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ORIGINAL ARTICLE

Auditory verbal hallucinations are related to cortical thinning in the left middle temporal gyrus of patients with schizophrenia

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Background. Auditory verbal hallucinations (AVHs) are one of the most common and severe symptoms of schizophrenia, but the neuroanatomical abnormalities underlying AVHs are not well understood. The present study aims to investigate whether AVHs are associated with cortical thinning.

Methods. Participants were schizophrenia patients from four centers across China, 115 with AVHs and 93 without AVHs, as well as 261 healthy controls. All received 3 T T1-weighted brain scans, and whole brain vertex-wise cortical thickness was compared across groups. Correlations between AVH severity and cortical thickness were also determined.

Results. The left middle part of the middle temporal gyrus (MTG) was significantly thinner in schizophrenia patients with AVHs than in patients without AVHs and healthy controls. Inferences were made using a false discovery rate approach with a threshold at $p < 0.05$. Left MTG thickness did not differ between patients without AVHs and controls. These results were replicated by a meta-analysis showing them to be consistent across the four centers. Cortical thickness of the left MTG was also found to be inversely correlated with hallucination severity across all schizophrenia patients.

Conclusion. The results of this multi-center study suggest that an abnormally thin left MTG could be involved in the pathogenesis of AVHs in schizophrenia.

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Key words: Auditory verbal hallucination, cortical thickness, magnetic resonance imaging, middle temporal gyrus, schizophrenia.

Introduction

Auditory verbal hallucinations (AVHs) are one of the most devastating and common symptoms of schizophrenia (Hoffman, 2008), affecting up to 80% of patients (Andreasen & Flaum, 1991). Because schizophrenia is a highly complex mental disorder, studies of specific symptoms such as AVHs may unravel symptom-related alteration patterns and help to understand the brain mechanisms underlying AVHs.

Evidence has shown that language production and perception regions contribute to AVHs in schizophrenia patients. This involves abnormal neuroanatomical structures (Onitsuka *et al.* 2004; van Swam *et al.* 2012; Modinos *et al.* 2013), inter-cortical connections (Benetti *et al.* 2015), and brain activation (McGuire *et al.* 1995) in the temporal lobe of the speech-dominant hemisphere. For example, Onitsuka *et al.* (2004) reported that patients with auditory hallucinations had less gray matter volume than patients without hallucinations in the superior and middle temporal gyri of the left hemisphere, and that the volumes of these regions were negatively correlated with global rating of hallucinations. In connecting to the frontal lobe via the arcuate fasciculus, the temporal lobe, especially

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the left superior and middle gyri, is part of a pivotal pathway in the brain's language network (Glasser & Rilling, 2008). Indeed, the temporal lobe has well-established functional roles in auditory perception and language processing (Karnath, 2001; Giraud *et al.* 2004).

Numerous studies have investigated gray matter volumetric measures in trying to characterize structural abnormalities related to AVHs (Onitsuka *et al.* 2004; Palaniyappan *et al.* 2012; Modinos *et al.* 2013). However, cortical volume provides a mix of two separate neuroanatomical features because it is the product of cortical thickness and cortical surface area, and consequently confounds the different cellular mechanisms and genetic etiologies of these (Panizzon *et al.* 2009). By contrast, cortical thickness specifically reflects the cytoarchitecture of the cortex, including the density and arrangement of neurons, neuropil, and neuroglia, and is influenced by neuropathological effects on synaptogenesis, synaptic pruning, and myelination (Selemon & Goldman-Rakic, 1999; Tamnes *et al.* 2010). Patients with schizophrenia have been found to exhibit widespread reductions in cortical thickness (Goldman *et al.* 2009; Rimol *et al.* 2010), which implicates cortical thinning as a potential contributor to the symptoms of this condition, including AVHs. However, only a small number of studies have directly compared cortical thickness between schizophrenia patients with AVHs and those without AVHs (non-AVHs). Two of these were region of interest (ROI) studies that focused on auditory areas, and though both found that AVHs were associated with cortical thinning in the Heschl's gyrus, this was in the left hemisphere for one (Mφrch-Johnsen *et al.* 2017) but in the right hemisphere for the other (Chen *et al.* 2015). A further study used an alternative, vertex-wise analysis and found AVHs to be associated not only with cortical thinning in language areas of the dominant hemisphere, but also with increased thickness in regions relating to self-monitoring (van Swam *et al.* 2012). A vertex-wise analysis of the whole brain examines each vertex on the cortex, and therefore allows the entire cortex to be explored rather than only a limited selection of predefined ROIs. Given the currently limited and inconsistent evidence, the extent and nature of contributions that cortical thinning makes to AVHs remains to be determined.

The aim of the current study was to investigate associations between cortical thinning and AVHs in schizophrenia patients. Rather than choosing brain regions a priori, we used a data-driven, whole brain approach that could produce a broader picture of how cortical thickness relates to AVHs. Further, we obtained participants from four different sites, giving us a relatively large overall sample size as well as inherent replication. We hypothesized that, compared with schizophrenia patients without AVHs, patients with AVHs would show cortical thinning in language-related brain regions. We also anticipated that the amount of thinning in these regions would be related to the extent or severity of AVHs.

Materials and methods

Participants

A total of 263 patients with schizophrenia were recruited from four hospitals (centers) in China: Peking University Six Hospital (PKUH6, $n = 69$); Beijing Huilongguan Hospital (HLG, $n = 55$); Xijing Hospital (XJ, $n = 73$); and Henan Mental Hospital (HM, $n = 66$).

Schizophrenia diagnoses were confirmed by psychiatrists using the Structured Clinical Interview for DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) Axis I Disorders (SCID-I, patient edition). The exclusion criteria included any other current neurologic disorder, a history of other serious medical illness, substance dependence, pregnancy, electroconvulsive therapy within the past 6 months, or a diagnosis of any other Axis I disorder. A total of 115 patients were assigned to an AVH group based on a score of 4 or more on the hallucination assessment (P3) sub-scale of the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Another 93 patients had never experienced hallucinations, as indicated by self-report and a P3 score of 2 or less, and were assigned to a non-AVH group. We excluded 55 patients with a P3 score of 3 from these groups, as they experience AVHs only occasionally. We evaluated AVH severity in the AVH group, using the Auditory Hallucinations Rating Scale (AHRS) (Hoffman *et al.* 2003). A group of 261 healthy controls (HCs) were recruited from the local community near each center through advertisements. None of the HCs had a personal history of psychiatric illness, or a family history of psychosis among first-, second-, or third-degree relatives. All of the study participants were Han Chinese in origin, right-handed, and had no contraindications to magnetic resonance imaging (MRI) scanning. The AVH, non-AVH, and HC groups were all matched for age and gender. The study was approved by the local ethical review board at each center. All participants provided written informed consent.

MRI data acquisition

The MRI scanners used in this study were all from 3T Siemens. Scanning protocols for all four centers were overseen by a single, experienced expert to ensure

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equivalent and high-quality data acquisition. T1-weighted MPRAGE structural MRI scans were obtained using the following optimized acquisition parameters: repetition time = 2530 ms; echo time (TE) = 3.44 ms (an exception was TE = 2.43 ms for the HM center); inversion time = 1100 ms; flip angle = 7°; matrix size = 256 × 256 × 192; and voxel size = 1 × 1 × 1 mm^3. Foam pads and earplugs were used to reduce head motion and scanner noise.

Cortical thickness measurements

The images were processed using the full stream in the publicly available FreeSurfer stable release 5.3.0 (http://surfer.nmr.mgh.harvard.edu/), which has been described and validated elsewhere (Dale *et al.* 1999; Fischl *et al.* 1999; Fischl & Dale, 2000). In brief, the following stages were included: Talairach transformation, intensity inhomogeneity correction, removal of non-brain tissues, intensity normalization, tissue segmentation, automated correction of topology defects, and surface deformation to form the boundary surface triangulations. The generated cortical surfaces were then carefully reviewed and manually edited for technical accuracy. Manual editing included (1) pial edits, and (2) white matter and control point edits conducted using tkmedit. The pial edits were required if the pial surface appeared not to follow the gray matter/cerebrospinal fluid boundary in the volume (e.g. parts of the pial surface have extended into the dura or cerebellum). White matter and control point edits were made where white matter regions were classified as non-white matter. Vertex-wise cortical thickness was then calculated as the shortest distance between the white and pial surface at vertices over the entire cortical mantle. Measurements for each vertex were mapped onto a common spherical coordinate system. The maps were smoothed using a Gaussian kernel of full width at half maximum of 10 mm.

Statistical analysis

The demographic characteristics of the groups were compared using analysis of variance and χ^2 tests.

We analyzed group × center interaction effects and main effects of group (i.e. AVH, non-AVH, and HC) at each vertex on the surface mantle. These analyses were performed with FreeSurfer 'command-line' group analysis stream using a general linear model. Group × center interaction effects were controlled for age and gender. We also controlled for center when modeling main effects of group. To correct for multiple comparisons, a false discovery rate approach with a threshold of $p < 0.05$ was used. Subsequent comparisons among all three groups were performed in the regions with significant main effects of group using post hoc two-sample *t* tests with a Bonferroni-corrected threshold of $p < 0.016$ (i.e. 0.05/3 groups).

In order to assess the extent of replication and consistency across our four centers, we used a meta-analytic method for all brain regions showing significant effects. The meta-analysis was conducted with the metafor package in R (Viechtbauer, 2010). Hedge's *g* was used as the measure of effect size to provide an unbiased standardized mean difference that incorporates a correction for small sample sizes. Random-effects models were used for the meta-analyses in consideration of the potential variation caused by having center as a factor. Spearman correlations were used to assess relationships between cortical thickness and hallucination assessment (P3) scores across all schizophrenia patients (i.e. those with a score of 3 were included alongside the AVH and non-AVH groups), and relationships between cortical thickness and AHRS scores within the AVH group, adjusted for age, gender, and center.

Results

Demographic and clinical characteristics

Demographic and clinical characteristics of the AVH, non-AVH, and HC groups are presented in Table 1. There were no statistically significant differences in age or gender distribution among the groups, but both the AVH and non-AVH groups had significantly fewer years of education than HCs (post hoc results for AVH *v.* non-AVH, $p = 0.770$; AVH *v.* HC, $p = 0.003$; non-AVH *v.* HC, $p < 0.001$). The AVH group not only had significantly higher hallucination scores, but also significantly higher PANSS total scores than the non-AVH group. The AVH and non-AVH groups did not differ in duration of illness; age of onset; medication dosage; or positive (excluding P3), negative, and general symptom scores.

Cortical thickness

We found main effects of group for cortical thickness, mostly in prefrontal and temporal areas, and the insula (online Supplementary Fig. S1). Post hoc analyses revealed a significantly thinner middle part of the left middle temporal gyrus (MTG, cluster size = 319.83 mm^2) for the AVH group than for the non-AVH group (Fig. 1*a*). The thickness of this region was not significantly different between the non-AVH and HC groups (Fig. 1*b*). Results of post hoc analyses demonstrated that both the AVH and non-AVH patient groups showed cortical thinning compared with the HC group. The AVH group had significant thinning in a number of regions across the frontal, temporal, insula, and occipital lobes, while the non-AVH group

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Table 1. *Demographic and clinical characteristics of the participants*

	AVH $N = 115$	non-AVH $N = 93$	HC $N = 261$	Statistics $F/\chi^2/t$	p
Age, years	26.41 (5.66)	27.31 (5.06)	26.83 (5.47)	$F = 0.71$	0.49
Gender (male:female)	52:63	47:46	137:124	$\chi^2 = 1.69$	0.43
Education, years	12.37 (3.75)	11.76 (3.97)	13.68 (3.43)	$F = 11.73$[a]	<0.001
Duration of illness, months	49.45 (51.49)	48.06 (41.11)		$t = 0.21$	0.83
Age of onset, years	22.92 (4.91)	24.12 (5.61)		$t = -1.64$	0.10
CPZ-eq at scan (mg/d)[b]	416.2 (186.6)	379.5 (198.8)		$t = 1.13$	0.26
PANSS					
P3 (hallucinations)	5.03 (0.78)	1.29 (0.46)		$t = 43.04$	<0.001
Positive (excluding P3)	20.21 (3.69)	20.25 (3.35)		$t = -0.07$	0.94
Negative	18.27 (4.81)	18.34 (5.41)		$t = -0.1$	0.92
General	37.52 (5.65)	38.53 (5.17)		$t = -1.34$	0.18
Total	81.04 (9.08)	77.88 (8.37)		$t = 2.61$	0.01
AHRS	23.43 (6.73)				

AHRS, Auditory Hallucinations Rating Scale; AVH, schizophrenia patients with auditory verbal hallucinations; CPZ-eq, chlorpromazine equivalents; HC, healthy controls; non-AVH, schizophrenia patients without auditory verbal hallucinations; PANSS, Positive and Negative Syndrome Scale.

Mean and S.D. are reported unless otherwise specified.

[a] Post hoc tests revealed significantly less years of education for both patient groups than for the healthy controls.

[b] Data were missing for 47 AVH and 20 non-AVH patients.

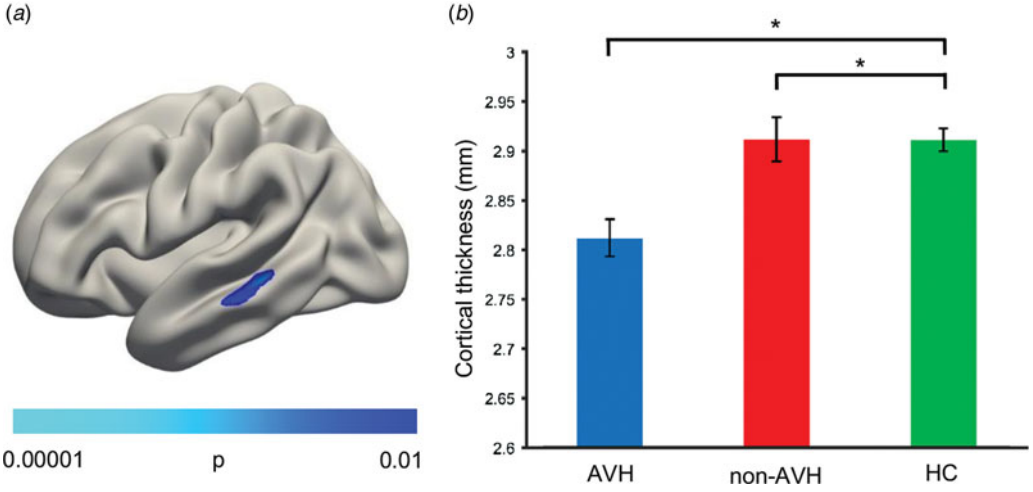

Fig. 1. Cortical thickness comparisons among AVH, non-AVH, and HC groups. (*a*) The AVH group showed a thinner left MTG than the non-AVH group. The color bar indicates p values. (*b*) Average cortical thickness in the left MTG; error bars represent the standard error of the mean; *$p < 0.001$. AVH, patients with auditory verbal hallucinations; non-AVH, patients without auditory verbal hallucinations; MTG, middle temporal gyrus; HC, healthy controls.

had thinning that was more spatially concentrated (online Supplementary Fig. S1). Our meta-analysis demonstrated the consistency of these results across the four centers (Fig. 2), as the levels of heterogeneity measured by the I^2 statistic were low, and no significant group × center interaction effects were observed across the whole brain. The effect sizes for the difference in left MTG thickness between AVH and non-AVH groups across our four centers were between −0.89 and −0.24. There was a negative association between left MTG thickness and hallucination assessment (P3) scores across all schizophrenia patients ($n = 263$, $r = -0.15$, $p = 0.015$), but no significant association between left MTG thickness and either AHRS ($n = 115$, $r = 0.08$, $p = 0.388$) or P3 ($n = 115$, $r = 0.13$, $p = 0.179$) scores in the AVH group.

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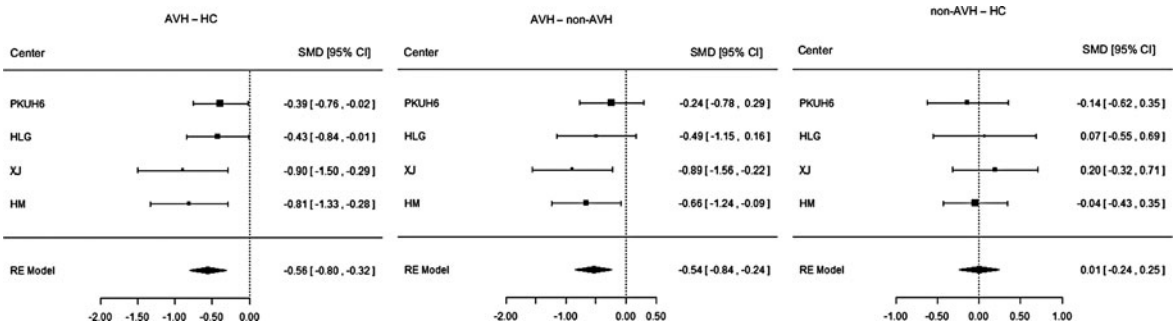

Fig. 2. Forest plots showing differences in thickness of the left MTG between pairs of groups at each center: AVH, non-AVH and a HC group. Values are the SMD and 95% CI. The size of the black squares representing mean values for a center is proportional to the weight assigned to that center in the pooled estimate using a RE model. AVH, patients with auditory verbal hallucinations; non-AVH, patients without auditory verbal hallucinations; MTG, middle temporal gyrus; HC, healthy controls; SMD, standard mean difference; CI, confidence interval; RE, random-effects.

Discussion

The present study used an automated, data-driven approach to investigate whether abnormalities in cortical thickness are associated with AVHs in patients with schizophrenia. We performed surface-based, vertex-wise comparisons of cortical thickness among three groups of participants: schizophrenia patients with AVHs, schizophrenia patients without AVHs, and HCs. Compared with HCs, both groups of patients showed cortical thinning in numerous regions of the frontal and temporal lobes. However, patients with AVHs showed thinning of the middle of the left MTG compared not only with HCs, but also with patients without AVHs.

Our finding of an association between AVHs and thinning of the MTG is consistent with the temporal lobe playing critical roles in auditory and language processing (Cabeza & Nyberg, 2000), and being the brain area most commonly implicated in AVHs (Barta *et al.* 1990; Flaum *et al.* 1995; Levitan *et al.* 1999; Rajarethinam *et al.* 2000; Onitsuka *et al.* 2004; Neckelmann *et al.* 2006; Allen *et al.* 2008; Palaniyappan *et al.* 2012; van Swam *et al.* 2012; Modinos *et al.* 2013). Onitsuka *et al.* (2004) reported that smaller gray matter volume in the left MTG correlated with more severe hallucinations. In addition, functional activity analyses using functional MRI or positron emission tomography have demonstrated dysfunctional activations associated with auditory hallucinations in the MTG (McGuire *et al.* 1995; Woodruff *et al.* 1995; Lennox *et al.* 1999; Jardri *et al.* 2011). The MTG is a pivotal component of language pathways, with connections to frontal and other brain regions for language (Glasser & Rilling, 2008; Xu *et al.* 2015), and thus well placed to influence the development and experience of AVHs. A role for the MTG in AVHs among schizophrenia patients is also consistent with schizophrenia being a disorder of neurodevelopment (Lewis & Levitt, 2002). This is because the MTG is a phylogenetically late-developing region (Gogtay *et al.* 2004), with no homology in non-human primates (Binney *et al.* 2012), and can thus express a high degree of inter-individual variability in morphology caused by differences in neurodevelopmental processes such as neuronal migration and differentiation, intra- and inter-areal connections of nerve cells, synaptic development, and cytoarchitectonic formation (Rakic, 1988; Sanes *et al.* 2011).

Previous research has suggested that AVHs could be related to abnormalities in the inner monitoring of cognitive processes (Frith & Done, 1988) or the misinterpretation of inner speech (Catani & ffytche, 2005). Functional studies have implicated the left MTG in this process, with the area showing reduced activation in schizophrenia patients with AVHs during a task that involved monitoring inner speech (McGuire *et al.* 1995; Shergill *et al.* 2000). A feed-forward neurocognitive model of AVH proposed that, as one of the brain regions responsible for speech processing, the MTG is engaged when there is a mismatch between the perceived and predicted results of inner speech activity (Frith & Done, 1988; Seal *et al.* 2004). However, the neural mechanisms by which thinning of the MTG could contribute to AVHs are yet to be determined, though could be related to the neuroanatomical changes associated with thinning, including a loss of neurons or neuropils, reduced neuron size, or altered pruning, which may cause dendritic spine loss (Selemon & Goldman-Rakic, 1999; Sun *et al.* 2009; Moyer *et al.* 2015).

Our results show the importance of making direct comparisons between patients with AVHs and those without AVHs, rather than just between patients and HCs as some previous studies have done (Barta *et al.* 1990; Onitsuka *et al.* 2004; Neckelmann *et al.* 2006).

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Nevertheless, our findings do differ from those of previous studies that also compared patients with AVHs and patients without AVHs (van Swam *et al.* 2012; Chen *et al.* 2015; Mφrch-Johnsen *et al.* 2017). Two ROI-based studies found an involvement of the left or right Heschl's gyrus (Chen *et al.* 2015; Mφrch-Johnsen *et al.* 2017). Van Swam *et al.* (2012) reported increased thickness in the left middle frontal, posterior cingulate, parahippocampal and postcentral areas, and decreased thickness in the right posterior inferior temporal, postcentral and visual cortices. One possible explanation for the divergent findings between studies relates to differences in the patients investigated, including sample origin, age, duration of illness, and medication usage. For instance, in two of the studies with different results, the AVH group had a significantly longer duration of illness than the non-AVH group (mean difference of 2.6 and 5.9 years for Mφrch-Johnsen *et al.* 2017 and van Swam *et al.* 2012, respectively). This may potentially confound the results, because thinning has been shown to develop excessively over time in the frontal and temporal regions (van Haren *et al.* 2011). We ensured that our AVH and non-AVH patient groups were very closely matched on duration of illness, which at around 4 years was also <5.7–27 years of the other studies. Our ability to detect a significant difference between AVH and non-AVH groups, despite the shorter duration of illness, may have been facilitated by the increased statistical power afforded by having a relatively large sample of 208 participants, as compared with only 49 participants in the study by Chen *et al.* (2015).

Confidence in the validity of our result comes from them being consistent across our four separate centers, as demonstrated using meta-analysis. There is also supporting evidence in our finding that a thinner left MTG was associated with greater hallucination assessment scores. This is concordant with Onitsuka *et al.* (2004), who reported a negative correlation between structural abnormalities in the left MTG and scores on the global rating of hallucinations on the Scale for the Assessment of Positive Symptoms (SAPS). The present study did not find significant correlations between cortical thinning and P3 or AHRS in the AVH group. Most previous studies did not report correlations between hallucination symptom severity and brain structure (van Swam *et al.* 2012; Benetti *et al.* 2015; Garrison *et al.* 2015; Mφrch-Johnsen *et al.* 2017), but one study found inverse correlations with right Heschl's gyrus (Chen *et al.* 2015). There not being a correlation between P3 scores and cortical thickness could be because the range of both variables is restricted in the AVH group relative to all patients. A restricted range of cortical thickness values could similarly help explain the lack of correlation with AHRS scores, as could the presence in the AHRS of items such as belief in the origin of voices heard and the amount and impact of negative content, which likely involve multiple brain regions beyond the MTG.

Strengths of our study include a relatively large sample, which can enhance statistical power and thereby facilitate the detection of abnormalities associated with AVHs. In addition, the AVH and non-AVH groups were matched on a number of demographic and clinical variables, including age, gender, education level, handedness, ethnicity, duration of illness, age of onset, antipsychotic medication, and positive (excluding P3), negative and general symptoms. This helped to control patient-level variability and minimize any influence of confounding factors such as racial differences, medication effects, and other positive psychotic symptoms. Because all of our participants were Han Chinese, how well our findings generalize to other racial/ethnic groups needs to be investigated. Nevertheless, the present study has some limitations. First, the prospective meta-analysis may result in a somewhat circular analysis because it used the same data as for ROI selection. However, the overall claim of the present paper is not dependent on the results of our meta-analysis, and we believe the ROI-based meta-analysis supplements the primary results by assessing the contribution of each center to the pattern of group differences, as well as the consistency across our multiple centers. A second limitation is the possible confounding effects of antipsychotic medication. We were missing data on medication use for 32% of the patients (missing $n = 67$ out of $n = 208$ patients) and for this reason did not adjust for medication use in our analysis.

In conclusion, the present study demonstrated cortical thinning in the left MTG specific to schizophrenia patients with AVHs. This finding was replicated across four centers and further validated by an inverse correlation between thickness of this region and hallucination assessment scores. Our finding further implicates the temporal lobe in AVHs, and helps in understanding the neuroanatomical basis for these often devastating symptoms. While thinning of the MTG could contribute to abnormal monitoring of internal speech, the precise involvement of the MTG in AVHs remains to be determined.

Supplementary Material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717001520.

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Declaration of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Allen P, Larøi F, McGuire PK, Aleman A (2008). The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neuroscience & Biobehavioral Reviews* **32**, 175–191.

Andreasen NC, Flaum M (1991). Schizophrenia: the characteristic symptoms. *Schizophrenia Bulletin* **17**, 27–49.

Barta PE, Pearlson GD, Powers RE, Richards SS, Tune LE (1990). Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. *American Journal of Psychiatry* **147**, 1457–1462.

Benetti S, Pettersson-Yeo W, Allen P, Catani M, Williams S, Barsaglini A, Kambeitz-Ilankovic LM, McGuire P, Mechelli A (2015). Auditory verbal hallucinations and brain dysconnectivity in the perisylvian language network: a multimodal investigation. *Schizophrenia Bulletin* **41**, 192–200.

Binney RJ, Parker GJ, Ralph MAL (2012). Convergent connectivity and graded specialization in the rostral human temporal lobe as revealed by diffusion-weighted imaging probabilistic tractography. *Journal of Cognitive Neuroscience* **24**, 1998–2014.

Cabeza R, Nyberg L (2000). Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience* **12**, 1–47.

Catani M, ffytche DH (2005). The rises and falls of disconnection syndromes. *Brain* **128**, 2224–2239.

Chen X, Liang S, Pu W, Song Y, Mwansisya TE, Yang Q, Liu H, Liu Z, Shan B, Xue Z (2015). Reduced cortical thickness in right Heschl's gyrus associated with auditory verbal hallucinations severity in first-episode schizophrenia. *BMC Psychiatry* **15**, 152.

Dale AM, Fischl B, Sereno MI (1999). Cortical surface-based analysis. I. Segmentation and surface reconstruction. *NeuroImage* **9**, 179–194.

Fischl B, Dale AM (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences* **97**, 11050–11055.

Fischl B, Sereno MI, Dale AM (1999). Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *NeuroImage* **9**, 195–207.

Flaum M, O'Leary DS, Swayze VW, Miller DD, Arndt S, Andreasen NC (1995). Symptom dimensions and brain morphology in schizophrenia and related psychotic disorders. *Journal of Psychiatric Research* **29**, 261–276.

Frith CD, Done DJ (1988). Towards a neuropsychology of schizophrenia. *British Journal of Psychiatry* **153**, 437–443.

Garrison JR, Fernyhough C, McCarthy-Jones S, Haggard M, Australian Schizophrenia Research Bank, Simons JS (2015). Paracingulate sulcus morphology is associated with hallucinations in the human brain. *Nature Communications* **6**, 8956.

Giraud AL, Kell C, Thierfelder C, Sterzer P, Russ MO, Preibisch C, Kleinschmidt A (2004). Contributions of sensory input, auditory search and verbal comprehension to cortical activity during speech processing. *Cerebral Cortex* **14**, 247–255.

Glasser MF, Rilling JK (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex* **18**, 2471–2482.

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences* **101**, 8174–8179.

Goldman AL, Pezawas L, Mattay VS, Fischl B, Verchinski BA, Chen Q, Weinberger DR, Meyer-Lindenberg A (2009). Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Archives of General Psychiatry* **66**, 467–477.

Hoffman RE (2008). Auditory/verbal hallucinations, speech perception neurocircuitry, and the social deafferentation hypothesis. *Clinical EEG and Neuroscience* **39**, 87–90.

Hoffman RE, Hawkins KA, Gueorguieva R, Boutros NN, Rachid F, Carroll K, Krystal JH (2003). Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Archives of General Psychiatry* **60**, 49–56.

Jardri R, Pouchet A, Pins D, Thomas P (2011). Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *American Journal of Psychiatry* **168**, 73–81.

Karnath HO (2001). New insights into the functions of the superior temporal cortex. *Nature Reviews Neuroscience* **2**, 568–576.

Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Lennox BR, Park SB, Jones PB, Morris PG (1999). Spatial and temporal mapping of neural activity associated with auditory hallucinations. *Lancet* **353**, 644.

Levitan C, Ward PB, Catts SV (1999). Superior temporal gyral volumes and laterality correlates of auditory hallucinations in schizophrenia. *Biological Psychiatry* **46**, 955–962.

Lewis DA, Levitt P (2002). Schizophrenia as a disorder of neurodevelopment. *Annual Review of Neuroscience* **25**, 409–432.

McGuire PK, David AS, Murray RM, Frackowiak RSJ, Frith CD, Wright I, Silbersweig DA (1995). Abnormal monitoring of inner speech: a physiological basis for auditory hallucinations. *Lancet* **346**, 596–600.

Modinos G, Costafreda SG, van Tol MJ, McGuire PK, 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.

Moyer CE, Shelton MA, Sweet RA (2015). Dendritic spine alterations in schizophrenia. *Neuroscience Letters* **601**, 46–53.

Mørch-Johnsen L, Nesvåg R, Jørgensen KN, Lange EH, Hartberg CB, Haukvik UK, Kompus K, Westerhausen R, Osnes K, Andreassen OA, Melle I, Hugdahl K, Agartz I (2017). Auditory cortex characteristics in schizophrenia: associations with auditory hallucinations. *Schizophrenia Bulletin* **43**, 75–83.

Neckelmann G, Specht K, Lund A, Ersland L, Smievoll AI, Neckelmann D, Hugdahl K (2006). MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *International Journal of Neuroscience* **116**, 9–23.

Onitsuka T, Shenton ME, Salisbury DF, Dickey CC, Kasai K, Toner SK, Frumin M, Kikinis R, Jolesz FA, McCarley RW (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: an MRI study. *American Journal of Psychiatry* **161**, 1603–1611.

Palaniyappan L, Balain V, Radua J, Liddle PF (2012). Structural correlates of auditory hallucinations in schizophrenia: a meta-analysis. *Schizophrenia Research* **137**, 169–173.

Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, Jacobson K, Lyons MJ, Grant MD, Franz CE, Xian H, Tsuang M, Fischl B, Seidman L, Dale A, Kremen WS (2009). Distinct genetic influences on cortical surface area and cortical thickness. *Cerebral Cortex* **19**, 2728–2735.

Rajarethinam RP, DeQuardo JR, Nalepa R, Tandon R (2000). Superior temporal gyrus in schizophrenia: a volumetric magnetic resonance imaging study. *Schizophrenia Research* **41**, 303–312.

Rakic P (1988). Specification of cerebral cortical areas. *Science* **241**, 170–176.

Rimol LM, Hartberg CB, Nesvåg R, Fennema-Notestine C, Hagler Jr. DJ, Pung CJ, Jennings RG, Haukvik UK, Lange E, Nakstad PH, Melle I, Andreassen OA, Dale AM, Agartz I (2010). Cortical thickness and subcortical volumes in schizophrenia and bipolar disorder. *Biological Psychiatry* **68**, 41–50.

Sanes DH, Reh TA, Harris WA (2011). *Development of the Nervous System*. Academic Press: Burlington, MA.

Seal ML, Aleman A, McGuire PK (2004). Compelling imagery, unanticipated speech and deceptive memory: neurocognitive models of auditory verbal hallucinations in schizophrenia. *Cognitive Neuropsychiatry* **9**, 43–72.

Selemon LD, Goldman-Rakic PS (1999). The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biological Psychiatry* **45**, 17–25.

Shergill SS, Brammer MJ, Williams SCR, Murray RM, McGuire PK (2000). Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Archives of General Psychiatry* **57**, 1033–1038.

Sun D, Stuart GW, Jenkinson M, Wood SJ, McGorry PD, Velakoulis D, van Erp TG, Thompson PM, Toga AW, Smith DJ, Cannon TD, Pantelis C (2009). Brain surface contraction mapped in first-episode schizophrenia: a longitudinal magnetic resonance imaging study. *Molecular Psychiatry* **14**, 976–986.

Tamnes CK, Ostby Y, Fjell AM, Westlye LT, Due-Tonnessen P, Walhovd KB (2010). Brain maturation in adolescence and young adulthood: regional age-related changes in cortical thickness and white matter volume and microstructure. *Cerebral Cortex* **20**, 534–548.

van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry* **68**, 871–880.

van Swam C, Federspiel A, Hubl D, Wiest R, Boesch C, Vermathen P, Kreis R, Strik W, Dierks T (2012). Possible dysregulation of cortical plasticity in auditory verbal hallucinations – a cortical thickness study in schizophrenia. *Journal of Psychiatric Research* **46**, 1015–1023.

Viechtbauer W (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* **36**, 1–48.

Woodruff P, Brammer M, Mellers J, Wright I, Bullmore E, Williams S (1995). Auditory hallucinations and perception of external speech. *Lancet* **346**, 1035.

Xu J, Wang J, Fan L, Li H, Zhang W, Hu Q, Jiang T (2015). Tractography-based parcellation of the human middle temporal gyrus. *Scientific Reports* **5**, 18883.