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"Where Do Auditory Hallucinations Come From?"—A Brain Morphometry Study of Schizophrenia Patients With Inner or Outer Space Hallucinations

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Auditory verbal hallucinations are a cardinal symptom of schizophrenia. Bleuler and Kraepelin distinguished 2 main classes of hallucinations: hallucinations heard outside the head (outer space, or external, hallucinations) and hallucinations heard inside the head (inner space, or internal, hallucinations). This distinction has been confirmed by recent phenomenological studies that identified 3 independent dimensions in auditory hallucinations: language complexity, self-other misattribution, and spatial location. Brain imaging studies in schizophrenia patients with auditory hallucinations have already investigated language complexity and self-other misattribution, but the neural substrate of hallucination spatial location remains unknown. Magnetic resonance images of 45 right-handed patients with schizophrenia and persistent auditory hallucinations and 20 healthy right-handed subjects were acquired. Two homogeneous subgroups of patients were defined based on the hallucination spatial location: patients with only outer space hallucinations ($N = 12$) and patients with only inner space hallucinations ($N = 15$). Between-group differences were then assessed using 2 complementary brain morphometry approaches: voxel-based morphometry and sulcus-based morphometry. Convergent anatomical differences were detected between the patient subgroups in the right temporoparietal junction (rTPJ). In comparison to healthy subjects, opposite deviations in white matter volumes and sulcus displacements were found in patients with inner space hallucination and patients with outer space hallucination. The current results indicate that spatial location of auditory hallucinations is associated with the rTPJ anatomy, a key region of the "where" auditory pathway. The detected tilt in the sulcal junction suggests deviations during early brain maturation, when the superior temporal sulcus and its anterior terminal branch appear and merge.

Key words: hallucinations/spatial location/brain anatomy/MRI/schizophrenia/"where pathway"/temporoparietal junction

Introduction

Auditory hallucinations are cardinal for the diagnostic of schizophrenia,[1] but their clinical characteristics, eg, clarity, familiarity, number, loudness, content, or spatial location, are variable among patients.[2–5] Spatial location was considered a main clinical feature in classical psychiatry that distinguished 2 types of auditory hallucinations: outer space hallucinations, with voices heard outside the head, and inner space hallucinations, with voices heard inside the head.[6,7] According to Bleuler, "Two main classes [*Hauptklasse*] in general are differentiated by the patients: the voices which come from outside like ordinary ones—and those projected into their own bodies that have hardly any sensory components and are mainly designated as inner voices (Baillarger's psychic hallucinations)."[7] Kraepelin also distinguished "inward voice in the thoughts" and "voices in the ear."[8]

This distinction was confirmed by dimensional approaches. Indeed, even though no clinical or demographic difference could be detected between patients with inner space hallucinations and patients with outer

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space hallucinations,[2–4] statistical analyses identified 3 independent dimensions in auditory hallucinations: spatial location, language complexity, and self-other misattribution.[5]

The neural substrates of language complexity and self-other misattribution have already been investigated in schizophrenia patients with auditory hallucinations.[9] Brain imaging studies have reported structural and functional deviations in brain regions involved in language (left temporal cortex and Broca's area)[10–16] and self-other misattribution (cingulate and left temporal cortex).[11,17] In contrast, the neural substrate of hallucination spatial location remains unknown.

Studies in animals[18,19] and healthy humans[20] have provided evidence that, similar to the visual system,[21] the auditory cortex may also be organized along 2 pathways. The presumed "what" pathway comprises a ventral stream that is dedicated to sound features, while the "where" pathway denotes a dorsal stream that communicates information about spatial location.[22] In the latter system, the inferior parietal region[23,24] and the posterior superior temporal gyrus (STG)[25,26] are supposed to play a central role in spatial processing of auditory stimuli. Although there is no certainty of the laterality of these functions,[20] previous studies have suggested right hemisphere predominance in auditory spatial tasks.[24–26]

Based on the literature reviewed herein, we a priori hypothesized that brain regions implicated in normal auditory spatial processing, ie, the right superior temporal or inferior parietal region, would underlie spatial location of auditory hallucinations. More specifically, we expected structural differences in the right temporoparietal region between patients with inner space hallucinations and those with outer space hallucinations. In order to test this hypothesis, we compared anatomical magnetic resonance images (MRIs) of patients with only inner space hallucinations, patients with only outer space hallucinations, and healthy subjects using 2 complementary approaches: voxel-based morphometry (VBM)[27] and sulcus-based morphometry.[28]

Methods

Participants

Forty-five right-handed[29] patients with schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition Revised] [*DSM-IV-R*][1]) and persistent auditory hallucinations (29 men, 16 women; mean age = 31.8 y, SD = 8.2) and 20 healthy right-handed subjects (12 men, 8 women; mean age = 31.9 y, SD = 7.4) were recruited. The absence of psychiatric symptoms in the latter group was confirmed by a senior psychiatrist using the Mini-International Neuropsychiatric Interview.[30] Hallucinations were considered persistent when they lasted for more than 1 year, despite adequate pharmacological treatment and provided they had occurred daily during the past 3 months. Exclusion criteria were substance abuse or dependence, any other *DSM-IV-R* axis I diagnosis, severe head injury, neurological disorders, and contraindications to MRI scanning. Approval of the study was obtained from the Paris (Pitié-Salpétrière) ethics committee. After complete description of the study to the subjects, written consent was obtained.

Auditory hallucinations were evaluated using the 11-item auditory hallucinations subscale of the Psychotic Symptom Ratings Scale (PSYRATS[31]), including a semi-structured interview by 2 independent senior psychiatrists (J.L.M., M.P.; interrater reliability $R = 0.76$) who assessed the items retrospectively over a 2-week period (see table 1 for results). In order to optimize the homogeneity of the patient samples with respect to their hallucination spatial location, only patients with a clear spatial location were included. The inner space hallucinations subgroup comprised 15 patients who scored 1 on the location item of the PSYRATS ("Voices sound like they are inside head only"), and the outer space hallucinations subgroup comprised 12 patients who scored 4 ("Voices sound like they are from outside the head only"). Severity of clinical symptoms was also assessed using the Scale for the Assessment of Positive Symptoms[32] and the Scale for the Assessment of Negative Symptoms.[33] All patients were treated with conventional or atypical antipsychotic drugs.

To assess the long-term stability of hallucination spatial location, patients were contacted again several years (mean = 4.78 y, SD = 0.97) after scanning by a psychiatrist (M.P.) blind to the spatial location of their hallucinations at the scanning time. Long-term stability over time, evaluated as the percentage of patients with no change in hallucination spatial location since scanning, was 100% in patients with outer space hallucinations and 80% in patients with inner space hallucinations. Four patients with outer space hallucinations were not included for stability evaluation (1 patient dead and 3 patients lost to follow-up).

Except for the spatial location, there was no statistically significant clinical or demographical difference between the patient subgroups (cf. table 1). The healthy subject group did not differ significantly from the patient groups with respect to age ($F_{2.44} = 1.02$, $P = .36$) or gender ($\chi^2 = 0.23$, $P = .89$).

MRI Acquisition

High-resolution T1 anatomical images were acquired with a 1.5T General Electric Signa System scanner (General Electric Medical Systems, Milwaukee, WI) using a Spoiled Gradient Recalled (SPGR) sequence that provided a high contrast between gray and white matter (3-D gradient-echo inversion-recovery sequence, time inversion = 2200 ms, time repetition = 2000 ms, flip angle 10°, field of view = 24, 124 slices of 1.2 mm thickness,

Table 1. Demographic and Clinical Characteristics of the Patient Subgroups, Which Significantly Differed From Each Other Only With Respect To the Location of Auditory Hallucinations (Bold Font)

	Outer Space Hallucination Subgroup (N = 12), Mean (SD)	Inner Space Hallucination Subgroup (N = 15), Mean (SD)	Group Comparisons
Age, y	35 (11)	31 (8)	W =105.5, P = .28
Gender			
Male	63%	66%	χ^2 = 0.19, P = .65
Age at first onset, y	20.9 (9.6)	22.3 (8.5)	W = 98.5, P = .24
Duration of illness, y	14.4 (11.3)	8.7 (8.4)	W = 55, P =.25
PSYRATS auditory hallucinations			
Frequency	3.1 (0.9)	3.6 (0.6)	W = 61, P = .12
Duration	3.0 (0.9)	3.3 (1.0)	W = 68, P = .26
Location	**4.0 (0.0)**	**1.0 (0.0)**	***W* = 180, *P* < .001**
Loudness	2.0 (0.6)	2.0 (0.6)	W = 94, P = .82
Beliefs	2.7 (1.3)	2.2 (1.2)	W = 112.5, P = .26
Amount of negative content of voices	2.6 (1.1)	2.2 (1.5)	W = 101, P = .58
Degree of negative content	2.7 (1.4)	2.3 (1.8)	W = 100, P = .62
Amount of distress	2.3 (1.1)	2.5 (1.3)	W = 81.5, P = .68
Intensity of distress	2.2 (1.2)	2.0 (1.2)	W = 101, P = .59
Disruption to life caused by voices	2.0 (1.0)	2.7 (1.1)	W = 63, P = .17
Controllability of voices	3.3 (0.8)	3.5 (0.5)	W = 80, P = .6
Total score	30.0 (5.0)	27.3 (5.4)	W = 119.5, P = .16
Long-term stability of hallucination location	100 %	80 %	χ^2 = 0.11, P =.73
SAPS total score	34.7 (16.2)	37.1 (20.5)	W = 87, P =.9
SANS total score	39.3 (29.2)	39.9 (32.2)	W = 92, P = .94
Laterality			
Annett scale	84 (19)	92 (12)	W = 69, P = .27
Antipsychotic medication			
Milligram chlorpromazine equivalent/d	570 (954)	429 (299)	W = 49, P = .48

Note: Differences in gender and stability of hallucinations were evaluated using chi-square statistics (χ^2), other variables using Wilcoxon statistics (W). PSYRATS, Psychotic Symptom Ratings Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

acquisition time = 6 min). Conjugate synthesis combined with interleaved acquisition resulted in 124 contiguous double-echo slices with voxel dimensions of 0.85 × 0.85 × 1.2 mm^3. These MRIs were adapted to the reconstruction of the fine individual cortical folds required for sulcus segmentation.

Data Analysis

Voxel-Based Morphometry. Differences in local gray and white matter volumes between healthy controls, patients with inner space hallucinations, and patients with outer space hallucinations were assessed using the 4 standard steps of optimized VBM[27] with SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/): tissue segmentation, nonlinear spatial normalization on customized gray and white matter templates, modulation, and spatial smoothing at 8 mm. Voxelwise differences in brain tissue volumes between the 3 groups were examined using analyses of covariance (ANCOVAs), with group and gender as factors and age as numeric covariate, and followed by post hoc comparisons (t test contrasts). All analyses were performed on the whole brain using a voxelwise threshold at $P < .05$, familywise error (FWE) corrected for multiple testing.

Sulcus-Based Morphometry. In each subject's raw MRI, cortical folds were first automatically segmented,[28] and thereafter sulci of interest were manually labelled[34] blind to the subject condition using Brainvisa software (http://brainvisa.info/). The cortical sulci corresponded to medial surfaces located in the cerebrospinal fluid between the 2 cortical banks. This definition of the sulci provides a stable localization that is not affected by variation in the gray matter/white matter contrast and sulcus opening or thickness.[28] Such sulcus-based morphometry has recently been used to investigate sulcus anatomy in patients with schizophrenia[10,35] and patients with affective disorders.[36,37]

Differences in sulcus morphometric data between the 3 groups were examined using ANCOVAs with group

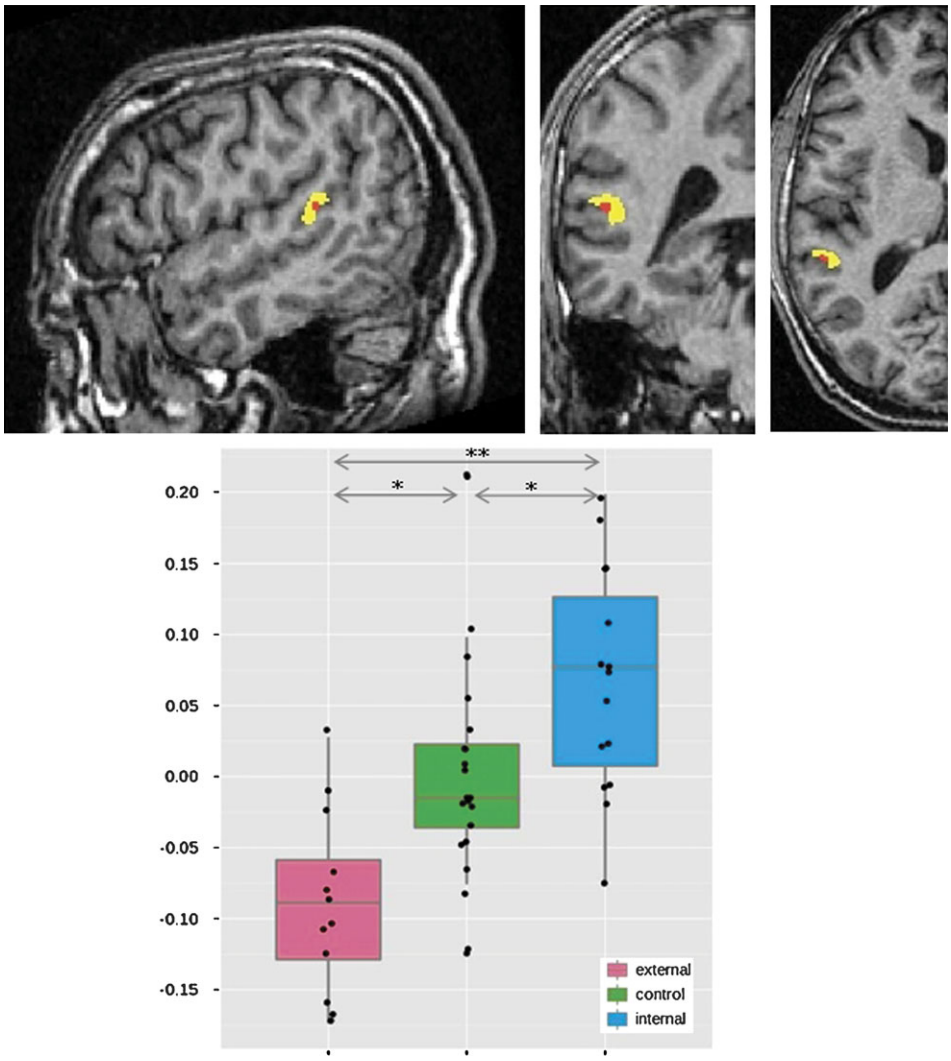

Fig. 1. White Matter Volume in the Right Temporoparietal Junction and Spatial Location of Hallucinations. (Up) White matter volume decrease in patients with outer space hallucinations in comparison to patients with inner space hallucinations (red: *P* corrected < .05; yellow: *P* uncorrected < .001, for illustration purpose). (Down) Box plot of white matter volumes at cluster voxel maximum (Talairach *x*, *y*, *z* = [54, −37, 13]) controlled for age and gender (pink: patients with outer space hallucinations, green: healthy controls, blue: patients with inner space hallucinations). ***P* corrected < .05 (whole-brain analysis); **P* corrected < .05 (small volume correction with the cluster of the contrast "inner space vs outer space" as mask).

and gender as factors and age as numeric covariate, and followed by post hoc comparisons (*t* test contrasts), as in VBM data analysis. Statistical analyses were carried out with R 2.5 software (http://www.r-project.org).

Results

Voxel-Based Morphometry

In comparison to patients with inner space hallucinations, patients with outer space hallucinations had decreased white matter volume in a single cluster of voxels located in the right STG, in the vicinity of the rTPJ (Montreal Neurological Institute coordinates *x*, *y*, *z* = [54, −37, 13], height threshold: $Z = 5.89$, *P corrected* = .02, cluster size = 21 mm^3) (figure 1). No other difference was found either in white matter or gray matter between patient subgroups, even at a less conservative threshold (*P* uncorrected < .001).

No significant gray or white matter volume difference was found in the whole brain between healthy subjects and patients with inner space hallucinations or between healthy subjects and patients with outer space hallucinations.

Of note, inspection of the white matter volume at the voxel maximum ([54, −37, 13]) ("inner space vs outer space" contrast) suggested a positive gradient between inner space hallucination, healthy, and outer space hallucination groups. Confirmatory analysis, using SPM2 small volume correction (SVC) with the cluster of the contrast "inner space vs outer space" as mask indicated significant opposite white matter deviations in the right STG in patient subgroups: in comparison to healthy

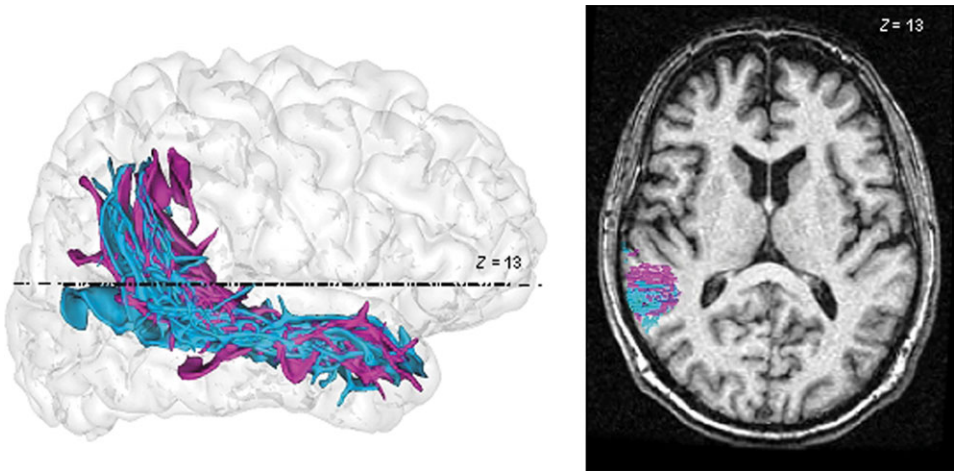

Fig. 2. Anterior-Posterior Variability of the Right Superior Temporal Sulcus (STS) and Its Anterior Branch (Also Called Angular Sulcus) in Schizophrenia Patients. Individual segmented sulci of patients with outer space hallucinations (pink) and inner space hallucinations (blue) were superimposed on a Montreal Neurological Institute (MNI) referential. (Left) The patient group sulci are shown on an individual's reconstructed right hemisphere cortex surface. (Right) The data are superimposed on the MRI of a subject from the study, at an axial slice ($z = 13$) where the maximum of voxel-based morphomery difference ($x, y, z = [54, -37, 13]$) was observed. Note the incomplete overlap between subgroups.

subjects, patients with inner space hallucinations had increased white matter volume, while patients with outer space hallucinations had decreased white matter volume (P corrected $< .05$; figure 1).

Addition of total tissue volumes as confounding covariates in the analyses did not change the results.

Sulcus-Based Morphometry

Differences detected with VBM have been shown to be potentially associated with a local sulcus displacement.[38,39] To test for such a sulcus displacement, we studied the position of the sulcus close to the VBM cluster ($x, y, z = [54, -37, 13]$).

The 3D reconstructions of individual sulci were therefore superimposed on the same referential as the VBM cluster with the individual nonlinear spatial transformation used for VBM analysis. Due to insufficient gray/white contrast, the sulcus segmentation of one patient with inner space hallucinations could not be processed. Visual inspection revealed that the VBM cluster was located in each subject in the rTPJ and intercepted, in some subjects, the superior temporal sulcus (STS) or its anterior terminal branch, but never the posterior terminal branch. In addition, visual inspection of the rTPJ z slices containing the VBM cluster suggested a difference in sulcus position between the patient subgroups (figure 2).

To quantify this difference of position, we defined in each subject's z slice the mean sulcal position by calculating the centre of the voxels (barycentre) that define the sulcus. (figure 3). The x (left-right) and y (anterior-posterior) coordinates of barycentres were compared between healthy subjects, patients with inner space hallucinations, and patients with outer space hallucinations. The analysis of the barycentres coordinates in z slices containing STS and its branches indicated significant group main effects in a set of contiguous rTPJ axial slices (-7, 15) (F statistic ranged from 3.34 to 6.75, $P < .05$).

Post hoc analyses revealed that in a subset of contiguous axial slices ($z = 0$–16) that corresponded to the localization of the sulcal junction between the right STS and its anterior branch; the barycentres were found to be more anteriorly positioned in patients with outer space hallucinations than in those with inner space hallucinations (T statistic ranged from 2.18 to 4.09, $P < .05$; figure 3). The anterior-posterior displacement was 4.8 mm ($P = .01$) in the axial slice ($z = 13$) where the VBM difference between patients with inner space hallucinations and patients with outer space hallucinations was maximum ($x, y, z = [54, -37, 13]$) (figure 3).

To further investigate the relationship between this anterior-posterior displacement and the spatial location of hallucinations, the clinical and demographic characteristics of individuals with extreme displacements were analyzed. Two subgroups of patients were defined based on the quartile position of the sulcal junction (ie, the y coordinates of the barycentres in the axial slice [$z = 13$]): the "anterior subgroup"—patients with the more anterior position ($N = 7$)—and the "posterior subgroup"—patients with the more posterior position ($N = 7$). The only characteristic that significantly differed between these 2 subgroups was the PSYRATS item 3 ("spatial location of hallucinations") (Wilcoxon $W = 35.5$, $P = .02$). Of note, the "posterior subgroup" was composed of 2 patients with inner space hallucinations and 5 patients with outer space hallucinations, and the

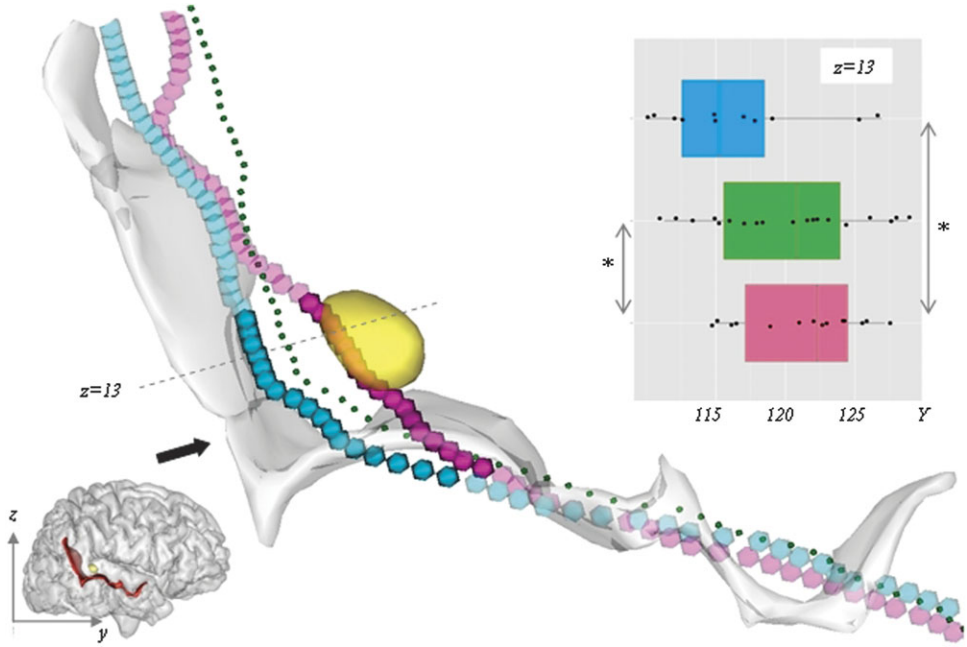

Fig. 3. Local Displacement of the Right Superior Temporal Sulcus and its Branch in Schizophrenia Patients and Healthy Subjects. In each axial *z*-slice, the position of the sulcus barycentre was averaged separately for patients with outer space hallucinations (pink spheres), patients with inner space hallucinations (blue spheres), and healthy subjects (green spheres). The yellow region indicates the VBM cluster where white matter volume was reduced in patients with outer space hallucinations in comparison to those with inner space hallucinations ($P < .001$, uncorrected for multiple testing for ease of visualization). These data are shown on a 3D reconstruction of one individual's right superior temporal sulcus and its branch (light gray). Around the junction between the right superior temporal sulcus and its branch (black arrow), the outer space hallucination subgroup showed an anterior displacement of barycentres, and the inner space hallucination subgroup a posterior displacement of barycentres, in comparison to the healthy group. This is also illustrated by the boxplot of the sulcus barycentre *y* coordinates ($z = 13$) in outer space hallucination subgroup, inner space hallucination subgroup, and healthy group. $*P < .05$.

"anterior subgroup" was composed of 6 patients with inner space hallucinations and 1 patient with outer space hallucinations ($\chi^2 = 4.66$, $P = .03$).

In addition, post hoc analyses indicated posterior, respectively anterior, displacement in a set of contiguous axial slices in patients with outer space hallucinations ($z = [10–13]$, t statistic ranged from 2.09 to 2.13, $P < .05$), respectively in patient with inner space hallucinations ($z = [3–4]$; t statistic ranged from 2.32 to 2.40; $P < .05$), in comparison to healthy subjects.

Discussion

In this first study investigating the neural substrate of hallucination spatial location, convergent anatomical differences between schizophrenia patients with internal hallucinations and patients with outer space hallucinations were detected using 2 complementary approaches in the rTPJ. Reduced white matter volume was found using VBM in the rTPJ of patients with outer space hallucinations compared with patients with inner space hallucinations. Further analysis revealed a sulcus displacement between the 2 patient subgroups around the junction of the STS and its anterior terminal branch (ie, the angular sulcus). In comparison to healthy subjects, opposite deviations in white matter volumes and sulcus displacements in rTPJ were found in patients with internal and patients with outer space hallucinations.

The spatial location of hallucinations is the main clinical factor related to these morphometric variations. Indeed, spatial location is the only factor that differed between the patient subgroups (cf. table 1), in line with the hypothesis that spatial location is an independent dimension of hallucinations.[2–5]

A general issue in assessing relationships between brain anatomy and psychiatric symptoms is the possible symptom instability.[10,40] Long-term stability of hallucination spatial location has been questioned. In a cross-sectional study, patients recently diagnosed with schizophrenia tended to report auditory hallucinations that were external, while those with longer histories described voices inside head, suggesting an internalization of the voices as the illness progressed.[3] This was not confirmed in another study reporting no association between age and spatial location of hallucinations.[4] In addition, it has been shown that in 80% of patients with hallucinations, the major hallucination characteristics did not change during the week preceding their assessment, in line with Bleuler observation that "in general schizophrenic hallucinations

are very prone to become stereotyped."[2,7] In the current sample of patients, the hallucination spatial location was longitudinally assessed and was found to be remarkably stable over several years.

The evaluation of phenomenological characteristics of the auditory hallucinations such as the spatial location largely depends on the reliability of the patient report.[41] Indeed, while most patients would accurately describe their experiences, some patients may exaggerate or minimize their experiences or may be unable to adequately describe them. In the current study, the lack of reliability evaluation may have induced noise and inconsistency in the symptoms measures and may underlie the wide range of variation in the morphometric data.

The same statistical design was used in voxel-based and sulcus-based morphometry in order to cross-validate the results obtained with each approach. False positives were limited in VBM using the FWE procedure based on random field theory[42] implemented in SPM2 software. Such approach could not be used for sulcus-based morphometry as the topology of the underlying random field was too complex to estimate. However, false positives in sulcus morphometry should be limited as it seems unlikely that the positions of sulcus barycentres differ by chance between the 2 patient subgroups in a set of $N = 17$ contiguous slices.

Spatial Location of Hallucinations and the rTPJ

White matter volume differences detected in the right STG, in the vicinity of the rTPJ, support our a priori hypothesis that spatial location of hallucinations share common neural resources with normal auditory location processes in the "where" auditory pathway. Indeed, this region has been implicated in normal auditory location by functional neuroimaging,[20,23,25,26] electrophysiology,[25,26,43] and studies with virtual lesions induced by transcranial magnetic stimulation.[44] The STG difference was localized to the right side, consistent with the presumed right hemisphere predominance in auditory spatial processing in humans.[24] One study on healthy volunteers reported increased activation in the left STG when healthy subjects heard voices "outside the head" in comparison to voices heard "inside the head."[45] However, this study was not designed to extract neural substrates to spatial location of voices, ie, shared neural substrates in both voices heard inside and voices heard outside the head. In addition, as suggested in Krumbholz et al,[46] the absence of expected contralateral activation in the right temporal cortex during audition of left lateralized "outside" stimuli in comparison to left lateralized "inside" stimuli[46] could suggest that hearing voices "outside the head" or "inside the head" both activated the right temporal cortex.[46] Such association between spatial location of auditory hallucinations and anatomical deviations in the "where" auditory pathway supports a recent cognitive model suggesting that key phenomenological features of hallucinations are linked to abnormal processing in the "what" and "where" pathways.[47]

Also, the present results are consistent with earlier observations in neglect syndrome patients.[48,49] Spatial neglect syndrome is a common neurological disturbance in which awareness of contralesional space is disrupted after unilateral (typically right-sided) stroke.[49] Although most research has focused on visual aspects of neglect, there is increasing evidence that patients show deficits in spatial localization of sounds as well. Even though the epicentre of the underlying brain damage in neglect syndrome has often been localized to the right parietal region,[50] recent studies on spatial awareness have suggested that such brain damage could, in fact, affect the right superior temporal cortex[48,51] or its junction with the parietal region.[15,52] Similarly to patients with neglect syndrome, patients with auditory hallucinations might provide a clinical model of spatial awareness specific to the auditory modality. Hence, our results suggest that within the rTPJ, the junction between STS and angular sulcus might be a key region for spatial awareness.

In schizophrenia, the right superior temporal region has repeatedly been associated with hallucinations in anatomical and functional brain imaging studies.[9,53] Functional impairment in this region during auditory verbal imagery in patients with hallucinations[15] supports its functional involvement in spatial location. Indeed, the act of imagining someone while speaking likely involves sound location processing. Discrepant results from studies that did not detect any association between this region and hallucinations[16] may result from designs not taking account the variability of hallucination phenomenology, including spatial location.[5]

Interestingly, the rTPJ has been associated with out-of-body experiences (OBEs), an illusory phenomenon.[54–56] OBE is a subjective episode in which people in near-death experience or in neurological conditions feel that their "self" is located outside their physical body. By combining multisensory information in a coordinated reference frame, rTPJ would be a key neural locus for self-processing and integration between personal and extrapersonal spaces.[54] It then might be speculated that the observed differences in rTPJ anatomy could contribute to differential attributions of spatial coordinates to hallucinations in an egocentric referential (external vs internal).

Sulcal Junction and Brain Maturation

The sulcal pattern observed in the adult brain results from fetal and childhood processes that shape the cortex anatomy from an initially smooth lissencephalic structure to a highly convoluted surface, constrained by a complex interaction between anatomical (cortical thickness and white matter connectivity) and functional

organization.[57–60] Differences in sulcal anatomy have been proposed to reflect developmental differences in functional and anatomical brain organization.[39,61] Hence, in the current context, differences in the anatamofunctional organization of the "where" pathway may lead to differences in STS anatomy as well as differences in spatial location of hallucinations. Our current results thus lead to the speculation that the preference for attaching either an "external" or "internal" location to auditory hallucinations could be associated with anatomical particularities of the junction between the right STS and its anterior branch. Given the wide range of variation in sulcal position in the control group and important overlap between groups (figure 3), one can consider that normal variation in the organization of the spatial mapping system leads to the variability in the spatial location of auditory hallucinations. Alternatively, deviations detected in patients can be considered pathological because sulcal positions were significantly different in patient subgroups in comparison to the control group.

Several schizophrenia studies have previously reported deviations in sulcus anatomy,[10,35,62–65] consistent with the common hypothesis that schizophrenia has a developmental component.[66] The deviation detected in the junction between the STS and its anterior branch suggests an early event that may have occurred between 25 and 29 weeks of gestation. Indeed, during normal development, the STS and its anterior branch first appear separately at 25–26 weeks and merge at about 28–29 weeks.[67,68] Many genetic, neurochemical processes and environmental factors contribute to the various stages of development from neuronal migration to cortex sulcation as a whole.[58,69–71] Pathological variations in some of these factors can presumably tilt the sulcus junction backward or forward. Hence, as sulcus morphology in an adult subject can be seen as the integration of both normative and pathological influences exerted on brain development, the "sulcal dysjunction" observed in patients might reflect an illness-associated developmental variation.

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