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Auditory Verbal Hallucinations and the Interhemispheric Auditory Pathway in Chronic Schizophrenia

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Abstract

Objectives—The interhemispheric auditory pathway has been shown to play a crucial role in the processing of acoustic stimuli, and alterations of structural and functional connectivity between bilateral auditory areas are likely relevant to the pathogenesis of auditory verbal hallucinations (AVHs). The aim of this study was to examine this pathway in patients with chronic schizophrenia regarding their lifetime history of AVHs.

Methods—DTI scans were acquired from 33 healthy controls (HC), 24 schizophrenia patients with a history of AVHs (LT-AVH) and 9 schizophrenia patients without any lifetime-hallucinations (N-LT-AVH). The interhemispheric auditory fibre bundles were extracted using streamline tractography. Subsequently, diffusivity indices, namely Fractional Anisotropy (FA), Trace, Mode, Axial and Radial Diffusivity, were calculated.

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Results—FA was decreased over the entire pathway in LT-AVH compared with N-LT-AVH. Moreover, LT-AVH displayed decreased FA and Mode as well as increased Radial Diffusivity in the midsagittal section of the fibre tract.

Conclusions—These findings indicate complex microstructural changes in the interhemispheric auditory pathway of schizophrenia patients with a history of AVHs. Alterations appear to be absent in patients who have never hallucinated.

Keywords

schizophrenia; brain imaging; MRI; diffusion tensor imaging; auditory verbal hallucinations

1. Introduction

Schizophrenia affects around 1% of the general population and patients afflicted with this disorder frequently present with heterogeneous symptoms, thus making it one of the most severe mental disorders for which we have no real understanding of the underlying aetiology and pathology (Frith and Johnstone 2003). Auditory verbal hallucinations (AVHs) rank among the most prominent and characteristic symptoms in schizophrenia (Schneider 1957) and describe the sensory experience of voices being heard in the absence of an appropriate external stimulus. As an explanation it has been suggested that patients with SZ exhibit a defect in self-monitoring and thus a failure to distinguish between internally and externally generated stimuli (Frith 1995). AVHs would therefore, originate from misattributing one's own inner speech generated in the frontal cortex to an externally located source. Accordingly, increased activation in acutely hallucinating patients has been primarily observed in frontal speech production and temporal speech perception areas, including the auditory cortex (Dierks et al. 1999, Shergill et al. 2000a, Shergill et al. 2000b, van de Ven et al. 2005) with a predominance of the left hemisphere. Yet, cortical activations could also be observed in subjects' right-sided cortical homologues (Dierks et al. 1999, Shergill 2000b). The findings of atypical function in different remote brain areas in hallucinating patients indicated that AVHs may be mediated by extensive cortical and subcortical disturbances within language-processing networks, rather than by focal impairments of single brain structures. This is in accordance with present concepts of SZ as the result of disturbed functional communication between spatially discrete, and not necessarily proximal, brain regions (Friston 2002). As a consequence, recent attention has been given to changes in distinct white matter (WM) tracts in SZ after structural neuroimaging studies had initially focused on grey matter abnormalities in schizophrenia (for reviews see Fitzsimmons et al. 2013, Shenton et al. 2001). In fact, numerous Functional Magnetic Resonance Imaging (fMRI), volumetric imaging, and Positron Emission Tomography (PET) studies argue in favour of disordered cerebral connectivity in SZ (Andreasen et al. 1997, Bullmore et al. 1997, Frith and Dolan 1996, McGuire and Frith 1996, Shergill et al. 2000b, Sigmundsson et al. 2001, Spence et al. 1997), yet they do not deliver information about fibre organization and microstructural changes in WM. In order to address these questions diffusion weighted imaging (DWI) techniques have been introduced providing a unique, non-invasive tool to assess alterations of WM in the brain. First introduced by Basser et al. in 1994, Diffusion Tensor Imaging (DTI) assesses the directionality of water diffusion within the brain. Since water molecules do not diffuse freely in WM but are guided by axonal tracts, cell

membranes, organelles, protein filaments and predominantly by myelin sheaths (Peled et al. 1998) information about the microstructure of WM tracts can be gained in vivo (Cercignani & Horsfield 2001). Fractional Anisotropy (FA) represents the most commonly used parameter in DTI studies and measures the fraction of the diffusion tensor that can be ascribed to anisotropic diffusion, that is to say the degree of diffusion directionality. In the event of unrestricted isotropic diffusion FA has a value close to 0 while it approaches 1 if water molecules are strongly guided into one direction. Besides FA, some other diffusion indices have gained importance recently and may be helpful for more detailed evaluation of microstructural alterations. Measuring the total quantity of diffusion within one voxel, Trace is independent of fibre directionality and increases when the overall displacement of molecules rises. Another diffusion parameter, which has been developed lately, is represented by Mode. It provides geometric information about the shape of the diffusion tensor and approaches a value close to 1 if the diffusion tensor is shaped like a tube, i.e. when the size of the tensor's second eigenvalue is close to the third. If the size of the second eigenvalue is close to the first and the diffusion is better described by a disk, Mode will converge a value of −1 (Ennis and Kindlmann 2006, Kindlmann et al. 2007, Whitford et al. 2010).

Changes in FA can be better characterized by the assessment of Axial Diffusivity (Axial), which is defined as the principal eigenvalue, and Radial Diffusivity (Radial) reflecting the mean of the second and third eigenvalue of the diffusion tensor. Representing the major direction of the diffusion tensor, Axial has been reported to decrease when axonal injury occurs (Budde et al. 2009, Song et al. 2002). Its counterpart Radial reflects the diffusion perpendicular to the course of neural axons. Accordingly, Radial increases when the confining myelin sheaths are defective and it has been presented as a relatively reliable marker for de- and dysmyelination in animal models (Harsan et al. 2006, Song et al. 2003, Song et al. 2005, Tyszka et al. 2006).

In schizophrenia, several WM tracts have been reported to exhibit altered diffusion with decreased FA values as the most frequent finding (for review see Kubicki et al. 2007). Regarding AVHs, most studies have investigated fronto-temporal linkages between language production and perception structures such as the arcuate fasciculus.(Hubl et al. 2004, Shergill et al. 2007). While the role of the arcuate fasciculus in speech perception and production is generally well established, there is increasing evidence for a substantial participation of the Corpus Callosum (CC) in the processing of auditory information. Findings from microscopic studies of the CC suggest that commissural fibre tracts from auditory areas in the temporal lobes are contained within the isthmus and the anterior part of the splenium (Aboitiz et al. 1992b), which are part of the caudal third of the CC. These interhemispheric connections have been demonstrated to link subregions of the primary and secondary auditory cortices in a tonotopic organisation (Aboitiz et al. 1992a, Bamiou et al. 2007, Lee and Winer 2008, Pandya 1986). According to the "callosal relay" model which postulates supremacy of the left hemisphere in speech perception while auditory signals are more dominantly transmitted in the right hemisphere (Zaidel 1986), stimuli entering the right hemisphere must be transferred to the contralateral side for processing (Hugdahl et al. 1997). Focussing on this physiological interhemispheric interplay, Friederici et al. (2007) observed the absence of an event-related N400 potential during a speech comprehension

task in patients with a lesion in the posterior third of the CC. Thus, the disruption of the CC in its posterior part is assumed to interfere with an efficient integration of prosodic and syntactic information contributing to disturbed language comprehension. Combining probabilistic tractography of callosal subregions containing interhemispheric auditory fibre tracts with an auditory speech perception task, it has also been shown that higher anatomical connectivity between superior temporal lobe areas correlated with better speech perception performance in healthy subjects (Westerhausen et al. 2009). Some evidence for the functional relevance of transcallosal auditory connectivity for AVHs in schizophrenia was provided by an EEG study investigating interhemispheric phase locking between the left and right primary auditory cortex (Mulert et al. 2011). SZ patients displayed reduced phase synchronization in comparison to HC suggesting disturbed connectivity in the interhemispheric auditory pathway. Moreover, there was a positive correlation between auditory hallucination symptoms and interhemispheric auditory connectivity. An important hint towards alterations of transcallosal auditory linkages in SZ patients with AVH was presented by a DTI study (Hubl et al. 2004) detecting increased FA values in the posterior third of the CC in acutely hallucinating patients. Based on these findings Mulert and colleagues (2012) were the first to explicitly investigate and demonstrate the interhemispheric auditory pathway by the means of DTI tractography. They observed increased FA in the traced fibre bundle in first-episode patients suffering from AVHs in comparison to patients without AVHs. Both of the above studies indicated stronger transcallosal connectivity in patients with acute AVH and we were henceforward interested in evaluating whether these alterations would also be present in chronic patients who have experienced AVHs during their illness history but were not necessarily hallucinating at the time of data acquisition. Briefly, our aim was to figure out if the increased FA values in first-episode patients are still present in chronic patients who experienced AVHs in the past and we therefore applied the same approach as Mulert et al. (2012). For a more detailed understanding of microstructural alterations we calculated we calculated Trace, Mode, Axial and Radial diffusivity in addition to FA.

Moreover, we aimed to analyse diffusion parameters in the midsagittal section of the fibre tract due to two different considerations. Firstly, we were interested in regarding our findings against the background of antecedent DTI studies examining interhemispheric connectivity. Most of them reported their results with reference to the median sagittal plane (e.g. Buchsbaum et al. 2006, Hubl et al. 2004, Knochel et al. 2012). Secondly and most importantly, we were aware of the fact that crossing or adjacent fibres tracts may interfere with the reconstruction of fibre bundles. Fractional anisotropy may be incorrectly low in a voxel covering crossing pathways and fibre tracking may consequently terminate in this region. Likewise, tracking can be shifted or switch to adjacent unrelated pathways when fibre merging or branching occurs (Mori 2007). Moreover, tractography has been shown to worsen if fibres run toward the lateral or inferior side of the brain due to partial volume and noise effects (Park et al. 2008). Since the interhemispheric auditory pathway leaves the CC with analogous orientation and since it passes several crossing tracts such as the internal capsule or the inferior longitudinal fasciculus, its tracking is especially interference-prone. The aforementioned limitations have been observed in recent DTI studies of callosal fibres connecting temporal regions of the left and right hemisphere (Hofer and Frahm 2006,

Vandermosten et al. 2013) and even though the traced streamlines in our study appeared to run in an anatomically correct course, we consequently expected clearer and less compromised diffusion values in the midsagittal section of the interhemispheric auditory pathway.

2. Materials and Methods

2.1 Subjects

This study was approved by the local ethics committee of the Ludwig Maximilian University of Munich and carried out in accordance with the Declaration of Helsinki. It was part of a larger clinical, imaging and genetics study at the Department of Psychiatry, Ludwig Maximilian University of Munich and DTI scans of our sample were already used for another study published recently (Clemm von Hohenberg et al. 2013). After a detailed description of the study, written informed consent was obtained from all participants.

Patients with schizophrenia—Patients with schizophrenia were recruited as outpatients affiliated with the Department of Psychiatry, Ludwig-Maximilians-University of Munich. All patients met DSM-IV and ICD-10 criteria for schizophrenia which was confirmed by four physicians and one psychologist using the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1994, Spitzer et al. 1992, Williams et al. 1992) to evaluate lifetime Axis I and II diagnoses. Chronic schizophrenia was defined as lasting at least five years (mean 16.58 years; range 5–34) following the inclusion criteria of recent studies (Knochel et al. 2012, Liu et al. 2010). Handedness was determined by the clinical interview. All clinical data were double rated by a senior researcher who revised medical records and checked if patients' statements were reasonable. None of the patients had a history of traumatic brain injury, mental retardation or neurological impairment. Additionally, none had substance abuse in the past six months. Prior to the six months period eleven patients had used cannabis and four patients had taken cocaine (not more than five times in their lifetime) Thirty-three patients met the aforementioned requirements.

Current psychopathology was assessed using the Positive and Negative Syndrome Scale "PANSS" (Kay et al. 1987). Moreover, information on current medication was employed to compute chlorpromazine (CPZ) equivalence doses as proposed by Möller (2000).

As it was our aim to investigate structural differences between schizophrenia patients with a history of auditory verbal hallucinations and patients who had never experienced any hallucinations, we used information from clinical interviews and chart records to divide the patient group into two subgroups. Hence, the group of patients without any lifetime hallucinations (N-LT-AVH) was comprised of nine SZ patients (eight men, one woman), whereas the LT-AVH group was comprised of twenty-four SZ patients (sixteen men, eight women). The mean age was 39.67 ± 3.39 years for N-LT-AVH and 43.50 ± 8.19 years for LT-AVH.

Healthy volunteers—Healthy control participants were drawn at random from the general population of Munich, Germany, and contacted by mail. Several screenings were conducted before volunteers were admitted to this study: a clinical interview including the SCID I and

SCID II to validate the absence of any lifetime psychotic disorder, an assessment of detailed medical and neuropsychiatric histories for both themselves and their first-degree relatives, the Family History Assessment Module (Rice et al. 1995) to rule out psychotic disorders among first-degree relatives, a neurological examination to exclude individuals with current central nervous system impairment and the Mini Mental Status Test (Folstein et al. 1975) with all volunteers who were older than 60 years to exclude subjects with cognitive impairment. Subjects were excluded if they had a history of drug dependence or abuse. Handedness was determined by the clinical interview. After the inclusion of all suitable SZ patients we selected 33 healthy control subjects from our data set who showed the best possible matching in terms of age, gender, education and handedness (twenty-four men, nine women; mean age = 44.97 ± 11.39 years).

2.2 Image Acquisition

All subjects were scanned on the same 1.5 Tesla MRI Scanner (Siemens Sonata, Siemens Medical Solutions, Erlangen, Germany) using a standard circular-polarized head coil. Brain Diffusion Tensor MRI was acquired in axial orientation using a diffusion-weighted single shot spin echo planar imaging (EPI) sequence. We obtained forty-four contiguous axial slices parallel to the anterior commissure – posterior commissure line covering the whole brain in a 128×112 scan matrix with diffusion encoding in 32 directions. Scan parameters were the following: FOV = 320×280; slice thickness = 2.5 mm; TE =83 ms; TR = 6600 ms; b-values 0 and 1000s/mm^2. All scans were visually checked to rule out structural abnormalities or artefacts.

Pre-processing—After conversion and visual inspection for severe scanning and motion artefacts, the diffusion-weighted images were corrected for motion and eddy-current distortions using affine registration with the baseline volume (FLIRT; Functional MRI of the Brain [FMRIB] Sofware Library [FSL]). Diffusion gradients were compensated for rotations. The images were masked to exclude non-brain areas by manually annotating a label map that was initialized using Otsu's method and the DTI model was fitted using a linear least squares estimation as implemented in the 3D Slicer (www.slicer.org).

ROI definition—In order to extract only fibres that were part of the inter-hemispheric auditory pathway, a seeding tractography technique was applied that selects only those tracts that are included in a specific combination of regions of interest (ROIs) (Conturo et al. 1999, Mori et al. 1999). A single technician who was blind to diagnosis, age and gender drew all of these ROIs. In the first step, a midsagittal ROI was applied generously over the posterior third of the corpus callosum where auditory fibres are crossing. Subsequently, deterministic (streamline) tractography (Oh et al. 2007) was initiated from every voxel defined by this ROI following the direction of the principal eigenvector. A step size of 0.5 mm was employed with a radius of curvature > 0.87 mm. As soon as a voxel showed a lower value of fractional anisotropy than 0.15, tractography was terminated. In order to increase the number of resulting fibres, we applied Jitter ten times, which is an optional tool of the Slicer software package. Whereas tracts are seeded on a regular grid throughout the volume without this option, Jitter allows tractography from different, randomly chosen, seeding points providing higher quantities of resulting fibre tracts. The seed points are no longer

strictly defined by a spacing parameter on the stationary grid but moved haphazardly to half the distance of the original spacing distance. In a following step, a second ROI was drawn on a coronal slice bilaterally at the level of the splenium in order to select only fibres that were connecting the auditory areas of both hemispheres. If fibres failed to pass through this ROI they were excluded from further analysis. Fig. 1 shows the resulting auditory fibre tract passing through the CC from one representative subject as well as the different ROIs.

If a fibre that was clearly anatomically incorrect happened to remain in the resulting bundle (e.g. fibres of the corticospinal tract) the fibre was removed from the bundle using the "delete manually" function.

DTI measurements—Fractional anisotropy (FA) was calculated for every voxel through which any of the obtained fibres passed. Mean FA was calculated for every subject by averaging FA of these voxels (Basser and Pierpaoli 1996) whereupon the resulting value was applied in the statistical analysis. Moreover, Trace was calculated by summing the three eigenvalues in every voxel, thus measures the magnitude of the diffusion tensor. Additionally, we computed Mode at every voxel.

Since different combinations of eigenvalues can produce the same FA values, FA is not sufficient to fully describe the shape or distribution of diffusion in the brain (Alexander et al. 2000, Alexander et al. 2007). Hence, two different indexes have been introduced to help discern further information about the microstructural processes: Axial and Radial Diffusivity. Axial Diffusivity describes the diffusivity along the principal axis and is simply generated by measuring the first eigenvalue, λ_1. This index has been shown to decrease in cases of axonal degeneration, whereas Radial Diffusivity increases when pathologies of myelination occur (Seal et al. 2008, Song et al. 2003, Song et al. 2002).

Trace, Mode, Axial and Radial Diffusivity were only calculated in case of a significant change in FA. To ensure intra-rater reliability, five randomly chosen scans were duplicated and reprocessed by the first rater 6 months after the first rating. Mean FA was calculated and applied for computing the intra-class correlation coefficients revealing excellent reliability (intra-class correlation coefficient = .994). Inter-rater reliability was estimated by duplicating five randomly chosen brain volumes, which were then edited by two different independent raters 4 months after the first rating. Again, high reliability was detected (intra-class correlation coefficient = .907).

We were specifically interested in examining the central callosal part of the interhemispheric auditory fibres without possible interference of diffusion in the peripheral sections. Therefore we used the tracts generated in the antecedent step to create a midsagittal label mask. This label mask was only defined by those voxels through which any of the produced auditory fibres passed. Again, FA was computed for every voxel and mean FA was calculated for each participant. All further analyses were repeated for the midsagittal section of the interhemispheric auditory pathway as described above in order to affirm possible findings and to further understand changes in the auditory pathway.

2.3 Statistical Analysis

All analyses were performed in SPSS version 19 (www.spss.com) with a personal computer. The significance level was placed at α = 0.05 for statistical significant results and at α = 0.10 for trend-wise effects in all analyses. Demographic variables were assessed using ANOVA and independent t-tests for the comparison of continuous variables (*age, duration of illness, CPZ equivalent*) and non-parametric procedures (Kruskal-Wallis- and Mann-Whitney-U-tests) for variables with ordinal scale (*education, PANSS scores*). For the comparison of categorical variables chi-square tests (*gender*) or Fisher's exact test (*handedness*; more than 20% of expected frequencies were less than 5) were applied.

All DTI parameters were checked for assumptions of normal distribution and equality of variances. If these assumptions were violated, non-parametric Kruskal-Wallis and Mann-Whitney U tests were applied.

An analysis of variance was computed with diffusion values as dependent variables and group as a fixed factor (patients with a history of AVHs, patients without a history of AVHs, healthy controls). If (and only if) the ANOVA revealed a significant or trend-wise group difference, post-hoc pairwise comparisons (Fisher's Least Significant Difference tests; Fisher's LSD) were carried out within the ANOVA design. Group differences were also assessed for the number of traced fibres (streamlines).

Given the unequal group sizes and the small group size of N-LT-AVH in particular, we were apprehensive of the risk to erroneously believe that assumptions for parametric tests were not being violated. Therefore, we re-ran statistical analyses with non-parametric tests as well.

In order to control for other possibly influential variables, separate analyses of covariance (ANCOVAs) were conducted post-hoc for the following covariates: age, gender, education (to assess differences between all groups), duration of illness, CPZ equivalents and PANSS scores (to assess group differences between N-LT-AVH and LT-AVH).

We computed Pearson correlations to assess the relationship between DTI measurements and age or duration of illness, respectively, as well as Spearman Rank correlations to detect potential associations between the PANSS hallucination items and DTI values. In order to control for multiple comparisons false discovery rate (FDR) corrections were applied (Benjamini and Hochberg 1995).

3. Results

The demographic and clinical characteristics of the investigated samples are presented in table 1. There were no significant differences between the three groups in terms of age, gender or level of education. Table 2 displays means and standard deviations of diffusion indices as well as the results of the ANOVA and Kruskal-Wallis tests.

Interhemispheric auditory fibre bundle—The ANOVA revealed a trend-wise group difference [$F(2,63) = 2.610$, $p = .081$] for FA. Post-hoc tests revealed significantly

diminished FA values in LT-AVH compared to N-LT-AVH [mean FA = .463 ± .027 vs. .490 ± .024; p = .026, d = 1.06]. The trend-wise overall group effect and the significant group difference between N(LT)AVH and (LT)AVH were confirmed when controlling for age, duration of illness, CPZ equivalents and PANSS scores in separate ANCOVAs. When controlling for education and gender the group effect narrowly missed the trend-level. None of the covariates was significantly related to FA.

No significant group differences were found in the comparison of HC to all SZ patients.

No significant associations were detected between diffusion values and age, duration of illness, psychopathological measures or chlorpromazine equivalents.

Midsagittal voxels of the interhemispheric auditory fibre bundle—When focusing only on the midsagittal voxels of the CC through which the auditory fibre bundles passed, the ANOVA revealed a significant group difference for FA [$F(2,63)$ = 4.237; p = .019] and Radial [$F(2,63)$ = 3.245; p = .046]. Since the assumption of normal distribution was violated for Mode, we used the non-parametric Kruskal-Wallis test to assess group effects and detected a significant group difference for Mode [$H(2)$ = 12.600; p = .002]. Group differences for FA and Radial were confirmed by Kruskal-Wallis tests as well.

Subsequent post-hoc analyses revealed significantly lower FA values in LT-AVH compared to N-LT-AVH [mean FA = .571 ± .080 vs. .641 ± .070; p = .013, d = .93]. FA was also significantly decreased in LT-AVH when compared with HC [mean FA = .613 ± .060; p = .026, d = .60] (Fig. 2).

Concerning Mode, LT-AVH had significantly lower values in comparison to N-LT-AVH [mean Mode = 0.806 ± 0.091 vs. 0.893 ± 0.045; U = 47.0, p = .014, d = 1.21] and to HC [mean Mode = 0.885 ± 0.062; U = 191.0, p = .001, d = 1.01] as assessed by the non-parametric Mann-Whitney U tests (Fig. 3).

In contrast, Radial diffusivity was considerably increased in LT-AVH compared to HC [mean Radial = .659 ± .142 vs. .575 ± .126; p = .023, d = .63] and marginally increased (statistical trend) when compared to N-LT-AVH [mean Radial = .560 ± .150; p = .066, d = .68] (Fig. 4).

All observed group differences for FA and Mode were again detected in post-hoc ANCOVAs when controlling for age, gender, education, duration of illness, CPZ equivalents and PANSS scores, while none of the covariates was significantly related to diffusion measurements. Group differences for Radial were confirmed equally except when including education as a covariate.

No significant group differences were found in the comparison of HC to all SZ patients except for Mode [mean Mode = .885 ± .062 vs. .830 ± .090; U = 344.0, p = .010, d = .71]. The difference between HC and SZ patients showed a medium size effect (Cohen's d = .71), while the differences between HC and LT-AVH (Cohen's d = 1.01) and between N-LT-AVH and LT-AVH (Cohen's d = 1.21) both had a large size effect.

After controlling for multiple comparisons none of the groups revealed a significant correlation between any of the diffusion indexes and age, duration of illness, CPZ equivalents or psychopathological measures of the PANSS score.

4. Discussion

The aim of this study was to investigate the relationship between microstructural processes in the interhemispheric auditory pathway and the occurrence of auditory hallucinations in chronic schizophrenia patients. It relates to a previous report of increased FA values in this fibre bundle in first-episode patients with AVH (Mulert et al. 2012). DTI scans were acquired and the transcallosal auditory fibre bundles were subsequently quantified by applying regions of interest and streamline tractography. We found decreased FA in patients with lifetime-AVHs, while patients without a history of AVHs revealed values similar to healthy control subjects. Moreover, hallucinating patients revealed decreased FA and Mode as well as increased Radial Diffusivity in the midsagittal section of the auditory callosal pathway.

Our findings of decreased anisotropy might seem conflicting in the context of the previous report of increased FA (Mulert et al. 2012) in the same anatomical region in hallucinating patients. Nevertheless, there is a major difference between patients in the two studies. While our previous study focussed on first-episode schizophrenia, patients in the present study had suffered from schizophrenia for a considerably longer time period (mean duration of illness = 16.58 years). Our current sample of participants was thus also considerably older than patients in the previous study (mean age of SZ = 42.45 vs. 26.9 years) as well as at a different stage of illness. Interestingly, most of the studies examining diffusion alterations in the CC report a decrease of FA in SZ patients who were much older than in Mulert's study and had been suffering from SZ for a considerably longer period of time (Agartz et al. 2001, Foong et al. 2000, Knochel et al. 2012, Rotarska-Jagiela et al. 2008, Whitford et al. 2010).

While the interhemispheric pathway connecting temporal brain areas has already been investigated in regard to language perception, integration and phonological awareness (Dougherty et al. 2007, Friederici et al. 2007, Westerhausen et al. 2009), our findings suggest an association of microstructural changes in this fibre bundle with the occurrence of AVH. Identifying an association does not automatically constitute a causal relationship and due to the design of this study with only one fibre tract being analysed we are not in the position to deduce conclusions about the specificity of our findings. Nevertheless, the fact that N-LT-AVH revealed similar diffusion values to HC and that patients with lifetime AVH showed significant differences is well in line with previous studies (for review see Steinmann et al. 2014). While the two preceding DTI studies (Hubl et al. 2004, Mulert et al. 2012) argued in favour of increased connectivity in hallucinating patients, evidence for decreased interhemispheric linkage derives from a study by Gavrilescu et al. (2010). Using fMRI authors observed significantly reduced interhemispheric connectivity between auditory cortices in patients with AVH when compared to patients without AVH and HC. Employing auditory assessments, McKay and colleagues (2000) observed significantly poorer results in hallucinating patients when compared to non-hallucinating patients and HC both in a speech perception and a dichotic speech test. Authors concluded consequently that

hallucinations may be associated with disruptions in the right auditory brain areas and/or dysfunction in interhemispheric connectivity. Similar conclusions were drawn in a recent EEG time revealing significantly increased interhemispheric transfer time values in patients with a history of AVH when single-syllable words were presented monaurally to each ear (Henshall et al. 2012). HC showed values close to zero and patients who had never experienced any hallucinations exhibited negative values. The prolonged interhemispheric transfer time in patients who had hallucinated in the past in comparison to patients without a history of AVH and HC may be attributed to abnormal cerebral lateralization in patients without a history of AVH or to dysfunctional transcallosal communication. The latter explanation is in well accordance with our finding of decreased interhemispheric connectivity in patients with a history of AVH.

Similar to Hubl's (2004) and Mulert's study (2012) there was no difference in FA between HC and patients with SZ when considered as one single group. The only diffusion parameter that revealed a group difference between HC and SZ patients was Mode with its values being significantly lower in SZ patients. When comparing effect sizes, the group difference between HC and SZ patients showed a medium size effect, while group differences both between (LT)AVH and HC and between (LT)AVH and N(LT)AVH had a large size effect, and we therefore assume that these group differences outweigh the group effect between HC and SZ patients. Consequently, altered transcallosal connectivity appears to be considerably associated with patients' proneness to AVHs. Explanations for increased FA values in first-episode patients with current AVH and decreased FA values in chronic patients with a history of AVH remain speculative, albeit WM changes in SZ appear to progress with time (Friedman et al. 2008, Mori et al. 2007, Rotarska-Jagiela et al. 2009).

Previous studies investigating the isthmus and splenium of the CC reported FA alterations in SZ (Agartz et al. 2001, Ardekani et al. 2003, Foong et al. 2000, Friedman et al. 2008, Knochel et al. 2012, Rotarska-Jagiela et al. 2008). In the present study, a more comprehensive examination of further diffusion parameters was performed investigating Trace, Mode, Axial and Radial Diffusivity, allowing for more precise conclusions about the microstructural sources of WM disruptions. Interestingly, decreased FA values in patients with lifetime-hallucinations were accompanied by increased Radial measures, while Axial Diffusivity was not different between groups. The combination of decreased FA, increased Radial and unchanged Axial Diffusivity has been observed in many DTI studies (Abdul-Rahman et al. 2011, Seal et al. 2008, Whitford et al. 2010). FA reductions occur generally in response to myelin disruption, axonal loss, decreased fibre diameter or reduced fibre coherence (Beaulieu 2002, Cercignani and Horsfield 2001). In order to distinguish between these pathomechanisms, Radial Diffusivity has been introduced as a putative measure of myelination while Axial Diffusivity enables conclusions to be drawn about changes of the axonal membrane (Song et al. 2003, Song et al. 2002). Bearing in mind that diminished anisotropy in the context of increased Radial has been proposed to concur with demyelination and has been observed in SZ (Harsan et al. 2006, Levitt et al. 2012, Naismith et al. 2010, Song et al. 2005, Whitford et al. 2010), our findings may indicate myelin abnormalities in the interhemispheric auditory pathway of SZ patients with lifetime-hallucinations. The proposed hypothesis of demyelination in SZ (Davis et al. 2003) has been supported by findings of abnormal or reduced oligodendrocytes in SZ (Flynn et al. 2003,

Hof et al. 2002, Hof et al. 2003, Uranova et al. 2007, Vostrikov et al. 2007), which represent that exact type of neuroglia responsible for creating the myelin sheath. Several studies also reported striking similarities between the disease patterns of schizophrenia and symptoms of demyelinating diseases such as metachromatic leukodystrophy (Black et al. 2003, Finelli 1985, Hyde et al. 1992). Furthermore, gene expression analyses suggest an associated down-regulation of oligodendroglial myelin-related genes in SZ (Aston et al. 2004, Hakak et al. 2001, Haroutunian et al. 2007, McCullumsmith et al. 2007, Prabakaran et al. 2004, Roussos and Haroutunian 2014, Tkachev et al. 2003).

Additionally, our finding of decreased Mode in patients with lifetime-hallucinations describes a rather oblate-shaped diffusion, i.e. the size of the second eigenvalue is close to the first. Mode is independent of differences in FA has been found to decrease in the presence of fibre crossings (Douaud et al. 2007, Kindlmann et al. 2007). Its decline in the midsagittal section of the auditory pathway might be again explained by a potential loss of overall directionality in the investigated fibre tract. Since the major influence of callosal fibre bundles on the diffusion tensor might shrink in the course of neurodegenerative processes, diffusion in adjacent fibre tracts might interfere to a greater extent than usual, thus leading to the impression that the density of fibre crossings has risen. Although the midsagittal callosal slice represents an area where fibre crossings should at least in theory be absent, marginal voxels may cover adjacent WM tracts with orthogonal direction (e.g. the cingulum) whose directionality has stronger effects on the tensor when interhemispheric diffusion is hindered. Another possible explanation is that increased Radial and thus a greater second and third eigenvalue lead to a decrease of Mode. To test this consideration, we ran a post-hoc correlation analysis between Mode and Radial in all subjects and found indeed a highly significant negative association (Spearman's rho = −.537, $p < .001$).

In a synoptic view of our study and preceding findings concerning interhemispheric auditory connectivity in SZ, we suggest that AVHs in schizophrenia are associated with microstructural alterations in the interhemispheric auditory pathway. These changes are still observable in chronic patients who are not necessarily hallucinating at the time of data acquisition. Alterations were found especially in the midsagittal section of the fibre bundle in patients that had experienced AVH in their lifetime when compared to N-LT-AVH and HC. Our findings of reduced FA and increased Radial indicate that abnormal transcallosal auditory connectivity in LT-AVH point to potential impairments in myelin sheaths.

Due to the cross-sectional design of our study we are not able to conclusively clarify the question whether structural differences between groups lead to patients' propensity for hallucinations or if their psychopathology may in turn cause alterations in brain connectivity within the context of neural plasticity. Dynamic modifications in cerebral connections take place throughout adulthood in response to varied afferent input (Pascual-Leone et al. 2005) and as well as structural alterations may contribute to patients' symptomatology it is also imaginable that the experience of symptoms may shape their cerebral microstructure. This question cannot be answered with our data, therefore, longitudinal studies including individuals at high risk for SZ are required in order to satisfactorily address this issue.

A limitation of the present study is the small group size of patients without lifetime hallucinations. We addressed this deficiency via the application of non-parametric analyses confirming our findings; nevertheless, replication with increased and more homogeneous group sizes would be desirable. Furthermore, the two patient groups differed in the negative and total PANSS scores, which might have a relevant effect on our results. Post-hoc analyses of covariance with PANSS scores as additional covariates confirmed group differences for diffusion parameters while PANSS scores had no significant effect on any of the measurements but the possibility of an influential effect cannot be entirely excluded.

After antipsychotic treatment has been shown to be associated with brain volume reductions (Bartzokis et al. 2009, Christensen et al. 2004, Konopaske et al. 2008, Lieberman et al. 2005, Wang et al. 2004) its influence on structural connectivity has been subject of a recent DTI study reporting FA reductions after 12 weeks of medication (Szeszko et al. 2014). However, authors could not exclude the possibility of disease progression that may account for their findings as well. While a long-term effect of psychotropic drugs on cerebral structures in our patient sample is quite imaginable their current medication does not seem to determine the group difference between N-LT-AVH and LT-AVH. The two groups did not differ significantly with regard to CPZ equivalents and the group difference remained significant when medication was included as a covariate. Moreover, FA changes have also been shown in unmedicated patients (Buchsbaum et al. 1998, Cheung et al. 2011, Gasparotti et al. 2009, Liu et al. 2013). Nevertheless, we are not able to fully distinguish the potential confounding influences of antipsychotic treatment on the observed group differences. The same applies to the lifetime history of substance abuse in SZ patients. While none of the participants took psychoactive substances during the past six months before data acquisition and none had a lifetime dependency, four N-LT-AVH and seven LT-AVH patients had taken substances in their past history. Longitudinal studies would be helpful to clarify these issues.

5. Conclusion

In summary, the present DTI study investigated WM alterations within the interhemispheric auditory pathway in chronic Schizophrenia patients and healthy controls, and detected a decrease of FA in patients with a history of AVHs. These findings were accompanied by increased Radial Diffusivity as well as decreased Mode, while patients without a history of hallucinations showed similar values to healthy control subjects. These results indicate that the interhemispheric auditory pathway may represent a WM structure participating in the pathogenesis of AVHs and that microstructural processes in LT-AVH, namely demyelination, may be responsible for the observed group differences.

Acknowledgments

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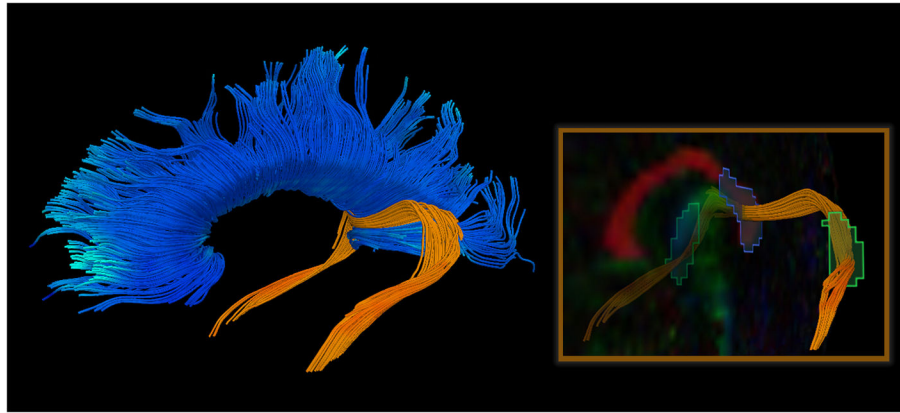
Figure 1. The interhemispheric auditory pathway
The orange fibres illustrate the interhemispheric auditory pathway while the blue fibres result from tractography of the entire CC. The midsagittal ROI (in blue) and coronal ROIs (in green) are depicted within the orange box.
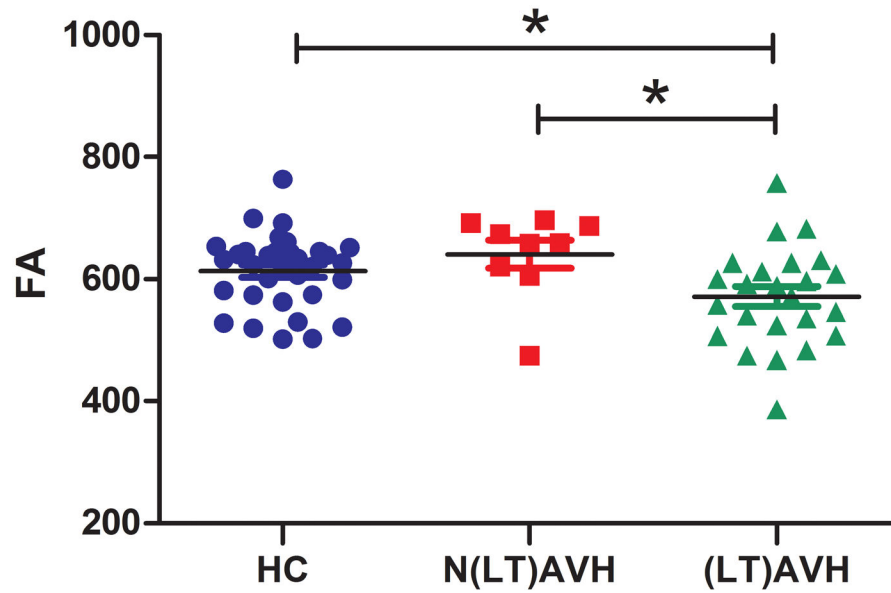
Figure 2. FA (midsagittal)

Scatterplot illustrating the variations in FA between groups for the midsagittal slice of the interhemispheric auditory pathway. Significant difference between all groups (ANOVA; p = .019) and significantly diminished FA values in (LT)AVH compared to N(LT)AVH (t-test; p = .029) and to HC (t-test; p = .027).

HC: healthy control subjects; N(LT)AVH: schizophrenic patients without lifetime-hallucinations; (LT)AVH: schizophrenic patients with lifetime-hallucinations; FA: fractional anisotropy.

The black bars represent FA means and the asterisks represent significant between-group differences.
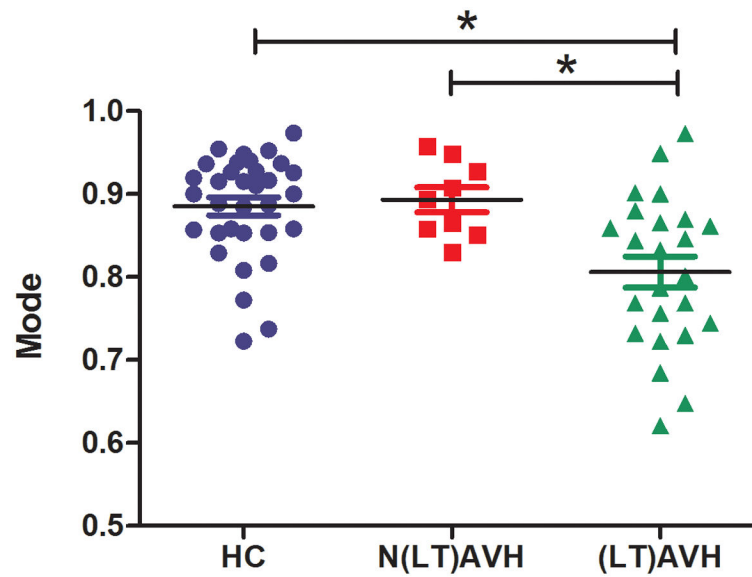
Figure 3. Mode (midsagittal)
Scatterplot illustrating the variations in Mode between groups for the midsagittal slice of the interhemispheric auditory pathway. Significantly diminished Mode values in (LT)AVH compared to N(LT)AVH (t-test; $p = .029$) and to HC (t-test; $p = .001$).
HC: healthy control subjects; N(LT)AVH: schizophrenic patients without lifetime-hallucinations; (LT)AVH: schizophrenic patients with lifetime-hallucinations.
The black bars represent Mode means and the asterisk represents the significant between-group difference.
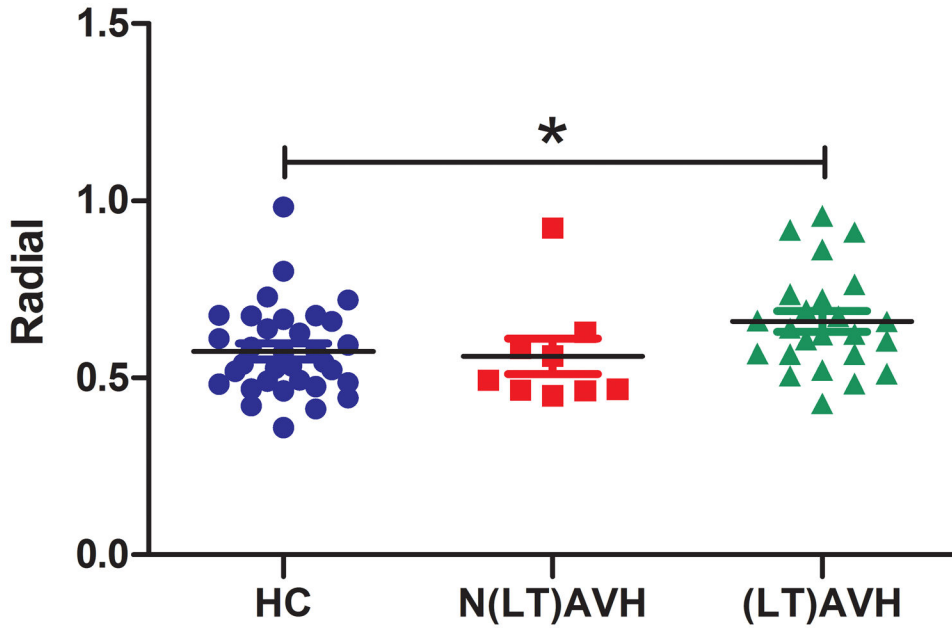
Figure 4. Radial Diffusivity (midsagittal)

Scatterplot illustrating the variations in Radial Diffusivity between groups for the midsagittal slice of the interhemispheric auditory pathway. Significantly increased Radial Diffusivity values in (LT)AVH compared to HC (t-test; p = .021) and marginally increased values in (LT)AVH compared to N(LT)AVH (t-test; p = .089).

HC: healthy control subjects; N(LT)AVH: schizophrenic patients without lifetime-hallucinations; (LT)AVH: schizophrenic patients with lifetime-hallucinations.

The black bars represent Radial means and the asterisk represents the significant between-group difference.

Table 1

Demographic and clinical details of the participants in this study

		Healthy control participants (n = 33)	Schizophrenia patients without lifetime hallucinations (n = 9)	Schizophrenia patients with lifetime hallucinations (n = 24)	Test statistic	p-value
Age (years)	mean (± SD)	44.97 (± 11.389)	39.67 (± 3.391)	43.50 (± 8.193)	$F_{(2,63)} = 1.092$	.342
Gender	n of M/F (percentage)	24/9 (72.7%/27.3%)	8/1 (88.9%/11.1%)	16/8 (66.7%/33.3%)	$X^2(2) = 1.630$	.443
Duration of illness (years)	mean (± SD)	-	15.78 (± 4.658)	16.88 (± 8.274)	$t(31) = -.374$	.711
number of hospitalizations	mean (± SD)	-	5.11 (± 4.457)	5.67 (± 4.498)	$t(31) = -.317$	.754
Education	median (range)	10 (4 – 14)	11 (6 – 14)	8 (2 – 14)	$H(2) = 2.916$	.233
Handedness	n of right/left/either	30/2/1	8/1/-	22/1/1	Fisher's exact test	.861
Medication type	n	-	one without medication, seven atypical, one typical	seventeen atypical, two typical, five both		
Medication dose (CPZ equivalents in mg/day)	mean (± SD)	-	147.778 (± 155.063)	144.167(± 204.321)	$t(31) = .048$	.962
DSM-IV subtype						
- paranoid (n)	n		5	19		
- disorganized (n)	n		3	4		
- catatonic (n)	n		1	1		
PANSS total score	median (range)		36 (30 – 44)	44 (30 – 85)	$U = 58.0$	.042
PANSS negative symptoms score	median (range)		7 (7 – 14)	13 (7 – 23)	$U = 58.0$	.038
PANSS positive symptoms score	median (range)		7 (7 – 11)	9 (7 – 25)	$U = 68.5$	.098

S.D., standard deviation; M, male; F, female; CPZ, chlorpromazine; PANSS, Positive and Negative Symptoms Score; education level ranging from 1 = no education to 14 = highest level of education according to the German education system (1 = no school education, 2 = special school without graduation, 3 = special school with graduation, 4 = secondary modern school without graduation, 5 = secondary modern school with graduation, 6 = secondary modern school with qualified degree, 7 = middle school without graduation, 8 = middle school with secondary school leaving certificate, 9 = gymnasium without graduation, 10 = gymnasium with graduation, 11 = university of applied sciences without graduation, 12 = university of applied sciences with graduation, 13 = university without academic degree, 14 = university with academic degree); KW, Kruskal Wallis test; MWU, Mann-Whitney-U test.

Demographic variables were assessed using ANOVA, independent t-tests, chi-square test, Kruskal-Wallis- or Mann-Whitney-U tests as appropriate.

Table 2

Diffusion measurements (mean ± S.D.; standard deviation) in the three different subgroups and results of the ANOVA and Kruskal Wallis analyses.

	HC (n = 33)	N-LT-AVH (n = 9)	LT-AVH (n = 24)	ANOVA	Kruskal Wallis
Interhemispheric Auditory Pathway					
FA	.472 (±.034)	.490 (±.024)	.463 (±.027)	$F_{(2,63)} = 2.610, p = .081$	$H_{(2)} = 4.588, p = .101$
Trace	3.005 (±.312)	2.958 (±.186)	3.040 (±.253)	$F_{(2,63)} = .303, p = .739$	$H_{(2)} = .811, p = .667$
Mode	.678 (±.065)	.708 (±.056)	.684 (±.053)	$F_{(2,63)} = .865, p = .426$	$H_{(2)} = 1.614, p = .446$
Axial	1.559 (±.124)	1.565 (±.072)	1.567 (±.115)	$F_{(2,63)} = .039, p = .962$	$H_{(2)} = .236, p = .888$
Radial	.723 (±.097)	.697 (±.060)	.737 (±.074)	$F_{(2,63)} = .724, p = .489$	$H_{(2)} = 1.908, p = .385$
number of fibers	101.15 (± 58.879)	105.11 (± 69.872)	113.08 (± 70.506)	$F_{(2,63)} = 1.020, p = .366$	$H_{(2)} = .453, p = .797$
Midsagittal section of the Interhemispheric Auditory Pathway					
FA	.613 (±.060)	.641 (±.070)	.571 (±.080)	$F_{(2,63)} = 4.237, p = .019*$	$H_{(2)} = 9.448, p = .009*$
Trace	2.802 (±.379)	2.826 (±.446)	3.018 (±.372)	$F_{(2,63)} = 2.294, p = .109$	$H_{(2)} = 4.838, p = .089$
Mode	.885 (±.062)	.893 (±.045)	.806 (±.091)	$F_{(2,63)} = 9.602, p < .001*$	$H_{(2)} = 12.600, p = .002*$
Axial	1.659 (±.152)	1.713 (±.180)	1.705 (±.164)	$F_{(2,63)} = .749, p = .477$	$H_{(2)} = 1.901, p = .387$
Radial	.575 (±.126)	.560 (±.150)	.659 (±.142)	$F_{(2,63)} = 3.245, p = .046*$	$H_{(2)} = 6.961, p = .031*$

HC, healthy control subjects; N-LT-AVH, schizophrenia patients without a history of auditory verbal hallucinations; LT-AVH, schizophrenia patients with a history of auditory verbal hallucinations.