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Auditory Cortex Characteristics in Schizophrenia: Associations With Auditory Hallucinations

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Background: **Neuroimaging studies have demonstrated associations between smaller auditory cortex volume and auditory hallucinations (AH) in schizophrenia. Reduced cortical volume can result from a reduction of either cortical thickness or cortical surface area, which may reflect different neuropathology. We investigate for the first time how thickness and surface area of the auditory cortex relate to AH in a large sample of schizophrenia spectrum patients.** ***Methods:*** **Schizophrenia spectrum (n = 194) patients underwent magnetic resonance imaging. Mean cortical thickness and surface area in auditory cortex regions (Heschl's gyrus [HG], planum temporale [PT], and superior temporal gyrus [STG]) were compared between patients with (AH+, n = 145) and without (AH−, n = 49) a lifetime history of AH and 279 healthy controls.** ***Results:*** **AH+ patients showed significantly thinner cortex in the left HG compared to AH− patients (d = 0.43, P = .0096). There were no significant differences between AH+ and AH− patients in cortical thickness in the PT or STG, or in auditory cortex surface area in any of the regions investigated. Group differences in cortical thickness in the left HG was not affected by duration of illness or current antipsychotic medication.** ***Conclusions:*** **AH in schizophrenia patients were related to thinner cortex, but not smaller surface area of the left HG, a region which includes the primary auditory cortex. The results support that structural abnormalities of the auditory cortex underlie AH in schizophrenia.**

Key words: psychosis/cortical thickness/cortical surface area/neuroimaging/magnetic resonance imaging/Heschl's gyrus

Introduction

Auditory hallucinations (AH) are the most frequently occurring psychotic symptom in schizophrenia, with a lifetime prevalence of around 70%.[1,2] These false auditory perceptions are often voices with a negative emotional valence, causing the patient great distress. In a longitudinal study following 150 psychosis patients for 20 years, 40%–45% of the schizophrenia patients had frequent or persistent hallucinations during this period,[3] and having AH at index hospitalization was associated with a reduced likelihood of recovery over the next 20 years.[4] Despite extensive efforts to elucidate the neural mechanisms underlying AH in schizophrenia patients,[5–7] so far the neurobiological underpinnings remain obscure.

Given the perceptual quality of the AH, the auditory cortex constitute an important region of interest (ROI) for exploring the underlying biological substrate of AH.[5,8] Evidence suggests that schizophrenia patients show deficits in basic auditory processing that may be consistent with auditory cortex pathology.[9] The auditory cortex includes the primary auditory cortex (in the Heschl's gyrus [HG]),[10] and surrounding auditory association cortex in the planum temporale (PT) and the superior temporal gyrus (STG).[11] Neuroimaging studies have demonstrated significant associations between AH and structural and functional auditory cortex alterations in schizophrenia patients.[6,12–14] In functional magnetic resonance imaging (MRI) studies, activation in auditory cortex regions was observed in schizophrenia patients while experiencing AH in the scanner.[15,16] Structural neuroimaging studies have demonstrated associations between greater severity of AH and "smaller" grey matter

volumes of HG[17–20] and STG.[19,21] However, "larger" grey matter STG volumes in hallucinating compared to non-hallucinating patients have also been reported[22] and still other studies have failed to find associations between severity of AH and grey matter volume in this region.[23–25]

Most previous structural MRI studies have used volumetric ROI[20,22] or voxel-based morphometry (VBM[17,19]) approaches, reporting data on cortical grey matter volume. Cortical volume is the product of cortical thickness and cortical surface area; hence volume alterations may result from altered thickness, area or both. Cortical thickness and area are determined by different processes in embryonic cortical development[26] and appear influenced by unrelated genetic mechanisms.[27] Furthermore, thickness and area show different trajectories in the normal aging brain,[28] and may be affected differently by disease processes. It is therefore of interest to investigate these 2 components independently. The FreeSurfer software allows for automatic reconstruction of the cortical surface from MR images to estimate cortical surface area and cortical thickness.[29]

A limited number of studies have investigated associations between AH and cortical thickness, with mixed results for the auditory cortex. Van Swam et al[30] found reduced cortical thickness bilaterally in the STG and in the left HG among 10 patients with AH compared to 10 non-hallucinating patients. However, cortical thickness in the HG in the hallucinating group did not differ from controls, and the non-hallucinating patients showed thicker cortex compared with controls. Oertel-Knöchel et al[31] investigated vertex-wise cortical thickness in 31 chronic schizophrenia patients, 29 first-degree relatives, and 37 healthy controls. A significant association was observed between thinner left STG cortex and increased predisposition towards hallucinations using the Revised Hallucination Scale in patients and relatives, but there was no correlation between Positive and Negative Syndrome Scale (PANSS) hallucination score and cortical thickness. Thinner cortex in the "right" HG was reported in 18 first-episode schizophrenia patients with persistent AH compared to 31 first-episode schizophrenia patients who had never experienced AH.[32] Sample sizes in studies investigating cortical thickness in relation to AH have been small, and discrepant findings could be due to limited statistical power. To our knowledge no study has examined the separate relationship between both auditory cortical surface area and thickness, and AH in schizophrenia patients.

We aimed to determine how auditory cortex thickness and surface area separately relate to AH in schizophrenia spectrum patients. Cortical thickness and surface area in 3 pre-selected ROIs in each hemisphere were compared between patients with (AH+) and without (AH−) a history of AH and healthy controls (HC). These ROIs cover cortical regions including the primary auditory cortex (HG)[10] and regions of auditory association cortex (PT and STG).[11] Based on previous MRI findings,[13,14] we hypothesized that AH would be associated with thinner auditory cortex and smaller surface area.

Methods

Subjects

The subject sample in the main analyses consisted of 194 schizophrenia spectrum patients (schizophrenia [n = 145], schizophreniform disorder [n = 21], schizoaffective disorder [n = 28]), and 279 healthy controls. Patients were recruited from psychiatric hospitals and outpatient clinics in the Oslo region as part of the ongoing Thematically Organized Psychosis (TOP) Research study. The healthy controls were randomly drawn from the national population registry covering the same geographical area as the patients and invited by letter to participate. They were screened for current or previous psychiatric disorder using a screening interview and the Primary Care Evaluation of Mental Disorders (Prime-MD[33]) and were excluded if they had ever experienced a psychiatric disorder including substance or alcohol misuse. Exclusion criteria for all participants were: age <18 or >65 years, IQ < 70, previous moderate or severe head injury or a neurologic illness. Before entering the study, all participants received oral and written information about the study and signed a written consent. The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate, and conducted in accordance with the Helsinki declaration.

Clinical Assessments

Diagnoses were set by trained psychologists or physicians, using the Structured Clinical Interview for DSM-IV axis I disorders (SCID-I) modules A–E.[34] The interviewers showed adequate overall agreement for diagnostic category (κ = 0.77, 95% CI 0.60–0.94).[35] Psychosocial functioning was assessed using the split version of the Global Assessment of Function (GAF-S and GAF-F) scale.[36] Data on current antipsychotic medication was collected from interviews at time of MRI, by reviewing case notes or at time of the clinical interview. Defined Daily Doses (DDD)[37] were calculated. Age of onset was defined as age when first experiencing positive psychotic symptoms (verified by SCID-I). Duration of illness (DOI) was calculated in years from age of onset to age at MRI scanning.

Auditory Hallucinations

Presence (AH+) or absence (AH−) of *lifetime AHs* was determined using the item B16 from the B-module of the SCID-I interview. We also had available information on *severity of hallucinations* at time of clinical interview rated with the PANSS item P3. This item rates the severity of hallucinations of all modalities, not just auditory, but AH have been shown to be the most frequent kind of hallucination

in schizophrenia patients.[38] Given that the median time from clinical interviews to MRI scan was 118 days (range 0 to 2168 days, interquartile range 325 days), PANSS P3 scores may not serve as a valid measure of current hallucinations at the time of MRI. Nevertheless, the PANSS is a widely used scale for measuring severity of hallucinations. We had available PANSS scores in 211 schizophrenia patients (which included the 194 patients that were studied for lifetime AH) and report results from group comparisons based on PANSS P3 in supplementary material.

MRI Acquisition

Patients and healthy controls underwent MRI on the same 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional 3-plane localizer, 2 sagittal T1-weighted magnetization prepared rapid gradient echo (MPRAGE) volumes were acquired with the Siemens tfl3d1_ns pulse sequence (echo time [TE] = 3.93 ms, repetition time [TR] = 2730 ms, inversion time [TI] = 1000 ms, flip angle = 7°; field of view [FOV] = 24 cm, voxel size = $1.33 \times 0.94 \times 1\,mm^3$, number of partitions = 160) and subsequently averaged together, after rigid-body registration, to increase the signal to noise ratio. There was no major scanner upgrade or change of instrument during the study period.

MRI Post Processing

All MRI scans were processed using the FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu), to automatically obtain measurements of cortical thickness and surface area in each hemisphere and in the auditory cortex. This processing method has been thoroughly described elsewhere.[39,40] Briefly, processing steps include motion correction, removal of non-brain tissue, automatic Talairach transformation, and intensity correction. Intensity and continuity information are used for reconstruction of grey/white matter boundary and pial surface. Cortical thickness is measured as the distance between grey/white matter boundary and pial surface at 160 000 vertices per hemisphere. Individual surfaces are averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns. A post processing control of the surface reconstruction, including manual editing of small inaccuracies, was performed by trained assistants, blinded for clinical data.

Regions of Interest

The cortical surface was automatically parcellated into anatomical regions using the Destrieux atlas included in the FreeSurfer software.[41] Cortical surface area and mean cortical thickness were obtained from 3 ROIs: the HG (*transverse temporal gyrus*), the STG and the PT (see supplementary figure S2 for illustration).

Statistical Analyses

Statistical analyses were performed using SPSS version 22.[42] Group differences in demographic and clinical data were tested using analysis of variance models (ANOVAs) for continuous normally distributed variables and Chi-square test for categorical data.

Separate general linear models (GLMs) were set up with mean cortical thickness and cortical surface area of left and right HG, PT and STG as dependent variables. Age, sex, and group (AH+, AH−, or HC) were entered as independent variables. The contrast of interest was between AH+ and AH−, but pairwise comparisons were also performed between patient groups and healthy controls to investigate the directionality of the findings. Additional models including total cortical surface area and mean hemispheric cortical thickness as covariates were also investigated to control for global group differences in cortical area and mean cortical thickness respectively. Cohen's *d* for group comparisons was calculated from differences in predicted means.[43] PANSS positive psychotic symptom score (excluding P3) (hereafter referred to as PANSS positive symptoms), PANSS negative symptom score, DOI and antipsychotic medication (current DDDs at time of MRI), were separately entered into the GLMs as independent variables to see if they affected observed group differences between AH+ and AH− patients. A confounding effect was considered to be present if including the variable altered the regression coefficients of interest >20%.[44]

General linear models were also performed to compare auditory cortex characteristics between patients with and without hallucinations according to PANSS P3 score (see supplementary material for more details on these analyses).

A modified Bonferroni correction method, accounting for correlations between outcome variables,[45] was chosen to control for multiple comparison when performing pairwise group comparisons between AH+ and AH−. Applying this method (in 6 ROIs, $\alpha = .05$), $P < .0129$ for cortical thickness analyses (intraclass correlation coefficient [ICC] = 0.428) and $P < .0130$ for cortical surface area analyses (ICC = 0.437) were considered statistically significant.

Results

Demographic, Clinical Data and Global Cortical Thickness and Surface Area Estimates

As presented in table 1, the AH+ group had a longer DOI compared to the AH− group. The AH+ group scored higher on the PANSS hallucination item (P3), and had a higher GAF-symptom score than the AH− group. However, there were no significant differences on GAF function score or PANSS positive symptom score when excluding P3. There were no differences between AH+ and AH− patients in age, handedness, or dose of current

Table 1. Subject Characteristics for Schizophrenia Patients With (AH+) and Without (AH−) Auditory Hallucinations, and Healthy Controls (HC)

Variable	AH+	AH−	HC			
Mean (SD) Unless Otherwise Specified	$N = 145$	$N = 49$	$N = 279$	$F/t/\chi^2/U$	Sig.	Post hoc
Age, y	31.1 (9.3)	30.9 (8.4)	34.7 (9.6)	8.484	<.001	HC > AH+ HC > AH−
Sex [n = male (%)]	82 (56.6)	33 (67.3)	147 (52.7)	3.739	.154	
Handedness [n = right handed (%)]	115 (88.5)	38 (84.4)	226 (92.6)	3.809	.149	
Age of onset, y	22.9 (7.2)	25.2 (7.0)	na	1.882	.061	
DOI MR, y	8.3 (7.7)	5.7 (5.5)	na	−2.129	.035	
GAF-S	40.4 (8.8)	45.5 (13.1)	na	2.549	.013	
GAF-F	42.1 (8.9)	44.7 (11.6)	na	1.586	.114	
PANSS P3 (hallucinations) [median (range)]	3.0 (1–6)	1.0 (1–5)	na	1806.00	<.001	
PANSS pos (excluding P3)	12.4 (4.6)	11.7 (4.6)	na	−0.893	.373	
PANSS neg	16.1 (6.7)	14.1 (6.1)	na	−1.838	.068	
PANSS total	64.2 (17.9)	57.9 (15.5)	na	−2.191	.030	
Hallucinations from other modalities						
Visual (n = 184)	61 (45.2%)	8 (16.3%)	na	12.775	<.001	
Tactile (n = 178)	33 (25.2%)	5 (10.6%)	na	4.363	.037	
Gustatory (n = 173)	12 (9.5%)	2 (4.3%)	na	1.278	.258	
Olfactory (n = 176)	36 (28.3%)	6 (12.2%)	na	5.045	.025	
DDD of AP at time of MRI	1.23 (1.25)	1.22 (.88)	na	-0.024	.981	
Mean cortical thickness, left, mm (SE)	2.286 (0.009)	2.275 (0.015)	2.352 (0.006)	23.956	1.24×10^{-10}	HC > AH+ HC > AH−
Mean cortical thickness, right, mm (SE)	2.280 (0.008)	2.272 (0.014)	2.345 (0.006)	24.601	6.93×10^{-11}	HC > AH+ HC > AH−
Total cortical area, mm^2 (SE)	172023.7 (1224.5)	170813.5 (2105.0)	177053.6 (881.9)	7.467	.001	HC > AH+ HC > AH−

Note: DOI, duration of illness; GAF, Global assessment of function; PANSS, Positive and negative syndrome scale; DDD, defined daily dose; AP, Antipsychotics; na, not applicable; MRI, magnetic resonance imaging; GLMs, general linear models. Group differences in demographic and clinical data were tested using students t test or ANOVA for continuous variables, and Chi-Square statistics for categorical data (sex and handedness). Mann-Whitney U test was used to test differences in scores on PANSS P3, as the distribution for this variable was heavily skewed. Handedness: 2 subjects were ambidextrous; these were included in the left-handed group for the statistical analyses. Mean cortical thickness and total surface area in each group are estimated marginal means from GLMs co-varying for age and sex.

antipsychotic medication at time of MRI. AH+ patients were more likely than AH− patients to experience hallucinations from other sensory modalities, most often visual (table 1). Among 163 patients with complete information regarding lifetime hallucinations, 44.8% reported a history of hallucinations from more than 1 modality. Compared to HC, both the AH+ and AH− group had a significantly lower mean age, and significantly thinner mean hemispheric cortex bilaterally and smaller total surface area (table 1).

Auditory Cortical Thickness

AH+ patients had significantly thinner cortex in the left HG compared to AH− patients (table 2, figure 1). Thinner cortex ($d = -0.21$), although not statistically significant, was also seen in the right HG in the AH+ compared to the AH− group. Compared to HC, only AH+ patients had thinner cortex in the left HG, but both patient groups had thinner cortex bilaterally in the PT and STG.

The group difference in left HG cortical thickness between AH+ and AH− patients was unchanged when including PANSS positive score (excluding P3), PANSS negative score, DOI or current dose of antipsychotic medication at time of MRI in the statistical model. None of these variables were associated with cortical thickness of the left HG.

When controlling for mean hemispheric cortical thickness, the significant group differences between AH+ and AH− patients in the left HG remained ($d = -0.52$, $P = .0014$), but AH+ no longer differed from HC ($d = 0.05$, $P = .625$), and AH− showed increased thickness compared to HC ($d = 0.58$, $P = .0003$; supplementary table S1).

Thinner cortex in the left HG was also seen in hallucinating patients compared to non-hallucinating patients when group comparisons were based on PANSS P3 scores ($d = -0.44$, $P = .003$, see supplementary material, section 3 for details on these results).

Auditory Cortex Surface Area

There were no significant differences in cortical surface area between AH+ and AH− patients after correction

Table 2. Comparison of Cortical Thickness (mm) in Auditory Cortex Between Schizophrenia Patients With (AH+) and Without (AH−) a Lifetime History of Auditory and Healthy Controls (HC)

	EMM					AH+ vs AH−	AH+ vs HC	AH− vs HC
	AH+	AH−	HC	*F*	*P*	*P*	*P*	*P*
L HG	2.126 (0.023)	2.245 (0.040)	2.193 (0.017)	4.375	.013	.0096*	.020	.229
R HG	2.201 (0.024)	2.261 (0.041)	2.258 (0.017)	2.007	.135	.203	.055	.945
L PT	2.266 (0.019)	2.263 (0.032)	2.354 (0.013)	8.626	.00021	.933	.00018	.0098
R PT	2.221 (0.021)	2.207 (0.037)	2.337 (0.015)	12.324	.0000061	.732	.000013	.0011
L STG	2.891 (0.019)	2.882 (0.032)	2.988 (0.014)	10.990	.000022	.825	.000031	.0026
R STG	2.926 (0.018)	2.912 (0.030)	3.007 (0.013)	9.087	.00013	.683	.00022	.0038

Note: EMM, estimated marginal means; L, left hemisphere; R, right hemisphere; HG, Heschl's gyrus; PT, planum temporale; STG, superior temporal gyrus. General linear regression models. Dependent variable: cortical thickness in the region of interest. Independent variables: age, sex, and group (AH+/AH−/HC). *P*-values displayed are uncorrected.
*Pairwise comparisons between AH+ and AH− that were significant after correction for multiple comparisons ($P < .0129$).

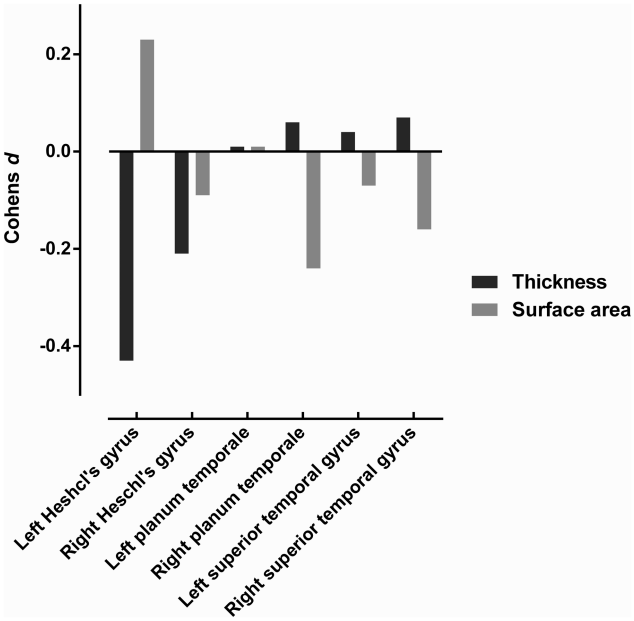

Fig. 1. Cohen's *d* (y-axis) for cortical thickness and surface area comparisons (covaried for age and sex) in regions of interest (x-axis) between schizophrenia patients with (AH+) and without (AH−) a history of auditory hallucinations. A positive Cohen's *d* indicates AH+ > AH−.

for multiple comparisons (table 3). In the left HG, the AH+ patients had larger surface area compared to AH− patients (figure 1), but this difference was not statistically significant. Larger surface area of the left HG in hallucinating patients was also seen when group comparisons were made based on severity ratings on the PANSS P3 at time of clinical interviews ($d = 0.26$, $P = .073$, see supplementary material, section 3).

When total surface area was included as a covariate, AH+ showed smaller surface area in the right PT compared to AH− ($d = -0.33$, $P = .044$), but this difference was not statistically significant after controlling for multiple comparisons.

Discussion

The main finding of the present study was that schizophrenia patients with a history of AH had thinner cortex in left Heschl's gyrus compared to schizophrenia patients without AH. This group difference was not affected by duration of illness or current antipsychotic medication. Furthermore, the group difference remained significant when controlling for global cortical thickness and there was no difference in global mean cortical thickness between the 2 groups, indicating that the thinner cortex of left Heschl's gyrus could not be explained by a general cortical thinning in the AH+ group. No significant differences were seen between AH+ and AH− patients in auditory cortex surface area.

Only a few previous studies have investigated if thickness of the auditory cortex is related to AH in schizophrenia patients,[30–32] and previous sample sizes have been small, ranging between 20–49 patients. The present finding of significant group differences between AH+ and AH− patients only in the *left* hemisphere is concordant with both Van Swam et al[30] who reported thinner cortex in the *left* HG in patients with AH compared to non-hallucinating patients, and Oertel-Knöchel et al[31] who found a negative correlation between predisposition towards hallucinations and cortical thickness in the *left* STG. Our findings differ from those of Chen et al[32] who reported significantly thinner cortex only in the *right* HG in patients with a lifetime history of AH compared to non-hallucinating first-episode schizophrenia patients. However, their supplementary data indicated that patients with AH also had reduced thickness in the left HG gyrus compared to non-hallucinating patients. In the present study, AH+ also had thinner cortex in the right HG, but this difference was not statistically significant.

Compared to healthy controls, the AH+ patients showed thinner cortex in the left HG, indicating that the group difference observed between AH+ and AH− was caused by the AH+ patients having abnormally thin cortex

Table 3. Comparison of Cortical Surface Area (mm^2) in Auditory Cortex Between Schizophrenia Patients With (AH+) and Without (AH−) a Lifetime History of Auditory and Healthy Controls (HC)

	EMM (SE)					AH+ vs AH−	AH+ vs HC	AH− vs HC
	AH+	AH−	HC	*F*	*P*	*P*	*P*	*P*
L HG	360.72 (6.92)	342.04 (11.90)	361.90 (4.99)	1.210	.299	.172	.891	.125
R HG	272.59 (4.77)	277.71 (8.21)	284.92 (3.44)	2.221	.110	.587	.038	.419
L PT	672.49 (12.37)	671.70 (21.26)	683.40 (8.91)	0.312	.732	.974	.477	.613
R PT	540.74 (9.03)	566.51 (15.53)	565.99 (6.51)	2.722	.067	.149	.025	.975
L STG	1464.67 (14.65)	1476.53 (25.18)	1473.01 (10.55)	0.136	.873	.682	.646	.898
R STG	1243.08 (14.30)	1270.36 (24.59)	1275.44 (10.30)	1.701	.184	.335	.069	.849

Note: General linear regression models. Dependent variable: cortical surface area in the region of interest. Independent variables: age, sex, and group (AH+/AH−/HC). *P*-values displayed are uncorrected. None of the results from the pairwise group comparisons between AH+ and AH− were significant after correction for multiple comparisons ($P < .0130$).

as opposed to the AH− patients having abnormally thick cortex. Some caution should be applied to this interpretation, as when controlled for mean hemispheric cortical thickness, AH+ no longer differed from HC in left HG cortical thickness, and AH− showed increased thickness. However, this result could be influenced by the large difference in mean hemispheric cortical thickness between patients and healthy controls (table 1).

The HG contains primary auditory cortex,[10] which is the initial cortical auditory processing site, receiving input from the medial geniculate thalamus nucleus. The PT and the lateral STG include auditory association areas surrounding the primary auditory cortex.[11] A stronger association of AH to primary auditory rather than to association auditory cortex has been indicated previously.[17,18] Gaser et al[17] found that severity of AH were significantly and negatively correlated with grey matter volumes in the left HG, and reported only trend-level significant associations with volumes in the surrounding region. Consistent with this, in the present study AH+ patients showed significantly thinner cortex only in the left HG, and we found thinner cortex bilaterally in the PT and lateral STG in both patient groups compared to healthy controls. Our results support that AH are associated with structural changes in brain regions involving the primary auditory cortex.

To our knowledge, there have been no previous studies on the relationship between AH and cortical surface area in schizophrenia. Cortical surface area was found to be overall smaller in schizophrenia patients compared to healthy controls in a previous study by our research group, in a largely overlapping sample.[46] We confirm smaller total cortical surface area in both patient groups compared to HC, however, we do not find significant differences in regional surface area of auditory cortex between AH+ and AH− patients. Our results suggest that structural abnormalities underlying AH in schizophrenia affect cortical thickness rather than cortical surface area. We observe an interesting pattern of thinner cortex and larger surface area in the HG in AH+ compared to AH− patients. This pattern of increased area should be interpreted with caution as it was not statistically significant. Nevertheless, opposing directions of alterations in cortical thickness and surface area emphasize the importance of separately measuring thickness and area when evaluating cortical volumes differences.

The neuropathology underlying the thinner cortex in patients with AH remains unknown. One of the most consistent postmortem finding in schizophrenia is reduced dendritic spine density, which has been found in several cortical regions.[47] It has been suggested that excessive pruning during adolescence may cause the dendritic spine loss.[47] Reduced somal size of pyramidal neurons and reduced density of dendrites and axon terminals in cortical layer 3 has been demonstrated in the primary auditory cortex and the auditory association cortex in schizophrenia.[48–50] Pyramidal neurons in layer 3 in the sensory cortex are involved in feedforwarding sensory signals to higher cortical areas. Sweet et al[49] suggested that the abnormalities observed from postmortem studies may give rise to impaired precision of early auditory processing.[51] Deficits in auditory processing, such as reduced tone matching abilities or abnormalities in electroencephalographic activity during early phases of auditory processing are evident in schizophrenia, and may contribute to mechanisms leading to AH.[9]

An alternative explanation for cortical thinning measured by MRI, is cerebral blood flow alterations in relation to hallucination status. Kindler et al[52] reported that a reduction in blood flow in the primary auditory cortex was associated with a decrease in psychopathology scores after treatment with repetitive transcranial magnetic stimulation in schizophrenia. To our knowledge there are no studies on the association between cortical thickness and regional blood flow fluctuations, however this is an interesting question to pursue in further investigations. We cannot make strong assumptions regarding the trait or state specificity of the observed cortical thinning in our study, which would require a longitudinal study design.

Strengths of the present study include a large sample of clinically well characterized schizophrenia spectrum patients which increases the possibility to detect subtle group differences in cortical thickness or area, and allows for control of possible confounding effects, such as antipsychotic medication, other positive psychotic symptoms and DOI. The Destrieux atlas provides a detailed parcellation of the auditory cortex, showing good concordance with manually drawn parcellations (concordance index ranging from 0.79 to 0.90 for the ROIs used in the present study[41]).

Findings of the present study should be interpreted in the context of some limitations. The study population was included as part of a large study that was not designed specifically to investigate AH. We therefore lack detailed information on the onset and frequency of AH, and response to treatment. Ratings of the PANSS item P3 offer more details regarding frequency and behavioral consequences of hallucinations over the last week before interview. However, due to a considerable time gap between the clinical interviews and MRI scanning for many of the patients in the present study, the PANSS score could not be used as valid state measure at time of MRI. Nevertheless, as the PANSS is a widely used scale, we report the results from comparisons based on the hallucination item, which concurred with the main result of thinner cortex in the left HG in patients with lifetime AH.

A significant proportion of patients in the AH+ group also experienced lifetime hallucinations from other sensory modalities (table 1). Hallucinations from more than 1 modality were found in 44.8% of patients, which is in agreement with Lim et al[2] who found that 53% of schizophrenia patients experienced hallucinations from more than 1 sensory modality. Similar results were demonstrated by Shinn et al[1] who suggested that biological mechanisms underlying hallucinations in psychotic disorders might affect multiple sensory modalities. We have used a hypothesis-driven approach, to investigate characteristics of the auditory cortex specifically in relation to AH in schizophrenia spectrum patients, and our sample size did not allow for analyses of other modalities of hallucinations. It is nevertheless possible that the observed group differences in the auditory cortex could be part of a wider pathological process affecting multiple sensory systems. Furthermore, it should be noted that other brain regions may also be of importance for explaining AH.[12]

In conclusion, we found a significant association between lifetime experience of AH and thinner cortex of the HG in schizophrenia spectrum patients. Our results suggest that previously described volume deficits related to AH in schizophrenia are mainly driven by thinner cortex in selected regions, and not reduced cortical surface area. The results demonstrate the importance of investigating cortical area and thickness separately, as one may risk losing important information by combining them into cortical volume. The HG contains primary auditory cortex, and the observed cortical thinning may be consistent with postmortem studies reporting decreased dendritic arborisation in this region. Increased knowledge on the neurobiological underpinnings of AH, which is the most frequent psychotic symptom of schizophrenia, will aid the search for disease mechanisms and a better treatment of schizophrenia.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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