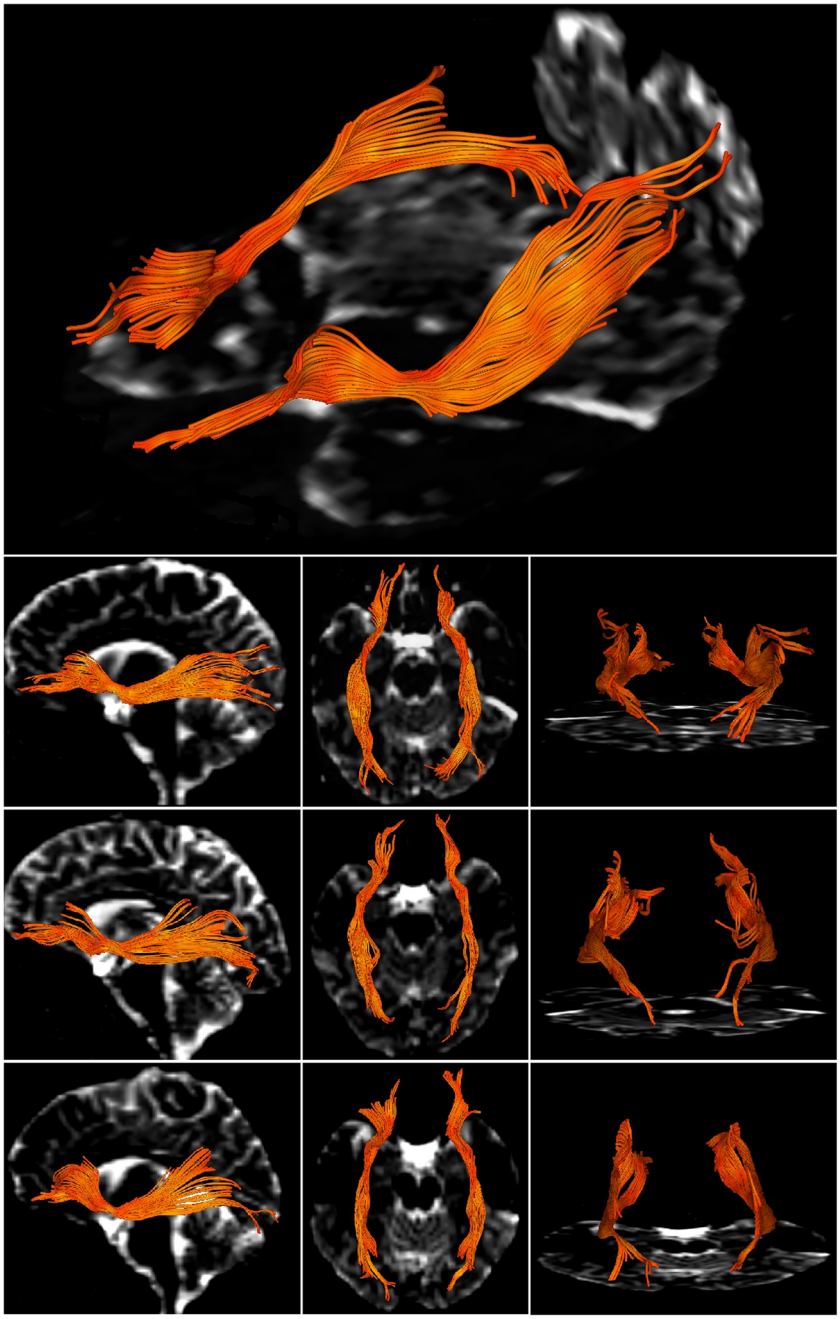

Fig. 1 The left and right inferior occipito-frontal fasciculi (IOFF), extracted using diffusion tensor tractography

$p < .001$, $\eta_p^2 = .662$], and a significant main effect for *hemisphere* [$F(1150) = 9.378$, $p = .003$, $\eta_p^2 = .059$]. There was also a significant *subregion*group* interaction [$F(6450) = 2.535$, $p = .029$, $\eta_p^2 = .033$] and a significant *hemisphere*group* interaction [$F(2150) = 4.659$, $p = .011$, $\eta_p^2 = .058$, but no significant *hemisphere*subregion*group* interaction [$F(6450) = 1.034$, $p = .401$, $\eta_p^2 = .014$]. Repeating the analysis as an ANCOVA, controlling for scanner location, rendered the main effect for *hemisphere* non-significant [$F(1149) = 2.613$, $p = .108$, $\eta_p^2 = .017$].

Follow-up contrasts identified significantly reduced FA in the left fronto-temporal segment in the SZ:AVH+ group compared to the SZ:AVH- group [$t(111) = 2.286$, $p = .034$, Cohen's $d = .421$], and in the SZ:AVH+ group compared to the HC group [$t(77) = 3.500$, $p = .001$, Cohen's $d = .816$]. In the left temporal segment, FA was found to be significantly reduced in the SZ:AVH+ group compared to the HC group [$t(77) = 3.857$, $p < .001$, Cohen's $d = .773$], and in the SZ:AVH- group compared to the HC group [$t(112) = 3.571$, $p < .001$, Cohen's $d = .811$]. Similarly, in the right temporal segment, FA was observed to be significantly reduced in the SZ:AVH+ group compared to the HC group [$t(77) = 3.875$, $p < .001$, Cohen's $d = .956$], and in the SZ:AVH- group compared to the HC group [$t(112) = 2.714$, $p = .008$, Cohen's

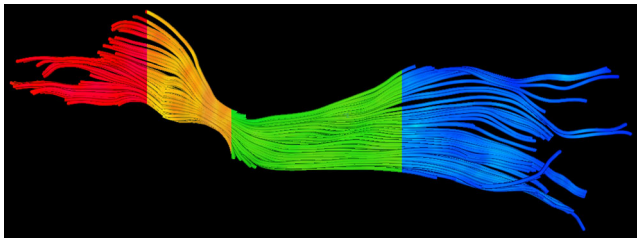

Fig. 2 The four subregions of the IOFF: the frontal segment (*red*), fronto-temporal segment (*yellow*), temporal segment (*green*) and the occipital segment (*blue*). These subregions are extracted from a representative particiapant's IOFF with diffusion tractography

d = .514]. In the left occipital segment, FA was also found to be significantly reduced in the SZ:AVH+ group compared to the HC group [$t(77) = 3.300$, $p = .002$, Cohen's $d = .749$], and in the SZ:AVH- group compared to the HC group [$t(112) = 3.778$, $p < .001$, Cohen's $d = .807$]. In the right occipital segment, FA was significantly reduced in the SZ:AVH+ group compared to the HC group [$t(77) = 2.222$, $p = .036$, Cohen's $d = .559$] and in the SZ:AVH- group compared to the HC group [$t(112) = 2.25$, $p = .030$, Cohen's $d = .433$]. No significant changes were observed in the pattern of results when controlling for scanner location.

On inspection of Fig. 3, the significant *group*hemisphere* interaction appeared to reflect the HCs exhibiting a pattern of left-greater-than-right FA over the IOFF subregions which was not apparent in the SZ groups. This was verified in the follow-up contrasts which found that in the HC group, FA was significantly increased in the left frontal segment compared to the right frontal segment [$t(39) = 2.852$, $p = .007$, Cohen's $d = .541$], the left fronto-temporal segment compared to the right fronto-temporal segment [$t(39) = 3.324$, $p = .002$, Cohen's $d = .592$] and in the left occipital segment compared to the right occipital segment [$t(39) = 2.040$, $p = .048$, Cohen's $d = .263$]. No significant between-hemisphere differences were observed in either of the schizophrenia groups.

Radial diffusivity (RD) A repeated-measures ANOVA identified a significant main effect for *subregion* [$F(3450) = 44.279$, $p < .001$, $\eta_p^2 = .228$] and a significant *hemisphere*group* interaction [$F(2150) = 3.487$, $p = .033$, $\eta_p^2 = .044$]. There was no significant main effect for *hemisphere* [$F(1150) = 2.390$, $p = .124$, $\eta_p^2 = .016$], no significant main effect for *group* [$F(2150) = 1.020$, $p = .363$, $\eta_p^2 = .013$], no significant *group*subregion* interaction [$F(6450) = 2.004$, $p = .081$, $\eta_p^2 = .026$] and no significant *hemisphere*subregion*group* interaction [$F(6450) = .465$, $p = .807$, $\eta_p^2 = .006$]. As the main effect of *group* and the *group*subregion* interaction were both non-significant, follow-up contrasts were not performed.

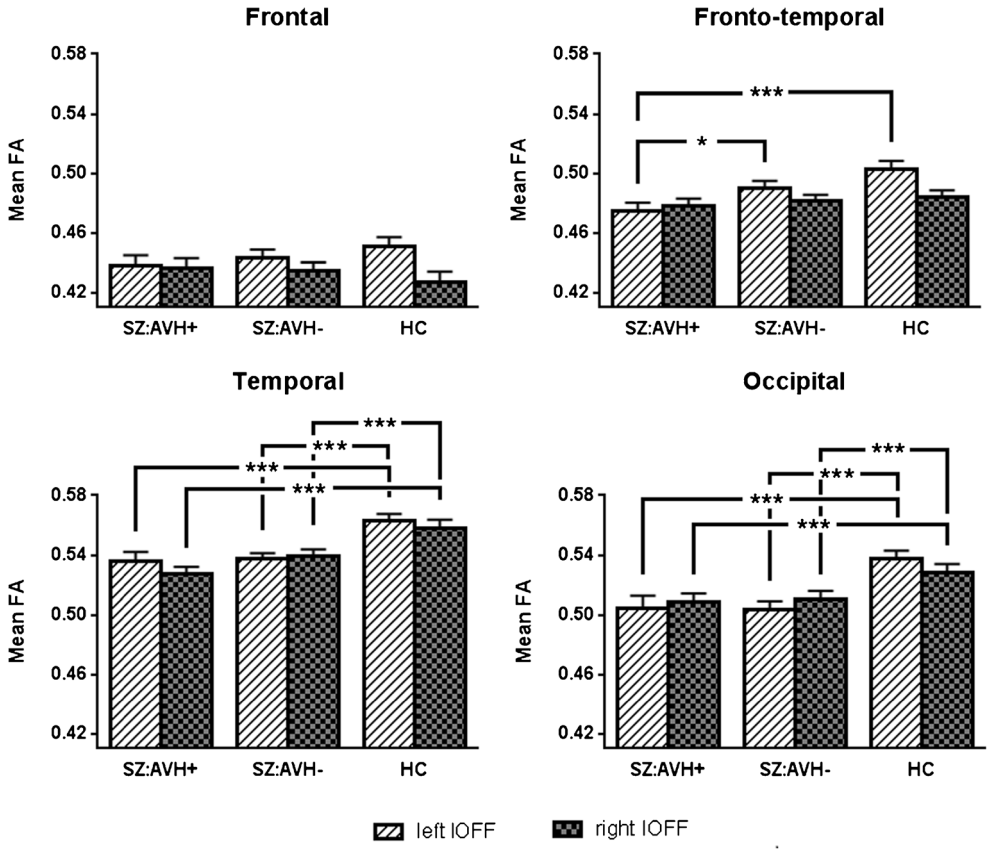

Fig. 3 Mean fractional anisotropy (FA) of the frontal, fronto-temporal, temporal and occipital subregions of the left and right inferior occipito-frontal fasciculus (IOFF), separated by group (SZ:AVH+, SZ:AVH-, HC). Error bars represent standard error of the mean. $^*p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$

Axial diffusivity (AD) A repeated-measures ANOVA identified a significant main effect for *hemisphere* [$F(1150) = 5.248$, $p = .023$, $\eta_p^2 = .034$] a significant main effect for *subregion* [$F(3450) = 542.914$, $p < .001$, $\eta_p^2 = .778$], but no significant main effect for *group* [$F(2150) = 2.978$, $p = .054$, $\eta_p^2 = .038$]. There was no significant *hemisphere*group* interaction [$F(2150) = .075$, $p = .928$, $\eta_p^2 = .001$], no significant *group*subregion* interaction [$F(6450) = 1.875$, $p = .097$, $\eta_p^2 = .024$] and no significant *hemisphere*subregion*group* interaction [$F(6450) = .663$, $p = .637$, $\eta_p^2 = .009$. As the main effect of *group* and the *group*subregion* interaction were both non-significant, follow-up contrasts were not performed.

Supplementary fractional anisotropy analysis: current versus remitted AVH

To investigate further the significant FA reductions in the left fronto-temporal segment in the SZ:AVH+ group compared to the SZ:AVH- group, a one-way ANOVA with *group* (4 levels; SZ:AVH+$_{current}$, SZ:AVH+$_{remitted}$, SZ:AVH-, HC) as the between-subjects factor was conducted in this subregion. Rates of delusions differed significantly between the three schizophrenia groups (Table 1), thus the ANOVA was repeated as an ANCOVA with delusions added as a covariate.

This analysis revealed a significant main effect of *group* [$F(3149) = 4.178$, $p = .007$, $\eta_p^2 = .078$]. Follow-up contrasts revealed that FA was significantly reduced in the SZ:AVH+$_{current}$ group [$t(56) = 3.280$, $p = .001$, Cohen's $d = 1.022$] and the SZ:AVH+$_{remitted}$ group [$t(59) = 2.313$, $p = .022$, Cohen's $d = .649$], compared to the HC group, as well as in the SZ:AVH+$_{current}$ group compared to the SZ:AVH- group [$t(90) = 2.244$, $p = .026$, Cohen's $d = .600$]. Additionally, the SZ:AVH- group showed significantly reduced FA compared to the HC group [$t(103) = 2.079$, $p = .039$, Cohen's $d = .424$]. No significant changes were observed in the pattern of results when controlling for scanner location and delusions.

Discussion

The present study used diffusion tensor imaging (DTI) to investigate whether the structural integrity of the IOFF was associated with the presence of AVH in patients with schizophrenia. While structural changes in the IOFF were identified in both SZ:AVH+ and SZ:AVH-, compared to healthy controls, in various subregions of the IOFF bilaterally, there was evidence to suggest that white matter alterations in fibers connecting frontal and temporal areas of the left IOFF were specifically associated with AVH. Integrity changes of the fronto-temporal fibers of the left IOFF were observed in both patients with current and remitted AVH, but were more pronounced in patients with current AVH. Hence, the findings of the present study suggest that while integrity changes in multiple areas of the IOFF bilaterally are associated with schizophrenia *generally*, alterations in the fronto-temporal fibers of the left IOFF may be associated with AVH *specifically*.

The results of the present study are consistent with the findings of Ćurčić-Blake et al. (2015), which found that schizophrenia patients with AVH had significantly lower FA in the anterior part of the left IOFF compared to schizophrenia patients without AVH. Rather than investigating the anterior and posterior parts of the IOFF, the present study segmented the IOFF into frontal, fronto-temporal, temporal and occipital areas. This investigation of the constituent subregions of the IOFF extends the findings of Ćurčić-Blake et al. (2015) by showing that the fibers connecting frontal and temporal areas are associated with state AVH. While Ćurčić-Blake et al. (2015) used a tract-based spatial statistics (TBSS) approach, the present study used a tractography-based approach to extract the IOFF. The overlapping findings of both studies, despite the use of different DTI techniques, enhances the confidence that integrity reductions in the anterior region of the left IOFF are specifically associated with AVH in schizophrenia.

As illustrated in Fig. 3, the significant *group*hemisphere* interaction in the FA data was driven by the healthy control group exhibiting a pattern of left-greater-than-right FA over three IOFF subregions (frontal, fronto-temporal and occipital) which was not evident in the schizophrenia groups. This lateralization of IOFF integrity has been reported previously in healthy control participants (Powell et al. 2006), as has the relative absence of IOFF lateralization in schizophrenia patients (Miyata et al. 2012). Given that the IOFF represents the major fasciculus in the ventral language stream (Duffau 2008; Almairac et al. 2014), this finding is consistent with Crow's model of schizophrenia as a failure of interhemispheric dominance for language (Crow 2004).

The dual processing model of the auditory system distinguishes between the ventral stream (IOFF), which is believed to be involved in converting auditory information into meaningful concepts, and the dorsal stream (arcuate fasciculus), which provides a direct connection between the primary site of speech initiation (Broca's area) and speech perception (Wernicke's area; Duffau 2008). In a previous study of the same participant sample, schizophrenia patients with a history of AVH were found to exhibit lower FA in the left arcuate fasciculus relative to both patients without a history of AVH and matched healthy controls (McCarthy-Jones et al. 2015). Taken together with the results of the present study, this suggests that AVH are associated with changes in the integrity of both the dorsal and ventral language stream. Alterations to the dorsal and ventral route may both be associated with AVH due to their effects on a common mechanism. Another possibility (not mutually exclusive) is that changes to these two tracts may have dissociable effects on AVH. For example, changes to the integrity of the dorsal stream may give rise to AVH (possibly because of its effects on corollary discharge

signalling), with changes to the ventral stream influencing their form. The association between IOFF damage and verbal preservation (Khan et al. 2014) could be used to hypothesize that reductions in the integrity of the IOFF specifically contribute to the well-documented repetitive nature of AVH (McCarthy-Jones et al. 2014).

The findings of this study are consistent with previous studies that have found reduced FA of the IOFF in patients with schizophrenia (Epstein et al. 2014; Liu et al. 2013; Liu et al. 2014; Palaniyappan et al. 2013) and individuals at ultra-high risk for psychosis (Walterfang et al. 2008). The precise functional role of the IOFF is still poorly understood (Martino and De Lucas 2014), but it is thought to extend beyond auditory processing and play a role in such diverse processes as visual processing (Catani and Thiebaut de Schotten 2008), attention (Doricchi et al. 2008), left unilateral neglect (Urbanski et al. 2008) and reading (Duffau 2008). It is therefore possible that structural abnormalities to the IOFF may be involved in the etiology of symptoms in schizophrenia other than AVH. For example, abnormal FA in the IOFF has been observed in color-music synesthesia, a condition in which musical sounds elicit concurrent visual color perceptions (Zamm et al. 2013). Although AVH are the most common form of hallucinations in schizophrenia, approximately 14 % of patients report hallucinations in the visual modality (Mueser et al. 1990). It is therefore conceivable that changes to the integrity of the IOFF are not limited to the development of AVH, but instead contribute to the occurrence of hallucinations in various modalities.

This study had a number of limitations. First, the data used in this study was collected from five cities across Australia. While all five scanners were the same make and model and built according to identical specifications, it is possible that imparities between scanners affected DTI metrics. Secondly, contemporary DTI studies typically acquire multiple b0 scans in order to acquire highly precise and unbiased estimates of FA. Since the data for this study has been collected over several years according to the same protocol, the acquisition of only one b0 scan presents a limitation. Thirdly, data on duration of antipsychotic drug use was incomplete and dosage data was not available for all patients. The confounding effects of medication exposure on the results of this study can therefore not be ruled out. It should be noted, however, that there were no significant between-group differences in scanner location or antipsychotic drug use. Finally, we used contrasts to unpack the simple effects underlying the observed main effects and interactions, and did not correct the significance level of post-hoc tests for multiple comparisons. It is hence possible that some of our results may have been Type I errors, although the consistency of our results with the findings of Ćurčić-Blake et al. (2015) suggests this was not the case.

In summary, this study found that while structural abnormalities of the IOFF bilaterally are associated with schizophrenia per se, changes of the fronto-temporal fibers in the left IOFF are specifically associated with AVH. Further research may wish to examine if the reduced structural integrity of the bilateral IOFF is associated with symptoms of schizophrenia other than AVH.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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