Structural Analysis of Heschl's Gyrus in Schizophrenia Patients with Auditory Hallucinations

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Key Words

Auditory verbal hallucinations • Schizophrenia • Heschl's gyrus • Asymmetry • Magnetic resonance imaging • Volumetry • Plasticity

Abstract

Background/Aims: Heschl's gyrus (HG) is functionally involved in the genesis of auditory verbal hallucinations (AVH). This dysfunction seems to be structurally facilitated. The aim of the study was to analyze macrostructural features of HG in a group of patients reporting AVH who demonstrated white matter diffusion tensor imaging abnormalities reported previously. **Methods:** 3-D anatomical MR scans were obtained (patients with and without history of AVH, controls). HG was delineated by manual segmentation. Cortical folding, absolute and relative volumes, laterality were analyzed. **Results:** According to the literature, in the collapsed group of patients, the normal left-greater-than-right laterality of HG was attenuated. We found a trend towards a higher number of duplicated HG in hallucinating patients. We also found a bigger volume of HG in the right hemisphere in hallucinating patients. This effect was caused by gray and white matter increase. **Conclusions:** This is the first study on manual volumetry of HG in a group of schizophrenia patients with AVH

compared to patients without AVH. In a previous analysis of the diffusion tensor imaging data of the here presented sample, we found higher directionality of the arcuate fasciculus in patients with AVH, facilitating abnormal co-activation in the auditory cortices in the hallucinating brain. As these abnormal activations are frequent in hallucinating patients, the here described volume increase of HG might be interpreted as compensatory plastic adaptations of the contralateral regions. We suggest that this volume increase of HG is caused by the symptomatology and not by the underlying disorder of schizophrenia.

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Introduction

Hallucinations are perceptions without sensory stimulus [1]. In schizophrenia, they are most frequently auditory verbal hallucinations (AVH) comprising fully formed sentences, often in the form of comments or commands [2]. This preponderance of AVH is consistent with the hypothesis that language and psychosis have a common evolutionary origin [3].

In the last two decades, an atlas of the functional neuroanatomy of AVH has emerged based on structural and

functional imaging studies: the occurrence of hallucinations is associated with activations in the language system that are predominantly located in the left hemisphere and include frontal motor-speech areas and temporal semantic areas [4–6]. Importantly, activation of the primary auditory cortex (PAC) was also reported [4]. This was interpreted as a simultaneous representation of the acoustic properties of a voice heard during a verbal thought, adding the attribute of ‘being alien’, and interfering with the normally felt quality of being ‘self-generated’. This activation seems to be a constituting factor of AVH mechanism, not only an epiphenomenon [7], since cortical responsiveness to external stimulation of the PAC is reduced during AVH. Diffusion tensor imaging data [8] suggests that these dysfunctions might be caused by a structural facilitation of the white matter (WM) paths connecting frontal with temporal auditory and language areas. Further, deep brain structures and the limbic system are involved with the cortical network, contributing to the affective and mnemonic features of AVH [9].

One of the most investigated brain regions in schizophrenia – especially concerning the investigation of AVH – is the left temporal lobe, containing – among others – primary and secondary auditory areas. Most literature focuses on volume of the planum temporale, unfortunately sparing the PAC. Although several studies have investigated the morphology of these structures, the resulting body of literature is conspicuously inconsistent, due to a potentially large part of methodological differences [10–12]. Most studies computed correlations between the volume of interest and the momentary presence of AVH at measurement time, disregarding the patients’ history of hallucinations. Few studies have followed a symptom-guided approach or focused on specific anatomical changes associated with AVH [for review, see 9]. Some studies have reported a negative correlation between the severity of the AVH and the volume of the superior temporal gyrus [13–17]. However, results are not unequivocal, since some authors have found the correlation in the anterior part [13], others in the transversal part [14] or in the total volume [15–17]. Explicitly negative results have also been published [18–21]. Studies that patients classified according to their history of hallucinations (instead of correlating with severity) have not supported these previous findings of a reduced volume in AVH [20, 21].

Only few studies focused on volume of Heschl’s gyrus (HG), hosting the PAC. For HG, however, in longitudinal studies initially normal left-sided volumes were found decreasing along with functional measures during the

course of the disorder. This was interpreted as an excitotoxic phenomenon [22, 23]. These studies indicate a progressive loss of left temporal volume as a marker for schizophrenia rather than a specific finding in AVH.

From a previous analysis of the diffusion tensor imaging data of the here presented sample, we know that the directionality of the WM as measured with diffusion tensor imaging in the temporal lobe differs between patients with and without AVH and healthy controls [8]. The interesting and meanwhile well-replicated [24, 25] observation was that there was an increase of directionality of fiber-tracks connecting HG with other brain regions selective for patients that frequently experienced AVH. This has been interpreted as a potential mechanism leading to abnormal co-activation in the auditory cortices in the hallucinating brain. This effect was initially reported to be left-sided. However, also the right hemisphere seems to be involved [8, 24, 25]. As repeatedly smaller HG in the course of the disease have been reported in the left hemisphere [23, 26], the hemisphere known to be mainly affected in schizophrenia, we hypothesized a compensatory, contralateral increase of volume of the HG that is specific to patients prone to hallucinations independent of the diagnosis of schizophrenia. This hypothesis is based on the fact of higher directionality in the arcuate fasciculus in hallucinating patients that might facilitate abnormal co-activation of the auditory cortex associated with plastic structural adaptations of the involved regions. This hypothesis is justified by studies that have shown an increase of gray matter (GM) and WM after frequent functional activation of the respective region. Accordingly, in the present volumetric MR study, total volumes, GM and WM volumes of HG in frequently hallucinating patients, in patients that reportedly had never experienced hallucinations and healthy controls were compared for the first time.

Methods

Diffusion tensor imaging data from the same subjects have already been published [8]. This paper presents volumetric data. Patient recruitment and scanning methods will thus be described only cursorily, whereas all information specific to this study will be described in detail (for all online supplementary material, see www.karger.com/doi/10.1159/000258637).

Subjects

Thirteen acute schizophrenic patients (ICD-10) with frequent AVH (H), 13 acute schizophrenic patients who never perceived AVH (N) and 13 healthy control subjects (C) were investigated. In N, 2 male subjects later were excluded due to ambiguous anatom-

ical proportions (large interrater disagreements). Groups were matched for sex and age; all subjects were right-handed. All but 2 patients received typical or atypical antipsychotic treatment in conventional dosages. The investigation was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. Before the investigation began, all patients and healthy control subjects gave their written informed consent to participate in the study.

Assessment of Psychopathology

Each patient was carefully assigned to one of the two groups, H or N. N included only patients who had never experienced AVH or pseudo-hallucinations, neither at the time of this investigation nor at any time in their previous history. In H, all patients were prone to hallucinations and experienced verbal AVH at the time of the present hospitalization as well as during all the prior exacerbations of their disease. Additionally, psychopathology and severity was assessed by application of the Positive and Negative Symptom Scale (PANSS) [27] and Clinical Global Impression Scale (CGI) [28].

MR Methods

A 1.5 T Signa MR-system (General Electric Medical Systems, Milwaukee, Version 5.8, equipped with 'echospeed' gradients of 22 mT/m) was used for the investigations. Individual whole brain 3-D anatomy was measured with a 3-D gradient echo sequence, providing 124 axial slices with 1.2 mm thickness, 240 × 240 mm field of view (FOV), and 256 × 128 pixel resolution. Further scanning parameters were as follows: 22 ms repetition time (TR), 8 ms echo time (TE), and a flip angle of 45°. Total 3-D scan time was 9.04 min.

Segmentation

Anatomical T₁-weighted 3-D high-resolution data have been rotated into the AC-PC line as well as in the other two axes to correct for potential tilts without normalization or transformation. Each individual anatomical data set was automatically segmented in a first step at the GM-cerebrospinal fluid boundary (fig. 1b) and in a second step at the GM-WM boundary (fig. 1c) using BrainVoyagerQX[®] standard procedure. Thus, we were able to measure the total brain volume, the WM volume and, by subtracting the WM volume from the total brain volume, the GM volume (fig. 1d). In addition, the volume of HG was manually segmented. The original voxel size of 0.94 × 1.88 × 1.20 mm³ was interpolated to a voxel size of 1 × 1 × 1 mm³ as given default size for any anatomical BrainVoyagerQX[®] analysis. All segmentations were carried out in the BrainVoyagerQX[®] software using the segmentation tool.

Definition of HG

HG is located in the superior part of the temporal lobe, namely in the first transverse temporal gyrus [29, 30]. HG segmentations commonly follow the early definition of HG given by Pfeifer [31]. Specifically, we accepted landmarks to identify HG in the anatomical data (fig. 2) as published by Yousry [32]. Borders of HG were set according to Kwon [33].

A very important point was to determine whether HG was single or double. When multiple gyri were present, PAC is confined to the anterior portion of the gyrus. Thus, tissue located behind the first Heschl's sulcus were not assigned to the volume

Fig. 1. Segmentation of 3-D structural MRI data. **a** Anatomical T₁-weighted 3-D high-resolution data have been rotated into the AC-PC line without normalization or transformation. **b** Segmentation of the individual anatomical data at the boundary between the GM-cerebrospinal fluid. **c** Segmentation of the individual anatomical data at the GM-WM boundary. Thus, total brain volume and the WM volume could be determined. **d** GM volume was computed subtracting the WM volume from the total brain volume. These segmentations were computed automatically using BrainVoyagerQX[®].

of the HG but assumed to be part of planum temporale. In HG, the presence of a common stem indicates a single gyrus. Only when a sulcus intermedius deepens throughout its length to cleave the gyrus in two is the deep long sulcus called Heschl's sulcus and two HG are considered to be present.

All volumes were segmented by two independent raters who were blind to the diagnoses. Segmentations were performed by each of the raters and the average volume sizes across raters were further analyzed. In 2 cases of low interrater accordance (value $[(\text{rater 1} - \text{rater 2})/(\text{rater 1} + \text{rater 2})] < 0.2$), ambiguous anatomy was assumed, and the subjects were excluded from further analysis.

For further analysis, the number of voxels of the respective volume was counted automatically with in-house programming using Matlab[®] routines. Absolute (ml) and relative (absolute partial volume/total brain volume of the respective hemisphere × 100) volumes were determined [11, 32].

Correction of the Number-of-HG Bias

In the case of two HG, only the volume of the first gyrus was assigned to volume of HG, because the volume of the second was assumed to belong functionally to the PT. We found that across groups, subjects with one HG had consistently larger HG volumes than subjects with two HG. The number of HG was therefore considered as a confounding variable. Its effect was corrected for by linear regression across all subjects, and separately for each hemisphere.

Statistical Analysis

ANOVAs and t tests were calculated for the demographic and psychopathological data and absolute and relative volumetric data using Statistica[®] software. Where specific and directed hypotheses were available, one-tailed t tests were applied. Bonferroni correction was computed where necessary. Results were ac-

Fig. 2. Segmentation of HG: HG was visually identified in the 3-D anatomical data according to the particular landmarks in the sagittal, coronal and axial slices. In the sagittal view (left) the Ω identifies HG, in the coronal slices (middle), HG was best seen in the slice where the fornices form a tent, close to the slice where the

two branches of the fornix unify. In the axial slice, HG could be best identified at the height of the adhesio interthalamica. (For optimal visualization of the respective structures, MRI slices of one subject have been chosen.)

cepted to be significant at a 5% level. The following comparisons were made:

- (1) In a very first step, we tested for volume differences between the hemispheres to investigate the reliability of our data in comparison with literature.
- (2) Then the specific hypothesis of bigger volumes in AVH was tested separately for the left and right hemisphere for total volume as well as for the GM and WM volume in the group of patients with AVH (H) versus the group of subjects without AVH (including C and N).
- (3) To support the hypotheses that eventual differences were associated with the symptom but not with the disorder, we tested the two groups differing for the symptom but not for the diagnosis (equal for diagnosis, different for symptom: H vs. N) – where we expected differences – and the two groups differing for the diagnosis but not for the symptom (equal for symptom, different for diagnosis: C vs. N) where no differences were expected.

Results

Subjects

Subjects did not differ in age (C [mean $\pm$ SD]: 33 $\pm$ 9y, H: 33 $\pm$ 8y, N: 31 $\pm$ 9y; $p = 0.82$, $F(2, 36) = 0.20$), and sex (5 females), or duration of the disease (patients only; H: 8 $\pm$ 7y, N: 9 $\pm$ 7y; $p = 0.76$, $t(24) = 0.31$). Positive PANSS (H: 23 $\pm$ 6, N: 18 $\pm$ 7) was significantly higher in H compared to N ($p = 0.03$, $t(24) = 2.27$) due to higher values in the hallucinations item. There was no difference between the patient groups for any of the other scores (CGI [H: 5 $\pm$ 1, N: 5 $\pm$ 1] ($p = 1.00$, $t(24) = 0.00$) or PANSS total score [H 88 $\pm$ 15, N: 80 $\pm$ 18] ($p = 0.25$, $t(24) = -1.18$) or PANSS-negative score [H: 21 $\pm$ 5, N: 22 $\pm$ 6] ($p = 0.47$, $t(24) = 0.73$)).

Total Brain Volume

Mean total brain volume ($n = 39$) was 0.987 ± 0.108 l, with 53% GM (left hemisphere [LH]: 50%; right hemisphere [RH]: 50%) and 47% WM (LH: 48%; RH: 52%) (table 1).

A repeated measurement ANOVA of the factor ‘group’ (C, H, N) and the dependent variables ‘hemisphere’ (LH, RH) and ‘tissue’ (WM, GM) indicated significant differences for hemisphere ($p < 0.001$, $F(2, 36) = 59.13$) and tissue ($p < 0.001$, $F(2, 36) = 32.42$). There were no significant group effects.

Post-hoc testing identified significantly greater GM volume compared to WM volume ($p < 0.001$, $t(38) = 5.76$). RH volume was significantly greater than LH volume ($p < 0.001$, $t(38) = 7.85$).

Macro-Anatomy of HG

HG is described as the first transverse temporal gyrus. It is found to be a single but sometimes as a double (or even triple) gyrus, too. We found higher variability of HG in the RH. Often it was more difficult to define the borders of HG in RH due to greater variance in morphology. In the LH, we found 32 single and 5 double HG (C: 1, H: 2, N: 2) and in the RH, 23 single and 14 double HG (C: 4, H: 7, N: 3). Across all subject groups, double HG was found more often in the RH than in LH ($\chi^2 = 4.3$, $p = 0.04$). Within groups, this remained a trend ($\chi^2 = 2.78$, $p = 0.09$) in H, without reaching significance in C ($\chi^2 = 1.8$, $p = 0.18$) or N ($\chi^2 = 0.2$, $p = 0.65$).

Volume of HG: Hemispheric Differences

Left-greater-than-right asymmetry for the total HG volume was found as expected in C ($t(12) = -2.78$, $p =$

Table 1. Total brain volumes for patients with hallucinations, patients without hallucinations and controls

	C		H		N	
Absolute, l						
Total brain volume	0.998 (0.109)		0.998 (0.118)		0.966 (0.096)	
GM volume	0.523 (0.389)		0.532 (0.067)		0.466 (0.053)	
WM volume	0.475 (0.768)		0.505 (0.062)		0.461 (0.064)	
	L	R	L	R	L	R
Total brain volume	0.49 (0.05)	0.50 (0.05)	0.49 (0.06)	0.51 (0.06)	0.48 (0.05)	0.49 (0.05)
GM volume	0.26 (0.02)	0.26 (0.02)	0.27 (0.04)	0.26 (0.03)	0.26 (0.03)	0.25 (0.03)
WM volume	0.23 (0.03)	0.24 (0.04)	0.22 (0.03)	0.24 (0.04)	0.22 (0.03)	0.24 (0.03)

Mean (SD) total brain volumes with GM and WM sub-volumes for the three groups. GM = Gray matter; WM = white matter; L = left; R = right; C = controls; H = patients with AVH; N = patients without AVH.

Table 2. Mean volumes of HG (SD) with GM and WM sub-volumes for patients with hallucinations, patients without hallucinations and controls and left-right comparison

	C				N				H			
	L	R	t (12)	p	L	R	t (10)	p	L	R	t (12)	p
Absolute, mm ³												
Total HG	2,448 (672)	1,780 (678)	2.78	0.02	2,244 (554)	1,836 (627)	2.01	0.07	2,412 (708)	2,298 (600)	0.52	0.61
GM of HG	1,902 (499)	1,177 (400)	4.02	<0.01	1,715 (459)	1,101 (397)	4.53	<0.01	1,926 (469)	1,426 (377)	3.05	0.01
WM of HG	545 (221)	603 (362)	-0.54	0.60	529 (141)	734 (356)	-1.79	0.10	485 (235)	871 (394)	-3.89	<0.01
Relative												
Total HG	0.49 (0.12)	0.35 (0.12)	2.81	0.02	0.49 (0.12)	0.38 (0.12)	2.33	0.04	0.49 (0.13)	0.46 (0.10)	0.75	0.47
GM of HG	0.38 (0.08)	0.23 (0.79)	4.05	<0.01	0.37 (0.10)	0.23 (0.08)	4.80	<0.001	0.39 (0.09)	0.28 (0.07)	3.34	0.01
WM of HG	0.11 (0.04)	0.12 (0.06)	-0.25	0.81	0.12 (0.03)	0.15 (0.07)	-1.62	0.14	0.10 (0.04)	0.17 (0.07)	-3.66	<0.01

Left-greater-than-right asymmetry for the total HG volume was found as expected in C, but not in N and H.

GM = Gray matter; WM = white matter; HG = Heschl gyrus; L = left; R = right; C = controls; H = patients with AVH; N = patients without AVH.

One-tailed t tests, Bonferroni correction for testing two hemispheres.

0.017), but not in either patient group N or H. For both sides, GM was bigger than WM (*absolute values*: R: GM = 1,242 ± 405 mm³, WM = 736 ± 379 mm³; L: GM = 1,855 ± 482 mm³, WM = 519 ± 202 mm³; *relative values*: R: GM = 0.251 ± 0.079, WM = 0.146 ± 0.069; L: GM = 0.383 (0.088), WM = 0.107 ± 0.039) with $p < 0.01$ (table 2; fig. 3).

Symptom Dependence of HG Volume

Bigger volume of the HG was observed in the right hemisphere (total volume: $t(35) = -2.27$, $p = 0.03$, GM of HG: $t(35) = -2.13$, $p = 0.04$) in subjects with AVH (H) compared to subjects without AVH (C and N) (table 3).

To support that these differences were associated with the symptom of AVH and not with the disorder, we com-

pared C versus N (groups are equal for symptom but different for diagnosis) and did not find differences. Whereas in the comparison of H versus N (groups are equal for diagnosis but differ in symptomatology) volumes were bigger in the RH for each volume (total HG: $t(24) = 2.39$, $p = 0.03$, GM: $t(24) = 1.99$, $p = 0.05$, WM: $t(24) = 2.15$, $p = 0.04$) (table 4).

Discussion

The functional anatomy of AVH includes auditory cortex and language-related brain regions. The present study examined morphological differences in the primary auditory regions that were chosen by virtue of

Table 3. Comparison for symptom dependence mean volumes of HG (SD) with GM and WM sub-volumes for subjects with symptoms of AVH (H) and subjects without AVH (C and N) for both hemispheres

	L				R			
	AVH	no AVH	t (12)	p	AVH	no AVH	t (10)	p
Absolute, mm ³								
Total HG	2,412 (708)	2,355 (616)	0.25	0.80	2,298 (600)	1,806 (642)	2.27	0.03
GM of HG	1,926 (496)	1,816 (480)	0.66	0.52	1,426 (377)	1,142 (392)	2.13	0.04
WM of HG	485 (235)	538 (185)	-0.74	0.46	871 (394)	663 (358)	1.63	0.11
Relative								
Total HG	0.488 (0.126)	0.491 (0.117)	-0.07	0.95	0.455 (0.100)	0.365 (0.119)	2.32	0.03
GM of HG	0.391 (0.089)	0.378 (0.089)	0.40	0.69	0.285 (0.073)	0.232 (0.078)	2.01	0.05
WM of HG	0.097 (0.043)	0.112 (0.037)	-1.10	0.28	0.170 (0.072)	0.133 (0.065)	1.62	0.11

Bigger volumes in symptom carriers were found in the right hemisphere for the total volume, mainly caused by an increase of GM. GM = Gray matter; WM = white matter; HG = Heschl gyrus; L = left; R = right; C = controls; H = patients with AVH; N = patients without AVH. One tailed t tests, Bonferroni correction for testing two hemispheres.

Table 4. Influence of the disorder to test whether the volume increase in the right hemisphere is caused by the symptom or by the disorder

	Equal for disorder/ different for symptom		Equal for symptom/ different for disorder	
	t (22)	p	t (24)	p
Absolute, mm ³				
R total HG	2.06	0.03	0.21	0.42
R GM of HG	1.63	0.05	-0.46	0.32
R WM of HG	1.80	0.04	0.89	0.19
Relative				
R total HG	2.47	0.01	0.72	0.24
R GM of HG	1.73	0.05	-0.05	0.48
R WM of HG	2.12	0.02	1.43	0.08

In the comparison between the two groups with schizophrenia (equal for disorder but different for expression of AVH), we found right hemispheric differences whereas there were no differences in the comparison between the groups with and without schizophrenia.

GM = Gray matter; WM = white matter; HG = Heschl gyrus; L = left; R = right; C = controls; H = patients with AVH; N = patients without AVH. One-tailed t tests.

their functional role in etiopathology of AVH. Macroscopic features such as volume, laterality and cortical folding of the PAC were assessed manually in three different subject groups: hallucinating patients, patients who never experienced hallucinations, and control sub-

jects. From the analysis of the diffusion tensor imaging data of the here presented sample, we know from the prior analysis of the diffusion tensor imaging data [8] that there was an increase of directionality of fiber-tracks connecting HG with other brain regions selective for patients that experienced frequent AVH. We interpreted this increase of directionality as a potential mechanism leading to the abnormal co-activation in the auditory cortices in the hallucinating brain. Thus, the pathological activation of HG would not be generated in the HG itself alone, but rather by abnormal, structurally facilitated input from other regions. In the present study, we found a volume increase in the right, but not in the left HG, supporting the hypothesis that frequent and abnormal activation might be associated with plastic structural adaptations of involved regions [33–35]. The volume increase seems to be due to increased WM and GM in hallucinating patients.

We found an increased volume of the auditory region in the RH. At first glance, this appears to be contradictory to the fact that the structural and functional alterations related to hallucinations were often found to be more pronounced on the left side. The findings, however, are not exclusively restricted to the LH since also the homologue contralateral regions are involved [8, 24, 25]. We conclude that the here described unilateral volume increase might be due to an interhemispheric compensation mechanism as known from stroke recovery [36, 37], which in this context can be understood as a cortical reorganization mechanism in hallucinating schizophrenia

Fig. 3. Volume of HG. WM (□) and GM (■) volumes of the left and right HG as well as total volume (sum of WM and GM volume) are shown. Volumes are printed separately for each study group, C (n = 13), N (n = 11) and H (n = 13). Total volume was significantly larger in the LH compared to the RH in C but not in H and N, where asymmetry was attenuated. GM was significantly larger than WM for all groups in both hemispheres. C = Controls, H = hallucinating patients, N = non-hallucinating patients, LH = left hemisphere, RH = right hemisphere. * $p < 0.05$.

patients [38]. Possibly the well-known and often replicated LH functional [39, 40] and structural deficits [26, 39, 41] in schizophrenia-related to language-related thought disorders and hallucinations are developmental and, due to a structural vulnerability, even progressive. Compensatory plasticity effects would then be observed only in the non-affected RH homologue regions [42, 43]. However, our findings of increased RH volume in AVH might indicate a predisposition [44–46] as well as an adaptation. This was described for WM of the auditory and language system [35, 47]. Together with the higher incidence of bifurcated HG in the RH, the right-sided WM excess may also be explained by a developmental pathology of the physiological hemispheric asymmetry.

There are relatively few studies that investigated the laterality and the volume of HG in schizophrenia. Some studies focusing on HG volume in schizophrenia reported as a main finding a progressive volume reduction predominantly of the left but not of the right HG [22, 23]. The finding was also found in schizotypy [48]. However, these studies were conducted on larger groups of schizophrenic patients, not selected for the presence of hallucinations.

Further, there are also greater volumes of HG in patients with AVH reported [31] (left: +5%, right: +8%) indicating that HG volume changes might be a dynamic phenomenon and object to compensatory plasticity as well as to excitotoxic degeneration according to the individual predisposition. However, the dynamic state of the language system during pathological activation, chronicity of the process and compensatory capacities of the contralateral homologue regions are not yet fully understood.

In contrast to all these studies on the volume of HG in schizophrenia, in our study, schizophrenia patients with and without hallucinations have been compared. In the above-listed studies, a group of schizophrenia patients independent of their lifetime symptomatology have been compared with healthy controls. Thus, this effect of volume loss in the HG seems to be a kind of vulnerability marker for schizophrenia spectrum disorders more than a marker for AVH. We could not support a significant general loss of HG volume, however the descriptive values for LH volumes in patients for most volumes were smaller compared to C.

In accordance with the literature – as reliability check – we found a significant left-greater-than-right laterality of the total volume of HG in C, whereas this was attenuated in H and N without significant hemispheric difference. Further, GM was bigger compared to WM volume in controls and schizophrenia patients [35, 49].

One limitation of the present study is the relatively small number of subjects that were however clinically rather homogeneous. From a statistical point of view, there is probably a trade-off between increasing the number of analyzed subjects, and reducing within-group variance by more stringent inclusion criteria, and it is at the moment unclear where the optimal choice is. Increasing the number of subjects is also problematic because this method is so time-consuming that large subject groups are hardly feasible, i.e. in HG volumetry the five most high-ranking studies investigated on average 20 (range 18–22) controls and 17 (range 13–21) patients [22, 31, 32, 48, 50]. Controversial results have been published in these papers, suggesting small and susceptible results for minor methodological differences.

In the present study, a reliable method was applied, aiming at a high-end methodological approach with manual segmentation, high resolution of the 3-D voxels in data with reported microstructural differences. We found that RH total volume of HG with contribution of WM and GM sub-volume were bigger in patients with frequent AVH compared to patients without AVH and

healthy subjects, probably caused by a reorganization mechanism and plasticity. However, the different results between this and other studies might be due to different sub-group recruitment, using here a clear long-term symptom-led inclusion strategy.

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