Psychiatry Research: Neuroimaging 302 (2020) 111088

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Hallucinating schizophrenia patients have longer left arcuate fasciculus fiber tracks: a DTI tractography study

Liv E. Falkenberg[a], René Westerhausen[b], Erik Johnsen[c,d], Rune Kroken[c], Else-Marie Løberg[c,e,f], Justyna Beresniewicz[g], Katarzyna Kazimierczak[g], Kristiina Kompus[g], Lars Ersland[g,h], Lydia Brunvoll Sandøy[g], Kenneth Hugdahl[c,g,i,*]

[a] Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Trondheim, Norway
[b] Department of Psychology, University of Oslo, Norway
[c] Division of Psychiatry and NORMENT Center of Excellence, Haukeland University Hospital, Bergen, Norway
[d] Department of Clinical Medicine, University of Bergen, Norway
[e] Department of Addiction Medicine, Haukeland University Hospital, Bergen, Norway
[f] Department of Clinical Psychology, University of Bergen, Norway
[g] Department of Biological and Medical Psychology, University of Bergen, Norway
[h] Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway
[i] Department of Radiology, Haukeland University Hospital, Bergen, Norway

ARTICLE INFO

Keywords:
MR
Auditory hallucinations
Diffusion tensor imaging
White matter
Neural tracts
Psychosis

ABSTRACT

The arcuate fasciculus (AF) has been implicated in the pathology behind schizophrenia and auditory verbal hallucinations (AVHs). White matter tracts forming the arcuate fasciculus can be quantified and visualized using diffusion tensor imaging (DTI) tractography. Although there have been a number of studies on this topic, the results have been conflicting. Studying the underlying white matter structure of the AF could shed light on the constrains for interaction between temporal and frontal language areas in AVHs. The participants were 66 patients with a schizophrenia diagnosis, where AVHs were defined from the Positive and Negative Syndrome Scale (PANSS), and compared with a healthy control group. DTI was performed on a 3T MR scanner, and tensor estimation was done using deterministic streamline tractography. Statistical analysis of the data showed significantly longer reconstructed tracks along the AF in patients with severe and frequent AVHs, as well as an overall significant asymmetry with longer tracks in the left compared to the right side. In addition, there were significant positive correlations between PANSS scores and track length, track volume, and number of track streamlines for the posterior AF segment on the left side. It is concluded that the present DTI results may have implications for interpretations of functional imaging results.

1. Introduction

One of the most salient symptom in schizophrenia and psychosis spectrum disorders is auditory verbal hallucinations (AVHs) (Ford et al., 2014; Parnas, 2013; Sartorius et al., 1986). AVHs are typically defined as the experience of hearing a "voice" in the absence of a corresponding external auditory source to explain the experience (Aleman and Larøi, 2008; Hugdahl, 2017; Pienkos et al., 2019; Waters et al., 2006 for a conceptual review). Looking for neuronal correlates of AVHs, several meta-analyses have implicated the language regions in the temporal and frontal lobes, particularly in the left hemisphere (Ćurčić-Blake et al., 2017; Jardri et al., 2011; Kompus et al., 2011; Kühn and Gallinat, 2012; Sommer et al., 2012). Functional connectivity studies, using various statistical approaches such as seed-voxel correlations and independent component analysis (ICA), have added to earlier imaging studies by showing altered connectivity between auditory and language regions (see Alderson-Day et al., 2015 for a review). The existing literature is however inconclusive when it comes to the direction of the alterations in AVH patients, with some studies showing an increase in specific and global connectivity (e.g. Chang et al., 2017; Diederen et al., 2013; van Lutterveld et al., 2014; Zhuo et al., 2020), while other studies have shown a decrease in connectivity (Clos et al., 2014; Sommer et al., 2012). Whether AVH causes increased or decreased functional grey matter connectivity is therefore an unresolved issue (see Alderson-Day et al., 2015; Scheinost et al., 2019).

* Corresponding author.
E-mail address: hugdahl@uib.no (K. Hugdahl).

https://doi.org/10.1016/j.pscychresns.2020.111088
Received 26 September 2019; Received in revised form 15 April 2020; Accepted 15 April 2020
Available online 22 May 2020

Functional magnetic resonance imaging (fMRI) connectivity is based on the statistical covariation of the blood-oxygenation-level-dependent (BOLD) signal between nodes or areas (disregarding the special case of effective connectivity) without any reference to the underlying neuroanatomy, or whether an increase or decrease in functional connectivity has a correspondence in structural, white matter, connectivity. Hugdahl (2017) labelled this lack of "convergence of evidence", by which was meant that for a finding at one level of explanation to be valid, there should be converging evidence obtained from a lower, or different, level of explanation (see also Hugdahl and Sommer, 2018). A converging approach would therefore be to look for white matter connectivity between brain anatomical regions implicated in functional connectivity studies. Two brain regions that are often implicated in functional neuroimaging studies of AVHs are the superior temporal gyrus, including the transverse, Heschl's, gyrus and the planum temporale on the one hand, and the inferior frontal, triangular, gyrus, on the other hand (Jardri et al., 2011; Kompus et al., 2011; Sommer et al., 2010). Functionally, these regions constitute the classic Wernicke and Broca regions for language perception and production, respectively, and these regions have over the years been associated with AVHs (Alderson-Day et al., 2015; Ćurčić-Blake et al., 2017; Hubl et al., 2007; Looijestijn et al., 2013; Woodruff et al., 1997 for reviews). The arcuate fasciculus (AF) (see Fig. 1) is a massive fiber bundle which runs longitudinally along the lateral anterior-posterior axis, connecting the Wernicke, speech perception area in the superior temporal gyrus with the Broca speech production area in the inferior frontal gyrus on the left side, with a corresponding extension on the lateral side of the right side. The AF consists of both short and long tracts, the short tracts connecting areas within a region, while the long tracts connect between regions (Catani et al., 2011; Catani and Thiebaut de Schotten, 2008).

The AF is suggested to be important for language processing, connecting temporal auditory areas with inferior frontal/precentral and inferior parietal regions. Using diffusion tensor imaging (DTI), Fernández-Miranda et al. (2015) found a clear asymmetry across the hemispheres for the AF with the left AF fiber track volume significantly larger than the homologous right volume (see also Ocklenburg et al., 2013 for similar findings).

The AF has also been implicated in the pathology behind schizophrenia and AVHs, most commonly by findings of disruptions of white matter integrity. In a meta-analysis, Geoffroy et al. (2014) found reduced fractional anisotropy (FA) values, quantified from diffusion tensor imaging (DTI) data, in schizophrenia patients with frequent AVHs, reflecting abnormality of white matter organization along the AF extension. Although only five studies were included in the meta-analysis, the results nevertheless pointed to the importance of relating findings of functional connectivity between temporal and frontal language areas to the underlying white matter structure. Previous studies have also found an increase in white matter volume in the regions connected by the AF (Mitelman et al., 2007), and that greater overall white matter volume predict higher positive symptom scores, including hallucination scores (Cahn et al., 2006).

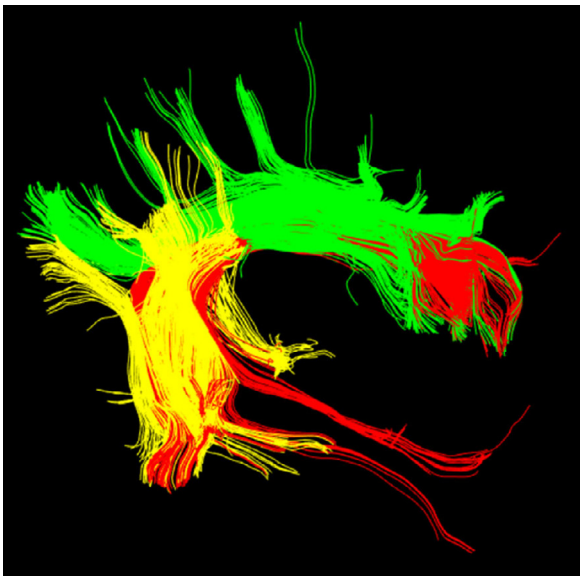

Fig. 1. The three segments of the arcuate fasciculus (AF): Anterior (green), long (red), and posterior (yellow). Adapted after Catani et al. (2011).

In the present study we sought to expand previous findings of altered structural connectivity in patients with severe and frequent AVHs (Alderson-Day et al., 2015; Scheinost et al., 2019 for overviews), by acquiring data from diffusion tractography to converge evidence from functional to structural levels of explanation (cf. Hugdahl and Sommer, 2018). We used the sub-division of AF tracts and the nomenclature from Catani et al. (2011), and divided the AF into its anterior, long and posterior segments (see Fig. 1 for illustration), and analyzed each segment for number of fibre tracks (TrackN), track length (TrackL), and track volume (TrackV) resulting from the diffusion fibre tracking. We compared these AF measures in the right and left hemisphere, as well as for schizophrenia patients with and without auditory hallucinations (as defined operationally from the Positive and Negative Syndrome Scale, (PANSS), interview questionnaire, Kay et al., 1987). We hypothesized that if an increase or decrease in AF tract connectivity, either increasing or decreasing length, volume or number of tracks. Second, we hypothesized that any effects would be more pronounced on the left side, considering previous studies of language asymmetry being constrained to the left hemisphere. The tractography measures were complemented with measure of fractional anisotropy (FA).

2. Methods

2.1. Subjects

The subjects were 66 patients with a diagnosis of schizophrenia spectrum disorder (SZ), according to the DSM-IV (American Psychiatric Association, 2000) diagnostic manual system and converted to the the ICD-10 (World Health Organization, 2016) system, 40 males and 26 females, with average age for the whole group 27.02 years (SD 9.18), and mean duration of illness of 4.32 (SD 5.01) years. For simplicity we will refer to this as "schizophrenia" patients. The patients were prescribed second-generation antipsychotics (olanzapine, clozapine, aripiprazole, quetiapine, paliperidone, or amisulpride). Sometimes patients were shifted from the start-up drug to another drug in the course of treatment for clinical reasons. Mean Definition of Daily Doses (DDD) was 1.062, SD 0.898, DDD values were missing from 17 patients. The patients were compared with a healthy control (HC) group consisting of 76 subjects, 47 males and 29 females, with an average age of 28.69 (SD 7.44) years (for some of the analyses the control group was reduced to 68 and the patient group to 63 subjects due to missing data). There were 54 right-handers in the SZ group, and 67 right-handers in the HC group. The SZ group was further divided into sub-groups depending on severity and frequency of auditory hallucinations as defined from the "hallucinatory behavior" item (P3) from the PANSS (Kay et al., 1987). Using the criterion of a score equal to or larger than "4" on the P3 item split the SZ group into a AVH+ sub-group (n = 30, 15 males, 15 females), and AVH- (n = 36, 25 males, 11 females). The study was conducted according to the Code of Ethics of the World Medical Assocoation (Declaration of Helsinki). The patient data were pooled from two studies, each approved by the Regional Committee for Medical Research Ethics in Western Norway (REK Vest), #2010/334 and #2016/800, respectively, and by the Norwegian Social Science Data Service (NSD) #15733/PB.

2.2. Diffusion weighted MR imaging

Diffusion weighted imaging was performed on a 3T GE Signa HDx MR system with the following scanning parameters; TE = 89 ms, flip angle = 90°, TR = 14000 ms, FoV = 220 mm, matrix = 128×128, Slice thickness, 2.4 mm, with total scan time 8.38 min. Diffusion sensitizing gradients were applied in 30 directions, with a weighing factor of b = 1000 s/mm^2, with 6 b0 images as reference, and a reconstructed voxel size of 1.72×1.72×2.24 mm. There was a scanner upgrade in about the middle of the project period, upgrading from the GE Signa HDx to the GE Discovery 750 system.

2.3. Tensor estimation and tractography

Data quality assessment, preprocessing, tensor estimation and tractography were done using the ExploreDTI v. 4.8.4 software (Leemans et al., 2009). First, diffusion weighted images were corrected for movement (including b-matrix rotation) and visually inspected for artefacts. Following voxel-wise tensor estimation, whole brain deterministic streamline tractography (tracking threshold FA = 0.2, angle threshold = 30∘) was conducted. Then, for each individual and hemisphere, the anterior, long, and posterior segments of the AF were segmented according to landmarks described by Catani et al. (2011). Manually placed “way masks” were drawn in the coronal and axial plane, with ‘exclusion-masks’ eliminating fiber tracks from the long segment in the anterior and posterior segment. Tractography was done in native space. Mean track volume (TrackV), track number (TrackN), and track length (TrackL) were extracted as macrostructural measures.

2.4. Statistical analyses

A first analysis was set up as a multifactorial general linear mixed model (GLM) analysis of variance (ANOVA), separately for the TrackL, TrackN, and TrackV measures, with Segments (anterior, long, and posterior) and Hemisphere (left/right) as within-subject factors, and Group (AVH+, AVH-, HC) as between-subjects factor, and with Age and Sex as covariates. Significant main and interaction F-values were Geisser-Greenhouse epsilon-corrected when appropriate for inflated degrees of freedom. Fisher's LSD test was used for follow-up tests of significant main- and interaction-effects, with an alpha level set to $p < .05$. A similar analysis of variance was performed for functional anisotropy (FA) data, based on a 3 (Groups) x 2 (Hemispheres) x 3 (Segments) factorial design. A second set of analyses was to correlate values for TrackN, TrackL, and TrackV, and FA values with scores for the hallucinations item (P3), which would then provide a quantification of the association between AF white matter structure integrity and severity and frequency of AVH. Spearman's rank correlations were applied because of the restricted range of the P3 values from 1 to 7, in practice from 1-6 since patients are seldom scored by clinicians as extreme hallucinators as a score of "7" would require.

3. Results

3.1. Track length (TrackL)

Fig. 2 illustrates the long fiber tracks in three representative subjects, one from each group of AVH-, AVH+ and HC.

The ANOVA showed a significant main-effect of Segment, $F(2,250$, G-G corrected df: 1.494, 186.80) = 145.029, $p < .0001$, partial eta^2 = .537, and of the interaction of Segment x Group, $F(4, 250$, G-G corrected df: 2.989, 186.83) = 3.020, p = .018, *partial eta*^{2} = .046. In addition, the Group effect was marginally significant, $F(2,125) = 2.999$, $p = .053$, *partial eta*^{2} = .045. The interaction-effect was followed-up with the LSD-test, comparing the three groups for each segment separately. For left hemisphere comparisons, this showed significant differences between the HC group and the AVH+ group ($p = .058$) for the long segment, and a corresponding trend for the difference between the AVH+ and AVH- groups ($p = .085$). For the right hemisphere, the corresponding comparisons for the right hemisphere were $p = .005$ for the comparison HC versus AVH- group, and $p = .0003$ for the comparison HC versus AVH+, while the comparison of AVH- versus AVH+ was not significant, $p = .362$ (see Fig. 3). There was in addition a significant track length asymmetry for the HC group with longer tracks on the left side, $p = .0001$, and a trend for a similar asymmetry for the AVH+ group ($p = .074$ (see Fig. 3).

3.2. Number of tracks (TrackN)

There were no significant main- or interaction-effects involving Groups for number of tracks.

3.3. Track volume (TrackV)

There were no significant main- or interaction-effects involving Groups for track volume.

3.4. Functional Anisotropy (FA)

There were no significant main- or interaction-effects involving groups for the fractional anisotropy measure.

3.5. Means and standard errors

Means and SE are given in Table 1, split for the various measures (TrackL, TrackV, TrackN, Fractional anisotropy, FA), Segments and Groups.

3.6. Correlations

Spearman correlation coefficients for the correlations between the various tracks and segments on the one hand, and PANSS P3 score on the other hand, are seen in Table 2.

The correlations were focused on significant relationships between severity and frequency of AVH (as measured from the PANSS P3 score) and track segments (as measured from the procedure described in the Methods section). As seen in Table 2, there were significant positive correlations (* = $p < .05$) for all three measures of the posterior segment in the left hemisphere. Fig. 4 shows the corresponding scatterplots, separately for the left and right hemisphere.

4. Discussion

The results showed significant effects for the long segments of the arcuate fasciculus (AF) fiber bundle, where patients with severe and frequent hallucinations were characterized by longer reconstructed fiber tracks (TrackL) than healthy controls, and marginally so also when compared to non-hallucinating patients. Interestingly, this was most profound for the left hemisphere AF bundle, connecting the receptive (Wernicke) and productive (Broca) language areas, respectively. The parameter TrackL refers to the average distance the tractography algorithm managed to reconstruct before the tracking abortion threshold (FA criteria or angle) is met. Thus, longer as compared to shorter tracks indicate easier to reconstruct tract bundles, possibly due to less deterioration by crossing fiber bundles. In the present case, this may suggest that the hallucinating group has increased connectivity between auditory areas in the temporal lobe and frontal and parietal areas associated with language (Fernández-Miranda et al., 2015). Previous studies have indeed found an increase in white matter volume in the regions connected by the AF bundle (see e.g. Mitelman et al., 2007), and that greater overall white matter volume predicted higher positive symptom score five years later (Cahn et al., 2006). A second finding in the present study was the significant positive correlations between PANSS P3 scores

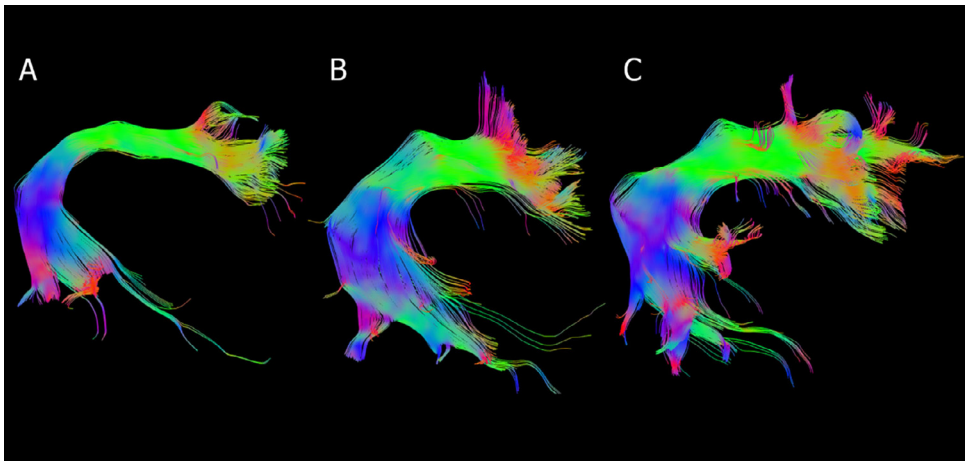

Fig. 2. Representative segments of the left arcuate fasciculus from A) a healthy control, B) a schizophrenia patient without auditory verbal hallucinations (AVHs) (PANSS P3 = 1), and C) a schizophrenia patient with frequent AVHs (PANSS P3 = 5). Note: Radiological convention applied. AVHs, auditory verbal hallucinations; PANSS, positive and negative syndrome scale; P3, positive item number 3 – hallucinatory behavior. Color coding: Red: Long segment, Green: Anterior segment, Purple: Posterior segment

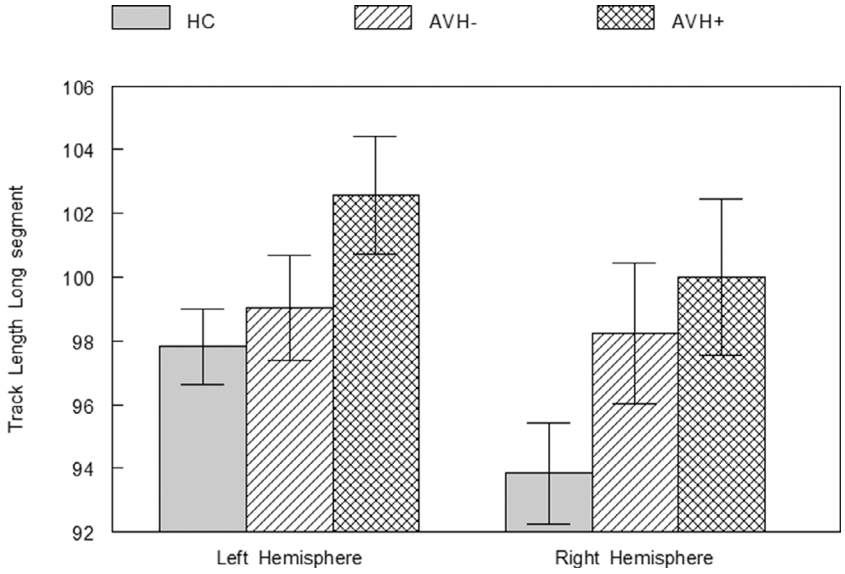

Fig. 3. Means and SE for the three groups HC (healthy controls), AVH- (without hallucinations), AVH+ (with hallucinations) group for Track Length of the long segment data.

and left hemisphere AF measures in the posterior segment, largely covering the peri-Sylvian region, including parts of auditory and speech perception cortex. It should be noted that the correlations were found only in the left hemisphere, which is also the language dominant hemisphere (Sperry, 1974; Tervaniemi and Hugdahl, 2003; Van der Haegen et al., 2013).

The present results of differences in left hemisphere tract length between hallucinating and non-hallucinating schizophrenia patients, and the positive correlation between severity of hallucinations and both track length, track volume and number of fiber tracks may have implications for the trait/state distinction. Since the PANSS scores were taken within a week before the MR scanning the present results pertain more to trait than to state effects, even in the absence of life-time measures of hallucinations. It is therefore conceivable that the results reflect long-term differences in brain white matter anatomy, which are not affected by antipsychotic medication, at least not in the age range covered in the study.

From the present findings it is not possible to disentangle whether it is the larger AF that allows for AVHs to be experienced, or if these segments increase in size due to the presence of AVH. It could indicate that in these individuals, the information flow between language areas could have multiple destinations and origins not found in HC, so that e.g. more tracts reach frontal and parietal areas from the auditory areas, thus leading to a perception of a voice that is not there.

The present DTI tractography results can be seen as extending previous functional studies showing increased BOLD connectivity in hallucinating patients between temporal and frontal language areas (e.g. Chang et al., 2017; Diederen et al., 2013; van Lutterveld et al., 2014). The reason for this suggestion is that an increase in length of the long segment AF fibers could facilitate neuronal connectivity between the areas being connected by the AF in the temporal and frontal lobes, which in turn could contribute to a kind of functional hyper-activity in these regions during hallucinatory episodes (Jardri et al., 2011; Kompus et al., 2011). This suggestion hinges however on an interpretation of increased tract length as facilitation information transfer and efficiency, which is contrary to findings and interpretation by van den Heuvel et al. (2010) who have argued for a negative relation between tract length and transfer efficiency. We leave the option for interpretation of the current findings in either direction, and do not take a firm stand on this issue, awaiting further research. It has previously been shown that functional hyper-activity in the language areas in the temporal lobe in hallucinating patients (Ćurčić-Blake et al., 2017; Hugdahl et al., 2015) goes together with reduction in grey matter volume (Modinos et al., 2013; Neckelmann et al., 2006), and that patients with schizophrenia in general have reduced grey matter volume in both temporal and frontal regions (Williams, 2008 for a meta-analysis). The

Table 1
Means and standard errors (SE) for the different measures, split for segments (anterior, long, posterior), and groups.

			Cntrl	AVH-	AVH+
Anterior	TrackN	Mean	436.23	473.72	444.62
		SE	20.82	30.18	38.99
	TrackL	Mean	65.61	65.8	65.84
		SE	0.49	0.67	0.82
	TrackV	Mean	12498.26	13247.95	12513.66
		SE	431	586.51	855.56
	FA	Mean	0.43	0.43	0.43
		SE	0.002	0.004	0.005
Long	TrackN	Mean	295.97	330.99	345.54
		SE	19.09	32.1	33.92
	TrackL	Mean	95.84	98.79	101.35
		SE	1.34	1.67	1.62
	TrackV	Mean	8593.83	9644.34	9897.78
		SE	358.92	672.98	631.85
	FA	Mean	0.46	0.46	0.47
		SE	0.003	0.004	0.005
Posterior	TrackN	Mean	344.48	344.57	383.3
		SE	16.03	25.04	25.17
	TrackL	Mean	60.33	60.24	61.17
		SE	0.34	0.51	0.62
	TrackV	Mean	10672.45	10702.85	11623.68
		SE	341.1	532.31	541.59
	FA	Mean	0.43	0.43	0.43
		SE	0.002	0.003	0.004

Legend
TrackN = Track Numbers
TrackL = Track Length
TrackV = Track Volume
FA = Fractional Anisotropy
Cntrl = Control group
AVH- = Non-Hallucinating group
AVH+ = Hallucinating group

Table 2
Spearman correlation coefficients for correlations between PANSS P3 scores and number of tracks (TrackN), track length (TrackL), track volume (TrackV) and Fractional anisotropy (FA), separately for the left and right hemisphere.

	PANSS P3	
	Left Hemisphere	Right Hemisphere
TrackN_Ant	-0.107	-0.102
TrackL_Ant	-0.061	0.054
TrackV_Ant	-0.155	-0.103
TrackN_Long	0.036	0.152
TrackL_Long	0.124	0.044
TrackV_Long	-0.040	0.181
TrackN_Post	0.345*	-0.080
TrackL_Post	0.293*	-0.122
TrackV_Post	0.351*	-0.070
FA_Ant	-0.154	-0.069
FA_Long	-0.061	-0.068
FA_Post	-0.027	-0.094

* = $p < .05$

present study extends these previous findings for grey matter abnormality in hallucination-prone individuals, by showing that also white matter structures are affected by hallucinations.

It is interesting to note that there were no significant group-effects for the FA measure in the present study as seen in Table 1 (cf. Chawla et al., 2019). This was somewhat surprising since FA values is the more common measure of white matter integrity when using DTI (see Catani et al., 2011; Di Biase et al., 2020; Mori, 2007; Psomiades et al., 2016; Xie et al., 2019 for examples). It should be noted however that even if most studies have found alterations in FA values in hallucinating patients, the direction of the change has been divergent across studies. For example, while Catani et al. (2011) and Di Biase et al. (2020) found reduced FA values in the arcuate fasciculus, Psomiades et al. (2016) and Rotarska-Jagiela et al. (2009) found increased values in the same tract. The current findings of no significant difference, neither reduction, nor increase, therefore adds to an unsolved issue in schizophrenia and hallucinations results. It could perhaps also be mentioned in this context that Di Biase et al. (2020) included a non-clinical hallucination group, where they did not find any change in FA values compared to control groups. The absence of significant findings for FA values in the present study could reflect that the critical parameters are tract length and composition rather than the degree of myelination of the fibers. FA is also subject to fluctuations across time, while track parameters, like length, volume and number of tracts, more reflect structural invariants that may better match trait differences in hallucinations as seen in the present study.

In conclusion, we have shown that white matter tracts of the arcuate fasciculus bundle, which connects temporal and frontal language areas in the brain, are affected in patients with severe and frequent hallucinations. Interestingly, increased track connectivity was observed not only for the long fibers connecting the Wernicke and Broca language areas in the superior temporal and inferior frontal gyri, respectively, but was also observed for the posterior segment fibers, primarily connecting the neurons within the auditory and speech perception areas in the peri-Sylvian region in the left hemisphere. The asymmetry for the long segment fiber tracks should also be noted, there was clearly (see Fig. 3) overall longer fiber tracks in the left compared with the right hemisphere, which was seen for both the healthy controls (HC) and with a trend for significance in the frequent hallucinating group (AVH +). Asymmetry of the AF have been observed previously, both in children and adults (Ocklenburg et al., 2013; Sreedharan et al., 2015; Takao et al., 2011), with left hemisphere tracts dominating over right hemisphere tracts. This could be an anatomical correspondence to functional dominance of the left hemisphere for language (Hellige, 1993; van den Noort et al., 2008). We extend these findings by showing that such an asymmetry also seems to be present in patients with frequent and severe auditory hallucinations, while the asymmetry is absent in schizophrenia patients without hallucinations. This may point to a specific relation between language and the experience of "hearing voices" in a hallucinatory episode, not seen otherwise in schizophrenia patients.

Several limitations should however be noted with the present results. First of all, the sample size was not exceedingly large when splitting the patient group into AVH- and AVH+ sub-groups, which should be kept in mind, as should the fact that we did not have complete data om medication, other than that all patients were on antipsychotic medication. Second, it could be argued that the hallucinatory behavior item of the PANSS interview scale is not unique for auditory verbal hallucinations. Although this is an often claimed argument we do not think it has invalidated our results since there is a clear focus on auditory verbal hallucinations in how the questions and conversations are set up for the PANSS P3 item, and auditory verbal hallucinations is the most frequent mode of hallucinations in schizophrenia. Moreover, even if we cannot completely exclude that some patients experienced hallucinations in other sensory modalities, the auditory modality typically would dominate even in such cases, and especially the more intense and severe the experience is. Larøi et al. (2019) found that that negative emotional content was the best predictor of experiencing auditory hallucinations. Similarly,

McCarthy-Jones et al. (2017) reported that up to 80% in their sample of 911 patients with schizophrenia experienced auditory hallucinations, followed by the visual and tactile modalities, such that the auditory modality dominated even in cases with overlap across modalities. What is a limitation though, is the lack of data pertaining to lifetime experiences of hallucinations, but such data were not available. A third limitation to be mentioned is that brain size could have an effect on the track length parameter, with longer tracks being positively related to larger brains. This is however not a likely explanation for the findings since the age and sex did not differ between groups, such that there is no obvious reason to assume that this could otherwise have caused the difference for the AVH+ group. If anything, one would have expected the opposite result if brain size would have had an effect, since

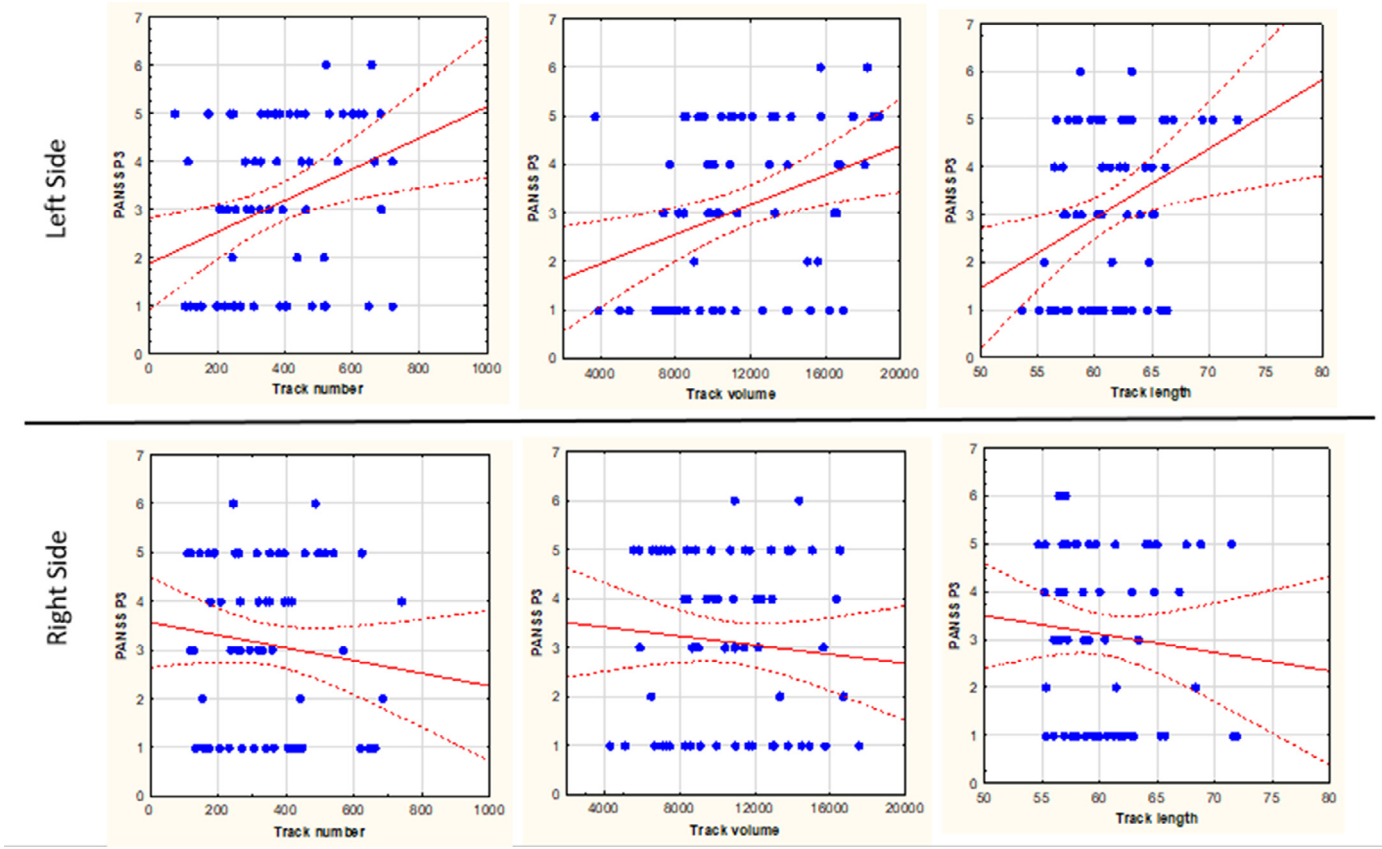

Fig. 4. Scatter-plots of the correlation between PANSS P3 scores (y-axis) and number of tracks, track volume, and track length for the posterior tract segment, split for the left and right side/hemisphere. The striped lines on both sides of the regression-line represent 95% confidence intervals.

it has been repeatedly shown that hallucinating patients have smaller grey matter volumes than non-hallucinating patients (Modinos et al., 2013; Neckelmann et al., 2006; Williams, 2008).

Funding information

The present study was funded by grants from the Helse-Vest Samarbeidsorganet #912945, and the European Research Council AdG #249516 to Kenneth Hugdahl.

Author contributions

LiEFa took part in collecting the data, analyzing the results, and commenting on the manuscript; ReWe took part in advising on how to analyze the data and analyzing the results, writing and commenting on the manuscript, ErJo, E-MLø, RuKr all took part in recruiting the recruiting the patient subjects and the clinical data, and commented on the manuscript, JyBe and KaKa took part in collecting the data and commented on the manuscript, KrKo took part in discussing the study, and read and commented on the manuscript, LaEr took part in setting up the MR sequences and oversaw the acquisition of the MR data, and commented on the manuscript, LyBSa edited and formatted, and read the manuscript, KeHu designed the study, analyzed the data, wrote the manuscript, and commented on the manuscript

Declaration of Competing Interests

Co-authors Kenneth Hugdahl and Lars Ersland owns shares in the company NordicNeurolab Inc. (https://nordicneurolab.com/) that produced add-on equipment for the acquisition of the MR data. Kenneth Hugdahl and Lars Ersland declare no conflict of interest, as do all other co-authors.

Acknowledgments

The authors want to thank the MR technicians at the Radiology Department of the Haukeland University Hospital, Bergen, Norway, and the study participants who made the study possible.

References

Alderson-Day, B., McCarthy-Jones, S., Fernyhough, C., 2015. Hearing voices in the resting brain: a review of intrinsic functional connectivity research on auditory verbal hallucinations. Neurosci. Behav. Rev. 55, 78–87. https://doi.org/10.1016/j.neubiorev.2015.04.016.

Aleman, A., Larøi, F., 2008. Hallucinations: The Science of Idiosyncratic Perception. American Psychological Association, Washington.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. Author, Washington.

Cahn, W., van Haren, N.E., Hulshoff Pol, H.E., Schnack, H.G., Caspers, E., Laponder, D.A., Kahn, R.S., 2006. Brain volume changes in the first year of illness and 5-year outcome of schizophrenia. Br. J. Psychiatry 189, 381–382. https://doi.org/10.1192/bjp.bp.105.015701.

Catani, M., Craig, M.C., Forkel, S.J., Kanaan, R., Picchioni, M., Toulopoulou, T., Shergill, S., Williams, S., Murphy, D.G., McGuire, P., 2011. Altered integrity of perisylvian language pathways in schizophrenia: Relationship to auditory hallucinations. Biol. Psychiatry 70, 1143–1150. https://doi.org/10.1016/j.biopsych.2011.06.013.

Catani, M., Thiebaut de Schotten, M., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44, 1105–1132. https://doi.org/10.1016/j.cortex.2008.05.004.

Chang, X., Collin, G., Xi, Y., Cui, L., Scholtens, L.H., Sommer, I.E., Wang, H., Yin, H., Kahn, R.S., van den Heuvel, M.P., 2017. Resting-state functional connectivity in medication-naïve schizophrenia patients with and without auditory verbal hallucinations: a preliminary report. Schizophr. Res. 188, 75–81. https://doi.org/10.1016/j.schres.2017.01.024.

Chawla, N., Deep, R., Khandelwal, S.K., Garg, A., 2019. Reduced integrity of superior longitudinal fasciculus and arcuate fasciculus as a marker for auditory hallucinations in schizophrenia: a DTI tractography study. Asian J. Psychiatr. 44, 179–186. https://doi.org/10.1016/j.ajp.2019.07.043.

Clos, M., Diederen, K.M., Meijering, A.L., Sommer, I.E., Eickhoff, S.B., 2014. Aberrant connectivity of areas for decoding degraded speech in patients with auditory verbal

hallucinations. Brain Struct. Funct. 219, 581–594. https://doi.org/10.1007/s00429-013-0519-5.
Ćurčić-Blake, B., Ford, J.M., Hubl, D., Orlov, N.D., Sommer, I.E., Waters, F., Allen, P., Jardri, R., Woodruff, P.W., David, O., Mulert, C., Woodward, T.S., Aleman, A., 2017. Interaction of language, auditory and memory brain networks in auditory verbal hallucinations. Prog. Neurobiol. 148, 1–20. https://doi.org/10.1016/j.pneurobio.2016.11.002.
Di Biase, M.A., Zhang, F., Lyall, A., Kubicki, M., Mandl, R.C.W., Sommer, I.E., Pasternak, O., 2020. Neuroimaging auditory verbal hallucinations in schizophrenia patient and healthy populations. Psychol. Med. 50, 403–412. https://doi.org/10.1017/S0033291719000205.
Diederen, K.M., Neggers, S.F., de Weijer, A.D., van Lutterveld, R., Daalman, K., Eickhoff, S.B., Clos, M., Kahn, R.S., Sommer, I.E., 2013. Aberrant resting-state connectivity in non-psychotic individuals with auditory hallucinations. Psychol. Med. 43, 1685–1696. https://doi.org/10.1017/s0033291712002541.
Fernández-Miranda, J.C., Wang, Y., Pathak, S., Stefaneau, L., Verstynen, T., Yeh, F.-C., 2015. Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain. Brain Struct. Funct. 220, 1665–1680. https://doi.org/10.1007/s00429-014-0751-7.
Ford, J.M., Morris, S.E., Hoffman, R.E., Sommer, I.E., Waters, F., McCarthy-Jones, S., Thoma, R.J., Turner, J.A., Keedy, S.K., Badcock, J.C., Cuthbert, B.N., 2014. Studying hallucinations within the NIMH RDoC framework. Schizophr. Bull. 40, 295–304. https://doi.org/10.1093/schbul/sbu011.
Geoffroy, P.A., Houenou, J., Duhamel, A., Amad, A., De Weijer, A.D., Ćurčić-Blake, B., Linden, D.E.J., Thomas, P., Jardri, R., 2014. The arcuate fasciculus in auditory-verbal hallucinations: a meta-analysis of diffusion-tensor-imaging studies. Schizophr. Res. 159, 234–237. https://doi.org/10.1016/j.schres.2014.07.014.
Hellige, J.B., 1993. Hemispheric Asymmetry: What's Right and What's Left. Harvard University Press, Cambridge.
Hubl, D., Koenig, T., Strik, W.K., Garcia, L.M., Dierks, T., 2007. Competition for neuronal resources: how hallucinations make themselves heard. Br. J. Psychiatry 190, 57–62. https://doi.org/10.1192/bjp.bp.106.022954.
Hugdahl, K., 2017. Auditory hallucinations as translational psychiatry: evidence from magnetic resonance imaging. Balk. Med. J. 34, 504–513. https://doi.org/10.4274/balkanmedj.2017.1226.
Hugdahl, K., Craven, A.R., Nygård, M., Løberg, E.-M., Berle, J.Ø., Johnsen, E., Kroken, R., Specht, K., Andreassen, O.A., Ersland, L., 2015. Glutamate as a mediating transmitter for auditory hallucinations in schizophrenia: A 1H MRS study. Schizophr. Res. 161, 252–260. https://doi.org/10.1016/j.schres.2014.11.015.
Hugdahl, K., Sommer, I.E., 2018. Auditory verbal hallucinations in schizophrenia from a levels of explanation perspective. Schizophr. Bull. 44, 234–241. https://doi.org/10.1093/schbul/sbx142.
Jardri, R., Pouchet, A., Pins, D., Thomas, P., 2011. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. Am. J. Psychiatry 168, 73–81. https://doi.org/10.1176/appi.ajp.2010.09101522.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.
Kompus, K., Westerhausen, R., Hugdahl, K., 2011. The "paradoxical" engagement of the primary auditory cortex in patients with auditory verbal hallucinations: a meta-analysis of functional neuroimaging studies. Neuropsychologia 49, 3361–3369. https://doi.org/10.1016/j.neuropsychologia.2011.08.010.
Kühn, S., Gallinat, J., 2012. Quantitative meta-analysis on state and trait aspects of auditory verbal hallucinations in schizophrenia. Schizophr. Bull. 38, 779–786. https://doi.org/10.1093/schbul/sbq152.
Larøi, F., Thomas, N., Aleman, A., Fernyhough, C., Wilkinson, S., Deamer, F., McCarthy-Jones, S., 2019. The ice in voices: Understanding negative content in auditory-verbal hallucinations. Clin. Psychol. Rev. 67, 1–10. https://doi.org/10.1016/j.cpr.2018.11.001.
Leemans, A., Jeurissen, B., Sijbers, J., Jones, D.K., 2009. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data, 17th annual meeting of international society for magnetic resonance in medicine, Hawaii, p. 3537.
Looijestijn, J., Diederen, K.M., Goekoop, R., Sommer, I.E., Daalman, K., Kahn, R.S., Hoek, H.W., Blom, J.D., 2013. The auditory dorsal stream plays a crucial role in projecting hallucinated voices into external space. Schizophr. Res. 146, 314–319. https://doi.org/10.1016/j.schres.2013.02.004.
McCarthy-Jones, S., Smailes, D., Corvin, A., Gill, M., Morris, D.W., Dinan, T.G., Murphy, K.C., O'Neill, F.A., Waddington, J.L., Bank, Australian Schizophrenia Research, Donohoe, G., Dudley, R., 2017. Occurrence and co-occurrence of hallucinations by modality in schizophrenia-spectrum disorders. Psychiatry Res 252, 154–160. https://doi.org/10.1016/j.psychres.2017.01.102.
Mitelman, S.A., Brickman, A.M., Shihabuddin, L., Newmark, R.E., Hazlett, E.A., Haznedar, M.M., Buchsbaum, M.S., 2007. A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia. Neuroimage 37, 449–462. https://doi.org/10.1016/j.neuroimage.2007.04.070.
Modinos, G., Costafreda, S.G., van Tol, M.-J., McGuire, P.K., Aleman, A., Allen, P., 2013. Neuroanatomy of auditory verbal hallucinations in schizophrenia: A quantitative meta-analysis of voxel-based morphometry studies. Cortex 49, 1046–1055. https://doi.org/10.1016/j.cortex.2012.01.009.
Mori, S., 2007. Introduction To Diffusion Tensor Imaging. Elsevier Science & Technology, Amsterdam.
Neckelmann, G., Specht, K., Lund, A., Ersland, L., Smievoll, A.I., Neckelmann, D., Hugdahl, K., 2006. MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. Int. J. Neurosci. 116, 9–23. https://doi.org/10.1080/00207450690962244.
Ocklenburg, S., Hugdahl, K., Westerhausen, R., 2013. Structural white matter asymmetries in relation to functional asymmetries during speech perception and production. Neuroimage 83, 1088–1097. https://doi.org/10.1016/j.neuroimage.2013.07.076.
Parnas, J., 2013. On psychosis: Karl Jaspers and beyond. In: Stanghellini, G., Fuch, T. (Eds.), One Century Of Karl Jaspers' General Psychopathology. Oxford University Press, Oxford, pp. 208–226.
Pienkos, E., Giersch, A., Hansen, M., Humpston, C., McCarthy-Jones, S., Mishara, A., Nelson, B., Park, S., Raballo, A., Sharma, R., Thomas, N., Rosen, C., 2019. Hallucinations beyond voices: a conceptual review of the phenomenology of altered perception in psychosis. Schizophr. Bull. 45, 67–77. https://doi.org/10.1093/schbul/sby057.
Psomiades, M., Fonteneau, C., Mondino, M., Luck, D., Haesebaert, F., Suaud-Chagny, M.-F., Brunelin, J., 2016. Integrity of the arcuate fasciculus in patients with schizophrenia with auditory verbal hallucinations: a DTI-tractography study. Neuroimage Clin. 12, 970–975. https://doi.org/10.1016/j.nicl.2016.04.013.
Rotarska-Jagiela, A., Oertel-Knoechel, V., DeMartino, F., van de Ven, V., Formisano, E., Roebroeck, A., Rami, A., Schoenmeyer, R., Haenschel, C., Hendler, T., Maurer, K., Vogeley, K., Linden, D.E.J., 2009. Anatomical brain connectivity and positive symptoms of schizophrenia: a diffusion tensor imaging study. Psychiatry Res. Neuroimaging 174, 9–16. https://doi.org/10.1016/j.pscychresns.2009.03.002.
Sartorius, N., Jablensky, A., Korten, A., Ernberg, G., Anker, M., Cooper, J.E., Day, R., 1986. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO collaborative study on determinants of outcome of severe mental disorders. Psychol. Med. 16, 909–928. https://doi.org/10.1017/s0033291700011910.
Scheinost, D., Tokoglu, F., Hampson, M., Hoffman, R., Constable, R.T., 2019. Data-driven analysis of functional connectivity reveals a potential auditory verbal hallucination network. Schizophr. Bull. 45, 415–424. https://doi.org/10.1093/schbul/sby039.
Sommer, I.E., Clos, M., Meijering, A.L., Diederen, K.M., Eickhoff, S.B., 2012. Resting state functional connectivity in patients with chronic hallucinations. PLoS One 7, e43516. https://doi.org/10.1371/journal.pone.0043516.
Sommer, I.E., Daalman, K., Rietkerk, T., Diederen, K.M., Bakker, S., Wijkstra, J., Boks, M.P.M., 2010. Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. Schizophr. Bull 36, 633–641. https://doi.org/10.1093/schbul/sbn130.
Sperry, R.W., 1974. Lateral specialization in the surgically separated hemispheres. In: Schmitt, F., Worden, F. (Eds.), The Neurosciences Third Study program. MIT press, Cambridge, pp. 5–19.
Sreedharan, R.M., Menon, A.C., James, J.S., Kesavadas, C., Thomas, S.V., 2015. Arcuate fasciculus laterality by diffusion tensor imaging correlates with language laterality by functional MRI in preadolescent children. Neuroradiology 57, 291–297. https://doi.org/10.1007/s00234-014-1469-1.
Takao, H., Hayashi, N., Ohtomo, K., 2011. White matter asymmetry in healthy individuals: a diffusion tensor imaging study using tract-based spatial statistics. Neuroscience 193, 291–299. https://doi.org/10.1016/j.neuroscience.2011.07.041.
Tervaniemi, M., Hugdahl, K., 2003. Lateralization of auditory-cortex functions. Brain Res. Rev. 43, 231–246. https://doi.org/10.1016/j.brainresrev.2003.08.004.
van den Heuvel, M.P., Mandl, R.C.W., Stam, C.J., Kahn, R.S., Hulshoff Pol, H.E., 2010. Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J. Neurosci. 30, 15915–15926. https://doi.org/10.1523/jneurosci.2874-10.2010.
van den Noort, M., Specht, K., Rimol, L.M., Ersland, L., Hugdahl, K., 2008. A new verbal reports fMRI dichotic listening paradigm for studies of hemispheric asymmetry. Neuroimage 40, 902–911. https://doi.org/10.1016/j.neuroimage.2007.11.051.
Van der Haegen, L., Westerhausen, R., Hugdahl, K., Brysbaert, M., 2013. Speech dominance is a better predictor of functional brain asymmetry than handedness: a combined fMRI word generation and behavioral dichotic listening study. Neuropsychologia 51, 91–97. https://doi.org/10.1016/j.neuropsychologia.2012.11.002.
van Lutterveld, R., Diederen, K.M., Otte, W.M., Sommer, I.E., 2014. Network analysis of auditory hallucinations in nonpsychotic individuals. Hum. Brain Mapp. 35, 1436–1445. https://doi.org/10.1002/hbm.22264.
Waters, F., Badcock, J., Michie, P., Maybery, M., 2006. Auditory hallucinations in schizophrenia: Intrusive thoughts and forgotten memories. Cogn. Neuropsychiatry 11, 65–83. https://doi.org/10.1080/13546800444000191.
Williams, L.M., 2008. Voxel-based morphometry in schizophrenia: Implications for neurodevelopmental connectivity models, cognition and affect. Expert Rev. Neurother. 8, 1049–1065. https://doi.org/10.1586/14737175.8.7.1049.
Woodruff, P.W., Wright, I.C., Bullmore, E.T., Brammer, M., Howard, R.J., Williams, S.C., Shapleske, J., Rossell, S., David, A.S., McGuire, P.K., Murray, R.M., 1997. Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. Am. J. Psychiatry 154, 1676–1682. https://doi.org/10.1176/ajp.154.12.1676.
World Health Organization, 2016. International classification of diseases for mortality and morbidity statistics (10th Revision).
Xie, S., Liu, B., Wang, J., Zhou, Y., Cui, Y., Song, M., Chen, Y., Li, P., Lu, L., Lv, L., Wang, H., Yan, H., Yan, J., Zhang, H., Zhang, D., Jiang, T., 2019. Hyperconnectivity in perisylvian language pathways in schizophrenia with auditory verbal hallucinations: a multi-site diffusion MRI study. Schizophr. Res. 210, 262–269. https://doi.org/10.1016/j.schres.2018.12.024.
Zhuo, C., Zhou, C., Lin, X., Tian, H., Wang, L., Chen, C., Ji, F., Xu, Y., Jian, D., 2020. Common and distinct global functional connectivity density alterations in drug-naïve patients with first-episode major depressive disorder with and without auditory verbal hallucination. Prog. Neuro-Psychopha. 96, 1–6. https://doi.org/10.1016/j.pnpbp.2019.109738.