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Neuroimaging auditory verbal hallucinations in schizophrenia patient and healthy populations

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Original Article

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Abstract

Background. Auditory verbal hallucinations (AVH) are a cardinal feature of schizophrenia, but they can also appear in otherwise healthy individuals. Imaging studies implicate language networks in the generation of AVH; however, it remains unclear if alterations reflect biologic substrates of AVH, irrespective of diagnostic status, age, or illness-related factors. We applied multimodal imaging to identify AVH-specific pathology, evidenced by overlapping gray or white matter deficits between schizophrenia patients and healthy voice-hearers.

Methods. Diffusion-weighted and T1-weighted magnetic resonance images were acquired in 35 schizophrenia patients with AVH (SCZ-AVH), 32 healthy voice-hearers (H-AVH), and 40 age- and sex-matched controls without AVH. White matter fractional anisotropy (FA) and gray matter thickness (GMT) were computed for each region comprising ICBM-DTI and Desikan–Killiany atlases, respectively. Regions were tested for significant alterations affecting both SCZ-AVH and H-AVH groups, relative to controls.

Results. Compared with controls, the SCZ-AVH showed widespread FA and GMT reductions; but no significant differences emerged between H-AVH and control groups. While no overlapping pathology appeared in the overall study groups, *younger* (<40 years) H-AVH and SCZ-AVH subjects displayed overlapping FA deficits across four regions ($p < 0.05$): the genu and splenium of the corpus callosum, as well as the anterior limbs of the internal capsule. Analyzing these regions with free-water imaging ascribed overlapping FA abnormalities to tissue-specific anisotropy changes.

Conclusions. We identified white matter pathology associated with the presence of AVH, independent of diagnostic status. However, commonalities were constrained to younger and more homogenous groups, after reducing pathologic variance associated with advancing age and chronicity effects.

Introduction

Auditory verbal hallucinations (AVH) are a cardinal symptom of schizophrenia, but can also occur in several other neuropsychiatric disorders, as well as in the healthy population (Daalman *et al.*, 2012). Despite transdiagnostic similarities (Daalman *et al.*, 2011), pathological substrates of AVH remain largely elusive, with contradictory findings as to specific brain regions and pathophysiological mechanisms involved.

Magnetic resonance imaging (MRI) studies comparing schizophrenia patients with and without AVH implicate volume and gray matter thickness (GMT) changes in predominantly language-related gray matter areas, such as temporal cortical regions, Broca's area, and prefrontal regions in the pathology of AVH (Kühn and Gallinat, 2012; Palaniyappan *et al.*, 2012). These findings cohere with a hypothesis that the generation of AVHs are caused by disrupted corollary discharges (Mathalon and Ford, 2008). This hypothesis posits that the abnormal integration of activity in cortical areas responsible for speech production and auditory perception results in the inability to accurately perceive self-generated signals as arising from external/internal sources or intrinsic activity (Catani and Ffytche, 2005; Stephan *et al.*, 2009).

In addition to pathology affecting gray matter regions, functional disintegration may result from disrupted anatomical connectivity involving the brain's white matter architecture (Whitford *et al.*, 2010*a*, 2011). Evidence for white matter pathology derives from diffusion MRI studies, reporting changes in diffusion tensor imaging (DTI) indices such as the fractional anisotropy (FA). However, little consensus exists regarding the location of abnormalities, with

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some studies reporting changes in circuits connecting speech areas (Seok *et al.*, 2007; Catani *et al.*, 2011; Kubicki *et al.*, 2011; Ćurčić-Blake *et al.*, 2015; Oestreich *et al.*, 2016; Psomiades *et al.*, 2016), and others in commissural fibers and subcortical–cortical connections (Hubl *et al.*, 2004; Mulert *et al.*, 2012; Xi *et al.*, 2016; Zhang *et al.*, 2018), which are outside language-linked circuitry. In addition, some studies report increased (Hubl *et al.*, 2004; Mulert *et al.*, 2012), and others, decreased FA (Seok *et al.*, 2007; Ćurčić-Blake *et al.*, 2015; Oestreich *et al.*, 2016) in schizophrenia patients with AVH. Thus, it seems that white matter pathology is associated with AVH in schizophrenia patients; however, the nature of microstructural deficits and specific tracts involved remains unclear.

We point to three primary reasons for heterogenous findings across prior DTI studies. First, schizophrenia is diagnostically characterized by complex clinical phenotypes, broadly categorized into positive, negative, and cognitive symptoms. Thus, previous observations of imaging marker abnormalities in groups of schizophrenia patients with AVH may not be specific to hallucinations, but rather relate to other symptom dimensions or illness-related factors (Ford *et al.*, 2014). Second, age-related changes have been shown to substantially impact white and gray matter abnormalities in schizophrenia (Jones *et al.*, 2006; Cropley *et al.*, 2016; Schnack *et al.*, 2016; Di Biase *et al.*, 2017, 2018). As such, mixed findings in previous AVH studies may reflect heterogeneity in age range and illness duration (which are intricately linked), where findings in older schizophrenia patients are confounded by more evolved pathologies associated with prolonged illness and cumulative medication effects (Ford *et al.*, 2014). Analyzing younger cohorts with shorter illness durations could potentially mitigate these confounding effects to elucidate AVH-specific phenomena. Third, methodological limitations may contribute to the lack of consensus, such that traditional DTI indices may not be able to distinguish specific microstructural features and as such, caution is warranted when interpreting FA changes, which may reflect various, non-specific underlying biological mechanisms across the studies (O'Donnell and Pasternak, 2015). For example, recent studies suggest that reduced FA is mostly ascribed to excess extracellular free-water (FW) fractions in patients with a first-episode of psychosis (Pasternak *et al.*, 2012; Lyall *et al.*, 2017), whereas in chronic schizophrenia patients, reduced FA reflects cellular-specific white matter deficits (Pasternak *et al.*, 2015; Oestreich *et al.*, 2017). It follows that FA changes associated with AVH could either originate from extracellular or cellular mechanisms, which may reflect distinct pathological processes (Pasternak *et al.*, 2016).

One way to address the first limitation, and isolate the contribution of AVH from the broader collection of schizophrenia sequelae, is to identify shared neurobiological deficits across voice-hearers, including schizophrenia patients (SCZ-AVH) and healthy individuals experiencing AVH who are otherwise healthy (i.e. no clinical diagnosis) and are not treatment-seeking (H-AVH; Larøi, 2012; Baumeister *et al.*, 2017). In an earlier study focused on the arcuate fasciculus (AF), we found altered white matter microstructure in SCZ-AVH, but not in H-AVH, possibly suggesting that FA alterations of the AF reflect disease-specific processes (de Weijer *et al.*, 2013). Here, we extend our examination to include both white and gray matter spanning the entire brain. To comprehensively characterize the structural neuropathology underlying AVH, multimodal imaging was used to probe overlapping abnormalities across both GMT and white matter microstructure (FA) between H-AVH and SCZ-AVH. As FA abnormalities may either reflect changes in extracellular FW pools or cellular-specific changes within the white matter tissue, we applied FW imaging to separately examine these distinct biological compartments and to provide insight into the microstructural underpinnings of any shared FA abnormalities. Moreover, to reduce patient heterogeneity associated with age-related effects and pinpoint AVH-specific pathology, all analyses were repeated on younger subjects with shorter illness durations and cumulative medication exposure.

Methods

Participants

This study was approved by the Human Ethics Committee of the University Medical Center, Utrecht. All participants provided written informed consent, consistent with the Helsinki Declaration of 1975, as revised in 2008. A total of 107 participants were included in this study: 35 patients with a schizophrenia-spectrum disorder (SCZ-AVH; mean age = 35.89 ± 10.41), 32 healthy voice-hearers (H-AVH; mean age = 39.06 ± 11.09) and 40 healthy controls (HC), without a history of AVH (mean age = 38.42 ± 13.25). Most subjects overlapped with subjects comprising the de Weijer *et al.* (2013) investigation (30/35 SCZ-AVH; 32/35 H-AVH; 35/40 controls). Key demographic and clinical characteristics are presented in Table 1.

Detailed recruitment and sample characteristics are described elsewhere (Daalman *et al.*, 2011). In brief, eligible SCZ-AVH patients were diagnosed with a schizophrenia-spectrum disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; First and Gibbon, 2004) and presented with AVHs. Diagnoses were confirmed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen *et al.*, 1992) by an independent psychiatrist. The Positive and Negative Syndromes Scale (PANSS; Kay *et al.*, 1987) was used to assess general psychopathology (PANSS total) and positive symptoms (PANSS positive subscale) in the patient group.

The H-AVH subjects were recruited via an online self-report questionnaire (www.verkenuwgeest.nl), which quantifies hallucination tendencies in healthy individuals (Larøi *et al.*, 2004). Respondents endorsing voice-hearing items were selected for telephone screening by trained psychologists and invited to participate if they met the following criteria: (i) voices were distinct from thoughts; (ii) voices were experienced at least once a month, for over 1 year; (iii) no lifetime history of diagnosis or treatment for psychiatric disorders; (iv) no alcohol or drug abuse for at least 3 months; and (v) no lifetime history of a chronic somatic disorder (Daalman *et al.*, 2011). Individuals fulfilling these criteria were invited to undergo a psychiatric interview. For both healthy groups (H-AVH and HC), the absence of current or history of diagnosable psychopathology, including substance abuse, was confirmed with CASH (Andreasen *et al.*, 1992) and with the Structured Clinical Interview for Personality Disorders (First and Gibbon, 2004) by an independent psychiatrist.

For both AVH groups, detailed characteristics of hallucinations were assessed using the Psychotic Symptom Rating Scale (PSYRATS; Haddock *et al.*, 1999). Four hallucination dimensions were measured with PSYRATS (Woodward *et al.*, 2014): Distress (Distress/Negative Content/Control), Frequency (Frequency/Duration/Disruption), Attribution (Attribution of voices: Location and Origin), and Loudness (Loudness). All clinical ratings were performed on the scan day by trained interviewers.

Table 1. Sample population and clinical characteristics: overall study population

	Controls	H-AVH	SCZ-AVH
	(*n* = 40)	(*n* = 32)	(*n* = 35)
Variables	*M* (SD)	*M* (SD)	*M* (SD)
Age	38.42 (13.25)	39.06 (11.09)	35.89 (10.41)
Years of education	14.40 (2.69)	13.81 (1.77)	13.11 (2.17)
Illness duration (years)	–	–	17.00 (10.40)
SPQ (total)	7.95 (6.24)	27.58 (13.05)	–
AVH (PSYRATS total)*	–	16.69 (4.08)	31.34 (5.38)
Distress (PSYRATS subscale)*	–	19.44 (5.67)	39.97 (7.47)
Frequency (PSYRATS subscale)*	–	7.84 (1.39)	9.24 (1.90)
Attribution (PSYRATS subscale)*	–	3.30 (1.39)	4.94 (1.55)
Loudness (PSYRATS subscale)	–	1.55 (0.93)	3.33 (1.80)
General psychopathology (PANSS total)	–	–	57.48 (12.76)
Positive symptoms (PANSS subscale)	–	–	14.45 (3.85)
	n (%)	*n* (%)	*n* (%)
Sex, female	21 (52.5)	20 (62.5)	17 (48.6)
Antipsychotics[a]			
None	–	–	7 (20.6)
Typical	–	–	6 (17.6)
Atypical	–	–	20 (58.8)
Both	–	–	1 (2.9)

*Significant difference between H-AVH and SCZ-AVH at the level of $p < 0.05$.
[a]Missing data for one patient.

MRI acquisition and pre-processing

All diffusion MRI and T1-weighted scans were acquired between 2007 and 2010 at the University Medical Center, Utrecht, on a 1.5 T Philips Achieva MR scanner using an eight-channel SENSE head-coil. No scanner upgrades were performed during the study lifetime. For diffusion MRI, 30 volumes of diffusion-weighted images (DWI) with non-collinear diffusion gradient directions, and a baseline (b0) volume were obtained with single-shot EPI-DTI imaging sequence. Acquisition parameters were as follows: *b*-value = 1000 s/mm^2, isotropic 2 mm × 2 mm × 2 mm voxels, image matrix = 128 × 128, repetition time/echo time = 7035/68 ms, FOV = 240 mm. A second set of diffusion volumes were acquired with the same parameters as the first set, but with a reversed *k*-space readout (anterior direction), to facilitate EPI distortion correction in the pre-processing pipeline. The parameters for T1-weighted images were as follows: slice thickness = 1 mm (without gap), field of view = 244 mm × 160 mm × 168 mm, repetition time/echo time = 9.87/4.6 ms, flip angle = 8°, data matrix size = 256 × 256.

Tract-based spatial statistics pipeline

Diffusion MRI data were pre-processed with FMRIB Software Library (FSL; Jenkinson *et al.*, 2012). This involved visual inspection for artifacts, during which eight scans were removed from the analysis (two controls, two H-AVH and four SCZ-AVH) due to poor image quality (movement artifacts, ghosting and signal drops). The remaining scans (sample population described in Table 1) underwent correction for EPI distortions by combining the phase flipped images; motion and gradient-induced eddy currents using affine registration to the first b0 image; brain masking performed with FSL's Brain Extraction Tool (BET; Jenkinson *et al.*, 2012) and subsequent manual editing in Slicer (https://www.slicer.org); computation of a FA volume by fitting a single tensor to the DWI data [as previously done in de Weijer *et al.* (2013)], as well as computation of the FW fraction and tissue-specific FA (FA_T) volumes by applying FW imaging (Pasternak *et al.*, 2009). FW imaging applies a regularization framework to fit a two-compartment (bi-tensor) model that separates the contribution of FW from that of tissue-specific diffusivity (Pasternak *et al.*, 2009). FW constitutes unrestricted extracellular water molecules found in cerebrospinal fluid, blood, or the interstitial space. Reduced FA may reflect increased partial volume of FW pools (e.g. in fibers adjacent to ventricles), rather than changes in the white matter microstructure. As such, disambiguating these distinct biological compartments (i.e. into FW and FA_T) provides insight into the extracellular and microstructural underpinnings of FA deficits.

We used FSL's tract-based spatial statistics (TBSS; Smith *et al.*, 2006) and ENIGMA-DTI protocols (http://enigma.ini.usc.edu/protocols/dti-protocols/) as a data-driven approach, which preclude the need for *a priori* hypotheses regarding tract/region-specific changes, in light of mixed findings across previous AVH studies. ENIGMA-DTI protocols were used to extract average diffusion (FA, FA_T, FW) estimates from white matter regions

of interest (ROIs; Jahanshad *et al.*, 2013). In brief, FA maps were registered to the common ENIGMA-DTI target, derived from 400 adult brains (Jahanshad *et al.*, 2013). Registration followed a two-step procedure performed with FSL (Jenkinson *et al.*, 2012): first, an affine transformation was computed to match the FA volume to the template (Andersson *et al.*, 2007); next, non-linear normalization applied the deformation field that warps the original FA volume to the template, setting the previous affine transformation as the starting estimate (Andersson *et al.*, 2010). The ENIGMA-DTI target was skeletonized with TBSS (Smith *et al.*, 2006) and FA voxels were projected onto the skeleton mask. The FA-derived transformations and projection parameters were used to project FA_T and FW maps onto the skeleton mask. Resulting skeletonized maps (FA, FA_T, FW) were used to extract values from a subset of white matter regions comprising the ICBM-DTI white matter labels atlas (38 ROIs in total: 17 left and right lateralized respectively, as well as four midline structures; online Supplementary Table S1; Mori *et al.*, 2005). To define ROIs, diffusion metrics were averaged over skeleton voxels traversing a given atlas region. Diffusion metrics were obtained from deep white matter structures (i.e. the skeleton) to minimize partial volume effects and from ROIs (rather than voxels), to reduce multiple comparisons and bolster statistical power, given the modest sample size.

GMT estimation

T1-weighted images were processed using the FreeSurfer automated neuroanatomical segmentation software (version 5.3; Fischl and Dale, 2000) to generate a three-dimensional model of the cortical surface for each participant. Surface-based cortical reconstruction was performed to derive the white matter and pial surfaces, from which GMT estimates were derived (Dale *et al.*, 1999; Fischl *et al.*, 1999, 2002, 2004; Fischl and Dale, 2000). All images were visually inspected to verify the accuracy of reconstructions and identify errors, including skull-strip errors, gross segmentation errors and white/gray matter and pial surface inaccuracies. Mean GMT was extracted from each region comprising the Desikan–Killiany atlas (68 cortical regions in total: 34 left and right lateralized, respectively; Desikan *et al.*, 2006) using standard procedures for ROI extraction, provided by FreeSurfer. Cortical thickness was examined in ROIs (rather than voxels), to reduce multiple comparisons and bolster statistical power, given the modest sample size.

Statistical analyses

Between-group differences and overlap

All statistical analyses were performed in MATLAB (version 2017b). Diffusion and GMT metrics were normally distributed, as assessed with one-sample Kolmogorov–Smirnov test and homogeneity of variances was checked by Levene's test. The FA and GMT measures were initially compared between SCZ-AVH and HC groups at each white matter ROI by general linear models (GLMs) to regress out variance associated with sex and age. The false discovery rate (FDR; Benjamini and Heller, 2007) was used to provide multiple comparisons error control across the regions (38 FA regions; 68 GMT regions). Regions showing a significant group effect after FDR correction were then compared by GLMs between H-AVH and HC groups. Regions surviving FDR correction were taken to reflect shared pathology between H-AVH and SCZ-AVH cohorts. To determine the nature of any overlapping FA deficits, subsidiary analyses examined FA_T and FW diffusion metrics in regions with overlapping FA abnormalities between H-AVH and SCZ-AVH. Support for a two-step GLM procedure was based on our aim to identify pathology affecting both AVH groups relative to HCs, irrespective of differences occurring between AVH groups (e.g. significantly lower FA in SCZ-AVH compared with H-AVH).

All analyses were repeated on a subsample of younger subjects (<40 years of age) to minimize the effects of aging, cumulative medication exposure, illness chronicity, or repeated AVH experiences. A threshold of 40 years of age was used to coincide with the median split – a robust statistical means to dichotomize data (Iacobucci *et al.*, 2015), as well as the timing of peak white matter maturation, as shown through diffusion imaging lifespan studies (Westlye *et al.*, 2009; Cropley *et al.*, 2016). Refer to Table 2 for demographic and clinical characteristics of the younger subsample.

Demographic and clinical characteristics

Analysis of variance was used to test differences in age and number of years educated between the three study groups. Differences in clinical variables (PYSRATS Total and four subscales) between H-AVH and SCZ-AVH groups were analyzed with independent *t* tests. Partial correlations were used to test relationships between clinical variables (PYSRATS Total and four subscales) and diffusion metrics across the pooled H-AVH and SCZ-AVH groups, after controlling for group membership as a binary variable. To investigate potential substrates of hallucinatory phenomena, correlations were confined to regions with overlapping pathology between H-AVH and SCZ-AVH groups. The Bonferroni correction provided error control across the correlation analyses (5 symptom scores) and thus, an adjusted *p*-value of 0.01 was considered statistically significant.

Results

Demographic and clinical characteristics

There were no significant differences in age or sex between SCZ-AVH, H-AVH, and HC groups ($p > 0.05$). Compared with controls, H-AVH and SCZ-AVH were educated for fewer years ($p < 0.05$; see Table 1). Hallucination severity differed between SCZ-AVH and H-AVH groups, with SCZ-AVH showing significantly higher total PSYRATS scores, as well as Distress, Frequency, and Attribution subscale scores compared with the H-AVH group ($p < 0.05$; see Table 1). The SCZ-AVH and H-AVH groups did not differ with respect to Loudness (PSYRATS subscale) scores ($p > 0.05$). There was no relationship between hallucination severity (total PSYRATS scores, as well as Distress, Frequency, and Attribution subscale scores) and age ($p > 0.05$). Furthermore, hallucination severity did not differ between younger and older subgroups within SCZ-AVH and H-AVH cohorts, respectively (online Supplementary Table S2).

Microstructural changes in SCZ-AVH and H-AVH

Compared with HCs, schizophrenia patients showed reduced FA in 34/38 ROIs ($_{FDR}p < 0.05$; online Supplementary Table S3). *Post-hoc* analyses constrained to these regions did not detect any differences between H-AVH and HCs ($_{FDR}p > 0.05$). In the younger subgroups, fewer regions (24/38) showed reduced FA in SCZ-AVH patients relative to HCs ($_{FDR}p < 0.05$; online

Table 2. Sample population and clinical characteristics: younger subset

	Controls ($n = 25$)	H-AVH ($n = 16$)	SCZ-AVH ($n = 24$)
Variables	*M* (SD)	*M* (SD)	*M* (SD)
Age	29.44 (5.24)	30.00 (7.21)	30.04 (4.52)
Years of education*	15.08 (2.04)	13.75 (1.00)	12.67 (1.94)
Illness duration (years)	–	–	10.13 (4.65)
SPQ (total)	7.28 (5.88)	32.00 (13.53)	–
AVH (PSYRATS total)*	–	16.94 (4.49)	31.82 (5.49)
Distress (PSYRATS subscale)*	–	20.06 (6.37)	40.45 (7.58)
Frequency (PSYRATS subscale)*	–	7.56 (1.26)	9.43 (1.85)
Attribution (PSYRATS subscale)*	–	2.88 (1.36)	5.2381 (1.58)
Loudness (PSYRATS subscale)	–	1.67 (1.03)	3.35 (0.88)
General psychopathology (PANSS total)	–	–	59.43 (13.58)
Positive symptoms (PANSS subscale)	–	–	15.33 (4.27)
	n (%)	*n* (%)	*n* (%)
Sex, female	14 (56.0)	9 (56.2)	8 (33.3)
Antipsychotics[a]			
None	–	–	5 (21.7)
Typical	–	–	4 (17.4)
Atypical	–	–	13 (56.5)
Both	–	–	1 (4.3)

*Significant difference between H-AVH and SCZ-AVH at the level of $p < 0.01$
[a]Missing data for one patient.

Supplementary Table S4). *Post-hoc* comparisons constrained to these regions revealed lower FA in younger H-AVH compared with HCs in four regions (Fig. 1*a*, *b*): (i) left ($t = 3.62$, $_{FDR}p = 0.001$); and (ii) right anterior limbs of the internal capsule (ALIC; $t = 3.22$, $_{FDR}p = 0.003$); (iii) splenium of the corpus callosum (SCC; $t = 2.87$, $_{FDR}p = 0.007$); and (iv) genu of the corpus callosum (GCC; $t = 2.85$, $_{FDR}p = 0.007$). Supplemental unconstrained comparisons (i.e. across all 38 white matter regions) did not reveal differences localized elsewhere in H-AVH subjects, suggesting that alterations were specifically confined to regions associated with schizophrenia pathology.

To investigate the nature of shared FA abnormalities, FA_T and FW diffusion metrics were examined within these four white matter regions. Significantly lower FA_T was found in SCZ-AVH and H-AVH relative to controls across these four regions ($_{FDR}p < 0.05$; Fig. 1*c*), indicating shared cellular-specific white matter pathology between SCZ-AVH and H-AVH groups. No FW differences emerged between SCZ-AVH and H-AVH relative to HC ($_{FDR}p > 0.05$; Fig. 1*d*). The impact of sex was not significant across any region or diffusion metric ($_{FDR}p > 0.05$).

GMT changes in SCZ-AVH and H-AVH

Compared with HCs, schizophrenia patients displayed reduced GMT spanning 55/68 ROIs ($_{FDR}p < 0.05$; online Supplementary Table S5). Across these regions associated with schizophrenia pathology, no significant differences were found between H-AVH and controls. However, two regions displayed reduced GMT in H-AVH subjects before correcting for multiple comparisons, including the left bank of the superior temporal gyrus ($t = 2.00$, $p = 0.049$, uncorrected) and the right fusiform gyrus ($t = 2.15$, $p = 0.035$, uncorrected). In the younger study groups, 37/68 ROIs showed lower GMT in SCZ-AVH compared with HCs ($_{FDR}p < 0.05$; online Supplementary Table S6). Within these regions, no significant GMT reductions were observed for younger H-AVH subjects compared with HCs ($_{FDR}p > 0.05$). Similar to the overall H-AVH group, younger H-AVH subjects displayed reduced GMT in three temporal regions before correcting for multiple comparisons: (i) the left bank of the superior temporal gyrus ($t = 2.48$, $p = 0.018$, uncorrected); (ii) the right fusiform gyrus ($t = 2.26$, $p = 0.029$, uncorrected); and (iii) the left middle-temporal gyrus ($t = 2.08$, $p = 0.044$, uncorrected). The impact of sex was not significant across any region ($_{FDR}p > 0.05$).

Clinical correlations with overlapping pathology in white matter microstructure

In the younger (<40 years) H-AVH and SCZ-AVH groups who displayed overlapping white matter pathology, there was a significant negative correlation between FA_T in the GCC and the degree of distress associated with AVHs ($r = -0.6$, $p = 0.007$, Bonferroni corrected). This relationship was significant in H-AVH subjects ($r = -0.6$, $p = 0.03$; Fig. 2*a*) and trended toward significance in SCZ-AVH patients ($r = -0.4$, $p = 0.08$; Fig. 2*b*). There was no relationship between FA and hallucination symptom severity

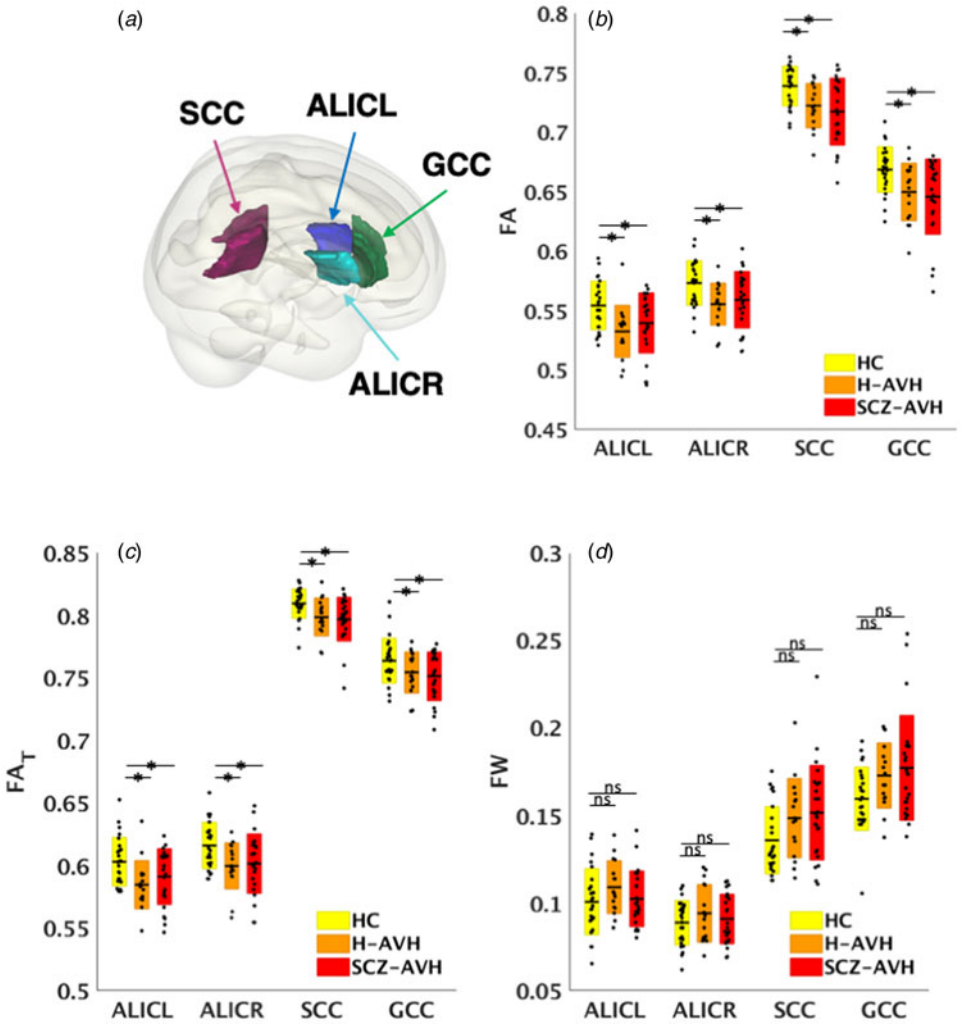

Fig. 1. Overlapping deficits between younger healthy voice-hearers and schizophrenia patients. (*a*) Surface rendering displays regions with overlapping FA and FA_T pathology. (*b*) Boxplots represent regions with overlapping FA pathology for healthy controls (HC), healthy voice-hearers (H-AVH), and schizophrenia patient (SC-AVH) groups across. (*c*) Regions with overlapping FA reductions were investigated for (*c*) cellular-specific (FA_T) and (*d*) free-water volume (FW) changes. Boxes represent standard deviations and dots reflect data points for each subject across the groups, after multiple comparison correction with the false discovery rate. Stars denote significant differences and ns, not significant. Overlapping pathology reflects regions where the H-AVH and SCZ-AVH patients displayed common significant differences from controls.

(PSYRATS total or subscale scores). No overlapping deficits emerged across FW or GMT metrics, and were hence, omitted from symptom correlations.

Discussion

We tested for overlapping abnormalities in regional white matter microstructure and GMT between schizophrenia patients and healthy voice-hearers, relative to age- and sex-matched HC. While significant differences were not identified in healthy voice-hearers overall, *younger* AVH groups displayed overlapping microstructural deficits across several white matter regions, regardless of a clinical diagnostic status. These abnormalities were driven by cellular-specific white matter deficits, rather than changes in the extracellular FW compartment and were correlated with the degree of distress associated with hallucinatory experiences. Schizophrenia patients also displayed globally reduced GMT, as well as more extensive white matter deficits than healthy voice-hearers, which could reflect more evolved AVH symptomatology or the compounding of other biological/psychological disease processes in schizophrenia.

Our findings indicate a crucial role for white matter deficits in AVH. Consistent with several previous studies (Hubl *et al.*, 2004; Xi *et al.*, 2016; Zhang *et al.*, 2018), white matter deficits affected the corpus collosum and internal capsule, confirming involvement of widely distributed commissural, frontal, reciprocal thalamo-cortical and auditory-linked circuitry in the generation of AVH. However, different white matter tracts have been implicated across prior reports, including the superior longitudinal fasciculus (Seok *et al.*, 2007; Ćurčić-Blake *et al.*, 2015), inferior longitudinal fasciculus (Seok *et al.*, 2007), inferior fronto-occipital fasciculus (Ćurčić-Blake *et al.*, 2015; Oestreich *et al.*, 2016), anterior thalamic radiation (Ćurčić-Blake *et al.*, 2015) and AF (the AF was not examined in the current study; Hubl *et al.*, 2004; Psomiades *et al.*, 2016). As nearly all previous studies examined AVH in the context of schizophrenia, abnormalities likely reflected a combination of disease processes and AVH-related phenomena. Indeed, we previously found decreased FA within

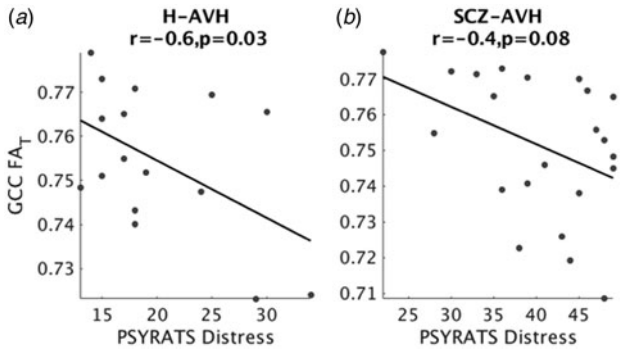

Fig. 2. Associations between FA_T and hallucination distress. Decreased FA_T in the genu of the corpus callosum (GCC) was associated with increased hallucination distress in (*a*) healthy voice-hearers (H-AVH) and (*b*) schizophrenia patients (SCZ-AVH). Correlations controlled for age.

the AF of schizophrenia patients, but not healthy voice-hearers (de Weijer *et al.*, 2011). It is further notable that several previous studies specifically focused on various language-linked white matter fibers of interest (de Weijer *et al.*, 2011; Ćurčić-Blake *et al.*, 2015; Oestreich *et al.*, 2016) and hence, may have missed abnormalities localized elsewhere.

Our findings, when considered together with previous work, suggest that white matter pathology underlying AVH involves pathways beyond language and auditory-linked circuits. The specific connections disrupted in younger AVH subjects could implicate auditory perception failures in AVH manifestation. Specifically, reduced interhemispheric (GCC) and thalamocortical (ALIC) information transfer to frontal regions could underlie attention and impulse control deficits, resulting in self-monitoring failures (Hugdahl *et al.*, 2008). In addition, the SCC carries fibers to temporal, parietal and occipital lobes and thus, deficits in this structure could interrupt information flow between regions which are crucial for delivering and coordinating speech percepts (Friederici *et al.*, 2007). These notions accord with a more sophisticated view of AVH as emerging from comprised structural connections between multiple extra-sensory, association and perception areas, as opposed to pathways specific to the sensory modality in question (Penfield and Perot, 1963; Stephan *et al.*, 2009).

After determining the spatial extent of AVH-specific pathology, we next sought to examine the possible mechanisms underlying connectional deficits. To this end, we applied FW imaging, allowing for greater interrogation of distinct biological compartments – not previously possible with conventional DTI metrics. Using this method, we could ascribe FA abnormalities to cellular-specific FA_T changes, i.e. decreased anisotropy of water diffusion in the tissue, as opposed to an increase in extracellular volume. Although FA_T cannot establish the exact tissue-specific pathology, taken together with repeated neuropathologic findings of altered oligodendrocyte morphology in schizophrenia patients (Uranova *et al.*, 2011, 2014), it is possible microstructural changes in AVH result from a myelin deficit. Indeed, myelin pathology has been proposed as the primary mechanism accounting for hallucinatory phenomena, by way of disrupting temporal coordination between spatially disparate neuronal populations, for example, through slowing of the conduction velocity and inducing synaptic changes (Whitford *et al.*, 2010*a*). With regard to the corollary discharge system, conduction delays could slow 'efference copies' of neural transmission of motor commands, which are consequently received too late by the auditory cortex to accurately predict and suppress the sensations of an impending action (Whitford *et al.*, 2010*a*). Of relevance to our findings, thalamic pathway involvement in corollary discharge failures can occur by way of impairing the updating of sensory information, resulting in less coherent percepts (Bellebaum *et al.*, 2005). Furthermore, the corollary discharge mechanism has been shown to rely on cross-hemispheric transfer for relaying corollary discharge signals (Colby *et al.*, 2005) and integrating auditory percepts (Westerhausen and Hugdahl, 2008). Therefore, our findings may accord with accumulating evidence that AVH involves dysfunctional corollary discharge mechanisms, and in particular, suggest that tissue-specific white matter changes involving key corollary discharge circuits contribute to the pathophysiology underlying AVH.

Decreased FA_T in the GCC was correlated to AVH-related distress (sum of PSYRATS items: negative content, distress, and control), which was significant in healthy voice-hearers and showed a tendency toward significance in patients. This association was not detected with the more general FA metric, suggesting that cellular-specific white matter changes are more sensitive to AVH symptom dimensions. White matter of the GCC interconnects interhemispheric prefrontal regions involved in a wide range of somatosensory, attention, and language processes (Hinkley *et al.*, 2012; Edwards *et al.*, 2014) and disruptions to this region were previously associated with stress (Jackowski *et al.*, 2008), early psychosis (Di Biase *et al.*, 2017), and positive symptoms in schizophrenia (Whitford *et al.*, 2010*b*). Extending this work, our findings indicate that anterior callosal fibers may be vulnerable to AVH-induced distress. Notably, greater self-reported distress accompanying psychosis symptoms may increase risk for developing full-blown psychotic symptoms and transition to other mental health difficulties (Yung *et al.*, 2005; Baumeister *et al.*, 2017). Consistent with this finding, we observed significantly higher distress scores in patients compared with healthy voice-hearers. Interestingly, this was accompanied by comparable FA_T reductions within the GCC across younger clinical and non-clinical AVH groups compared with controls, indicating that greater distress likely involves disruption to additional brain regions, as seen in patient groups. Given that self-reported distress increases risk for developing psychosis (Yung *et al.*, 2005; Baumeister *et al.*, 2017) and that GCC deficits transcend diagnostic status, white matter deficits involving the GCC in particular may signify poor outcomes for younger individuals with AVH symptoms.

Overlapping pathology and symptom correlations in this study were notably constrained to younger AVH groups, as no differences emerged between healthy voice-hearers and controls in the overall study population. We reasoned that pathological variance could increase with age, stress of repeated AVH experiences, and general medication exposure. These confounds could result in pathology that is differentially localized in spatial extent or severity, precluding group-level findings. Indeed, we observed greater variance in average FA across the overall sample (SD = 0.022) compared with the younger subset (SD = 0.019), in line with our expectation. Such inter-subject heterogeneity, combined with the subtle alterations that characterize these otherwise healthy individuals, may explain our null result in the overall healthy voice-hearing population. In contrast, we observed overlap across younger AVH subgroups, where homogenous pathology may relate more purely to AVH symptom constructs, rather than extraneous age, stress, or other chronicity effects. However, it is possible that similarities across younger subgroups might not

relate to AVH as an isolated construct, but rather as part of a general vulnerability to psychosis or schizophrenia-spectrum disorders (Sommer *et al.*, 2010). For example, it is conceivable that symptoms experienced by younger healthy voice-hearers worsen overtime or that other psychosis symptoms transpire, bringing about clinical risk for schizophrenia-spectrum disorders (Yung *et al.*, 2005). However, given that most younger healthy voice-hearers missed the peak window of risk for psychosis onset (i.e. late adolescence to early adulthood; McGrath *et al.*, 2016), and did not display other dimensions of psychopathology at the time of this study; it is reasonable to ascribe our observed white matter deficits specifically to dimensions of AVH, rather than psychosis risk more generally.

Insofar as we did not detect significant gray matter abnormalities in the overall or younger healthy voice-hearers, our findings do not support a central role for GMT alterations in AVH. However, it is noteworthy that the largest differences in healthy voice-hearers relative to controls, involved thinning of key brain regions for language processing and recognition, including the superior temporal gyrus, right fusiform gyrus, and left middle-temporal gyrus. Reduced thickness and volume in extra-sensory auditory regions are consistently reported in association with AVH within a schizophrenia context (Allen *et al.*, 2008; Palaniyappan *et al.*, 2012) and are proposed to reflect neuropil loss, which could underlie dysfunctional cortical activations (van Swam *et al.*, 2012). It may be speculated that our results did not survive multiple comparison correction because cortical thinning is mild in healthy voice-hearers. Notably, in addition to cortical thinning, the years of education and clinical presentation (i.e. AVH severity) of the healthy voice-hearers in this study exhibited intermediate properties of the patient and HC groups, in line with a quasi-dimensional view (Claridge and Beech, 1995) of AVH and other psychotic symptoms. However, it is alternatively possible that reduced thickness across these regions was due to chance and hence, non-essential to the pathophysiology underlying AVH. If gray matter abnormalities are indeed involved in the pathophysiology of AVH, it is our contention that they are spatially constrained to auditory association areas, relative to more widely distributed connectional deficits.

Limitations

Our findings of cellular-specific white matter changes were limited to younger study groups, comprising relatively small samples. Furthermore, a portion of these healthy voice-hearers may develop clinical risk or frank psychosis, and hence, we cannot discount the possibility that the observed changes relate to psychosis risk or other illness dimensions. Key risk factors that mediate vulnerability to psychosis and AVH manifestation, including environmental (e.g. trauma exposure; Fusar-Poli *et al.*, 2017) and genetic (e.g. family history of psychiatric illness; Agerbo *et al.*, 2015) factors, were unavailable for examination by the current study. Therefore, assessment of white matter pathology in younger individuals with AVH in larger samples utilizing risk assessments and longitudinal designs is warranted, in order to map symptom-linked white matter trajectories. Finally, while we observed cellular-specific deficits in AVH, we cannot disentangle the specific mechanisms accounting for changes within the tissue compartment (e.g. demyelination and axonal degeneration), or the relationship to functional or corollary discharge mechanisms. Future multimodal studies that combine advanced white matter mapping with functional parameters will help to resolve the precise pathophysiological mechanisms, the relationship to corollary discharge failures, as well as the temporal course of functional *v.* anatomical connectivity alterations invoked by AVH experiences.

Conclusions

In summary, we found evidence for overlapping white matter abnormalities across younger schizophrenia patients and healthy voice-hearers. These commonalities were characterized by cellular-specific deficits in white matter microstructure, involving callosal, frontal, and thalamo-cortical circuitry. However, the structural basis of AVH could not be straightforwardly ascribed to all AVH subjects, implying that advancing age and other illness-related contributions to brain structure possibly dilute associations with AVH. Future studies could address this complexity by longitudinally mapping the progression of white and gray matter abnormalities in individuals experiencing AVH.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the ethics committee of each participating institution and all participants provided written informed consent, consistent with the Helsinki Declaration of 1975, as revised in 2008.

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