Neuroanatomy of 'Hearing Voices': A Frontotemporal Brain Structural Abnormality Associated with Auditory Hallucinations in Schizophrenia

Christian Gaser[1]*, Igor Nenadic[1]*, Hans-Peter Volz[1], Christian Büchel[2] and Heinrich Sauer[1]

[1]Department of Psychiatry, University of Jena, Philosophenweg 3, D-07743 Jena, Germany and [2]Department of Neurology, University of Hamburg, Martinistr. 52, D-20246 Hamburg, Germany

*These two authors contributed equally to the study

Auditory hallucinations are a frequent symptom in schizophrenia. While functional imaging studies have suggested the association of certain patterns of brain activity with sub-syndromes or single symptoms (e.g. positive symptoms such as hallucinations), there has been only limited evidence from structural imaging or post-mortem studies. In this study, we investigated the relation of local brain structural deficits to severity of auditory hallucinations, particularly in perisylvian areas previously reported to be involved in auditory hallucinations. In order to overcome certain limitations of conventional volumetric methods, we used deformation-based morphometry (DBM), a novel automated whole-brain morphometric technique, to assess local gray and white matter deficits in structural magnetic resonance images of 85 schizophrenia patients. We found severity of auditory hallucinations to be significantly correlated ($P < 0.001$) with volume loss in the left transverse temporal gyrus of Heschl (primary auditory cortex) and left (inferior) supramarginal gyrus, as well as middle/inferior right prefrontal gyri. This demonstrates a pattern of distributed structural abnormalities specific for auditory hallucinations and suggests hallucination-specific alterations in areas of a frontotemporal network for processing auditory information and language.

Keywords: auditory, cortex, hallucination, morphometry, prefrontal, schizophrenia

Introduction

Schizophrenia is a complex and heterogeneous psychotic disorder with a wide range of symptoms including delusions, hallucinations, formal thought disorder, altered affect and cognitive functioning. Previous neuroimaging studies have suggested certain patterns of brain activity to be associated with sub-syndromes (Liddle *et al.*, 1992; Schröder *et al.*, 1996) or single symptoms. Positive symptoms such as auditory hallucinations have been associated with superior temporal cortical dysfunction (e.g. Dierks *et al.*, 1999; Lennox *et al.*, 2000). However, it has been difficult to establish structural correlates of these functional findings (Weiss and Heckers, 1999).

Auditory hallucinations are probably one of the most frequent and most challenging symptoms in schizophrenia (David and Busatto, 1998). During the course of illness about two-thirds of patients will experience this symptom (David, 1994). Most often these are auditory–verbal hallucinations (i.e. 'hearing voices', often conversing or commenting on the patient), but might include simple noise, sounds or music as well. While much research has focused on neuropsychological approaches (David, 1994), we still know little about the underlying neurobiology and the mechanisms leading to the occurrence of this symptom. The functional neuroanatomy of auditory–verbal hallucinations has recently been addressed in functional neuroimaging studies. These have revealed transient brain activation accompanying auditory hallucinations (Silbersweig *et al.*, 1995; Weiss and Heckers, 1999). Activated areas primarily included language-related areas such as superior temporal cortical regions (Lennox *et al.*, 2000), including the primary auditory cortex in one study (Dierks *et al.*, 1999), Broca's area (McGuire *et al.*, 1993), as well as the basal ganglia and anterior cingulate (Silbersweig *et al.*, 1995). Electrophysiological studies have also linked the superior temporal (Ishii *et al.*, 2000) or temporoparietal region (Line *et al.*, 1998) to auditory hallucinations in schizophrenia.

While many magnetic resonance imaging (MRI) studies have shown volumetric changes in cortical and subcortical areas in the schizophrenic brain (Wright *et al.*, 2000; Shenton *et al.*, 2001), there are only few studies on correlations with specific symptoms. Two groups found evidence for smaller posterior superior temporal cortex in patients with formal thought disorder (Shenton *et al.*, 1992; Menon *et al.*, 1995). Some preliminary evidence also links the superior temporal cortex (Barta *et al.*, 1990) and the anterior cingulate (Noga *et al.*, 1995) to hallucinations. However, these MRI studies were limited in resolution of studied MR images, as well as restricted to the analysis of single pre-defined regions of interest.

In this study, we tried to find evidence for regionally specific alterations accompanying auditory hallucinations in schizophrenia. Based on the functional studies (Line *et al.*, 1998; Dierks *et al.*, 1999; Lennox *et al.*, 2000) and a previous structural MRI study (Barta *et al.*, 1990), we set up a specific regional hypothesis for the perisylvian areas, i.e. the superior temporal cortical areas extending along the Sylvian fissure, as well as Broca's area. We applied deformation-based morphometry (DBM), a novel fully automated whole-brain morphometric technique (Gaser *et al.*, 1999), to high-resolution MR images to test the hypothesis that severity of auditory hallucinations might be related to focal brain shrinkage in perisylvian areas. The DBM method might overcome limitations of conventional volumetric assessments of brain structure, assessing differences on the voxel level over the entire brain and minimizing user bias (Gaser *et al.*, 2001). We have previously applied this method to detect structural changes in patients with schizophrenia (Gaser *et al.*, 1999; Volz *et al.*, 2000) and compared the method to conventional volumetry (Gaser *et al.*, 2001).

Methods

Subjects

We studied 85 right-handed patients with schizophrenia (33 females, 52 males; mean age 36.2 years, SD ±10.9), who were all on stable neuroleptic medication. Analyses comparing this population to healthy controls were reported earlier (Gaser *et al.*, 1999). Patients were

recruited from in- and out-patient units. Psychiatrists unaware of any imaging data examined patients to establish a diagnosis of schizophrenia according to DSM-III-R criteria (American Psychiatric Association, 1987). First, patients were recruited for whom either the psychiatrist-in-charge or a research psychiatrist had established a clinical ICD-10 diagnosis of schizophrenia (International Classification of Diseases, World Health Organization), based on semi-structured interviews and ICD-10 criteria used in clinical practice. Chart review was also taken into account, but only as supplementary information. Diagnosis had to be confirmed by a second psychiatrist (consultant or research psychiatrist), according to both ICD-10 and DSM-III-R criteria, and assessed individual psychopathology. Thorough screening was performed for all patients to exclude other psychiatric or neurological diagnoses, a history of severe head trauma, any major medical conditions and previous or current substance dependence. Mean duration of illness was 8.9 years (SD ± 8.2) and the mean number of hospitalization was 4.0 (SD ± 3.6). Psychopathology was assessed by trained raters using the Scales for the Assessment of Negative Symptoms (SANS; total mean score 44.95 ± 21.5; Andreasen, 1983) and Positive Symptoms (SAPS, total mean score 20.88 ± 17.3; Andreasen, 1984). In order to obtain a single variable for the severity of hallucinations, we pooled the three single SAPS items for auditory hallucinations (general)', 'voices commenting' and 'voices conversing' (each ranging from 0 to 5) to a single score for each patient. Recruitment of patients was performed irrespective of the presence of auditory hallucinations. Thus, the sample included both patients with and without a history of auditory hallucinations. Most of the patients studied here enrolled in other studies or research protocols as well and therefore multiple (up to three) SANS and SAPS scores over a (variable) period of up to several weeks before or after scanning MR scanning were available. As auditory hallucinations are often transient, but brain structure is relatively stable, we decided in these cases to take the maximum score of patients achieved in a SANS/SAPS interview, as the potential error from underestimating hallucinations was expected to be much higher than overestimating the score value. This means that the score reflected the maximum of ongoing auditory hallucinations in the period of at least 1 week before the scanning session. Of the 85 patients, 56 patients did not shown any hallucinations and their pooled auditory hallucination (AH) score was zero. Twenty-nine patients had scores between 1 and 15 (the maximum possible value). The distribution of the pooled AH scores is displayed in Figure 1. Using these single SAPS items has the advantage of applying a well-established and validated rating system, which is used in many studies with schizophrenia patients and has good reliability in trained raters. The study was approved by the ethical review board of the University of Jena and, after an explanation of the scanning protocol, all participants gave written informed consent.

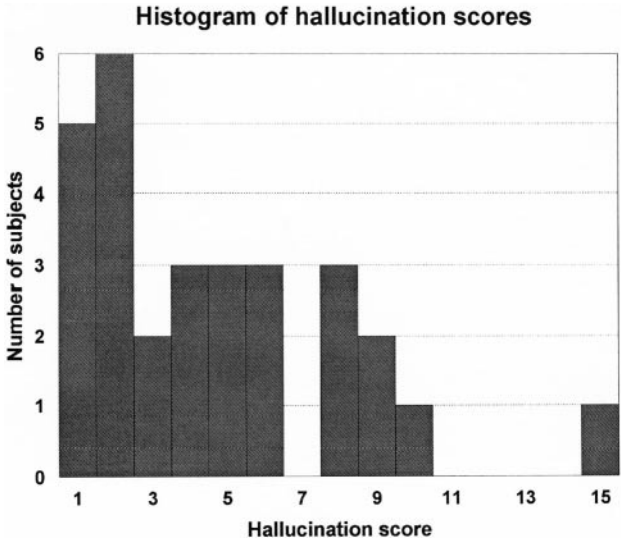

Figure 1. This figure plots the histogram describing the distribution of auditory hallucinations scores for patients with a hallucination score of at least 1 ($n = 29$). Subjects with no hallucinations ($n = 56$) are not shown.

Data Acquisition and Image Processing

High-resolution MRI was performed on a 1.5 T Philips Gyroscan ACSII system. We acquired 256 contiguous sagittal slices of 1 mm thickness using a T_1-weighted sequence (T_R = 13 ms, T_E = 5 ms, $\alpha = 25°$; field-of-view = 256 mm) with a matrix size of 256^3, resulting in an isotropic voxel size of 1 mm^3. For morphometric analysis of the data, we applied our DBM approach (Gaser *et al.*, 1999, 2001). This method is based on nonlinear image registration, commonly used for the spatial normalization of functional imaging data across subjects. The DBM method analyses deformations used to normalize images onto a standard template brain by introduction of local deformations ('warps') to the object brains, in order to infer on structural differences. We have recently validated our DBM approach in a direct comparison to semi-automated volumetric measurement in a group of schizophrenia patients (Gaser *et al.*, 2001). DBM has several advantages over conventional volumetric techniques (i.e. tracing of regions), including elimination of user-bias, minimization of partial volume effects and the opportunity to study the entire brain rather than pre-defined regions.

We used SPM99 spatial normalization routines (Ashburner and Friston, 1999) with an algorithm based on image intensity differences rather than landmarks or surfaces. First, we applied an affine transformation to normalize all images to the same stereotactic space (Talairach and Tournoux, 1988) of the template image (single subject brain as provided in the SPM package). This step corrects for the global differences of individual brains, such as brain size, as well as orientation in space, using transformations such as scaling, rotation, translation, or shearing. Hence, this step does not introduce changes to single structures, but applies changes to all voxels of the brain uniformly. It preserves the individual anatomy and does not introduce a bias for specific regions. The spatially normalized images were then resized to an isotropic voxel size of 2 mm. The second step of the normalization procedure accounts for the remaining local anatomical differences. This nonlinear registration is based on a regularized minimization of the residual squared intensity difference between an image and a template image, while simultaneously maximizing the smoothness of the deformations. The coefficients of a linear combination of $11 \times 13 \times 10$ three-dimensional discrete cosine transform basis functions were estimated to perform this nonlinear registration (Ashburner and Friston, 1999). Hence, in difference to the linear normalization routine, the nonlinear normalization changes local anatomical features rather than global parameters such as brain width. This includes changes of single structures such as gyri, for which local deformations are introduced to achieve similarity between the brain being normalized and the template brain.

The deformations applied to accomplish this nonlinear normalization were then used for computation of brain morphometric differences: we obtained a deformation field for each subject with a specific three-dimensional displacement vector in every voxel. This displacement vector defines the transformations required to map the voxel of one brain onto its corresponding position in another brain. Therefore it includes information of positional differences as well as changes in local volume. Rather than using the entire information, we extracted the local Jacobian determinant, a variable commonly used in continuum mechanics (Gurtin, 1987), from the deformation fields. This restricts information on morphometric differences to the volume information, i.e. local shrinkage or expansion, yielding more precise maps of volumetric differences than analysis of the entire deformation field, as shown previously (Gaser *et al.*, 2001).

Statistical Analysis

For our main statistical analysis we considered a general linear model for the volume change in each voxel, testing the linear relationship between the hallucination score and volume decrease of the assessed deformations. A general linear model matrix was set up, in which the hallucination score was entered as a parameter. Furthermore, SANS total score, SAPS total score without auditory hallucination sub-items and gender were defined as confounding variables to eliminate their possible effects. Hence, this analysis equals a multiple regression

model which tests for correlations between the hallucination score and volume changes in each voxel, while eliminating the effects of the potentially confounding variables mentioned above. In contrast to simple correlations, the variance introduced by the above confounds can thus be eliminated. We have preferred this statistical approach rather than a simple dichotomization, since it avoids certain problems associated with a group analysis (e.g. choice of cut-off values for dividing groups into 'hallucinating' and 'non-hallucinating' patients, sensitivity to false categorization of single patients, etc.).

Perisylvian areas (i.e. Broca's region and the superior temporal cortex, including the superior temporal gyrus with planum polare and temporale, extending up to the temporoparietal junction) were included in our hypothesis and therefore assessed without correction for multiple comparisons. For other cortical areas, we performed an exploratory analysis. Thus, we defined an overall threshold of significance of $P < 0.001$. As a result, we obtain statistical parametric maps for the entire brain showing voxels with a significant correlation to the hallucination score. To further minimize false positive errors, we applied a spatial threshold criterion: we only report clusters consisting of at least $k = 55$ voxels, corresponding to an extent threshold of $P < 0.01$.

Additionally, we performed supplementary analyses to further support our findings. These analyses were variations of the general linear model described above, the main difference being that we compared groups of subjects, rather than performing a correlation. Thus, each subject was assigned to a group, while the confounding variables as described above were also entered to correct for variance related to these. For the first additional analysis, we divided the patient group in those patients with versus those without hallucinations. For this group analysis, patients with a score of zero ($n = 56$) made up the 'non-hallucinating' group, whereas those with a score of 1 and above ($n = 29$) made up the second group of hallucinating patients. In a further variation of this analysis, we then re-grouped the patients with those of a score value of either zero or one being classified as 'non-hallucinating' ($n = 67$) and defining those with a score value of greater 1 ($n = 18$) as 'hallucinating'. In these supplementary analyses, the difference of the Jacobian determinant between the groups (rather than a correlation) was computed in each voxel, thus yielding maps to describe voxels in which the hallucinating patients showed focal volume loss compared to non-hallucinating subjects. While this approach was considered to be less stringent than the correlation analysis, it parallels more closely most previous morphometric studies. The second supplementary analysis was computed to confirm that effects were indeed related to hallucinations rather then other aspects of the disease. For this purpose, we included a sample of 75 healthy controls in the group of non-hallucinating subjects. These controls, taken from the previous study (Gaser *et al.*, 1999), were matched for sex and age to the schizophrenia group (22 women, 53 men; mean age 31.2 ± 9 years). They were all screened thoroughly before scanning to exclude any psychiatric or neurological history, developmental abnormality, history of head trauma, or major medical condition. They all scored zero on the auditory hallucination scale. We used the same statistical model of our main analysis to compute the correlation between hallucination scores and local volume decrease. We included hallucination scores as regressor variable and SANS, SAPS without auditory hallucinations, and gender as confounding variables. Thus, the second analysis equals our main analysis, but additionally includes a control group with zero values on the hallucination scores (SANS and SAPS values all being zero). Both supplementary analyses were performed to confirm results found in the main analysis.

Finally, we calculated correlations between the auditory hallucination score and certain selected demographic and psychopathological variables. This included testing relations with age, gender, the SAPS total score without auditory hallucinations, the SAPS formal thought disorder sub-items, the SAPS delusion sub-items and the SANS total score. In schizophrenia, certain symptoms are often found together with other specific psychopathological variables. For example, positive symptoms (such as those mentioned above) often occur together. These correlations were computed to show that auditory hallucinations could be well isolated from the complex psychopathology of the disease and had no substantial overlap in variance with the other main positive symptoms.

Results

DBM analysis revealed three cortical regions showing a significant ($P < 0.001$) correlation of local volume decrease with severity of auditory hallucinations in the main analysis (Table 1 and Figs 2 and 3): a right prefrontal region comprising parts of the middle and inferior frontal gyri (including parts of the right hemisphere homologue of Broca's area), the left transverse temporal gyrus (Heschl's gyrus, including the primary auditory cortex) and the inferior part of the left supramarginal gyrus (posterior to the planum temporale). While the latter two regions were included in the previous anatomical hypothesis, the prefrontal finding includes only part of the homologue of Broca's area and is hence based on the exploratory analysis of the entire brain.

Post-hoc inspection of secondary auditory areas surrounding Heschl's gyrus, which were implicated in an earlier study (Barta *et al.*, 1990), showed effects appearing only at a lower level of significance ($P < 0.01$).

The supplementary analyses confirmed the main finding. The three clusters were found for both group analyses of hallucinating versus non-hallucinating patients (irrespective of the chosen cut-off used to divide the sample) and for the supplementary correlational analysis including healthy control subject. In all analyses the three regions were significant ($P < 0.001$), while the location of the maximum voxels and the extent of the clusters varied slightly from the main analysis.

The only significant correlation between auditory hallucination score and the selected demographic and psychopathological variables was found for SAPS delusion sub-items (correlation coefficient $r = 0.366$, $P = 0.0003$). All other correlations were not significant ($P < 0.01$). In particular, there was no significant correlation of auditory hallucination score with age of subjects ($r = 0.04$), gender ($r = 0.052$), SANS total score ($r = 0.114$), SAPS formal thought disorder sub-items ($r =$

Table 1
Areas with reduced volume in relation to auditory hallucinations

x	*y*	*z*	*t*-score	Effect size *d* (95% confidence interval)	Region (Brodmann's area)
44	40	14	4.15*	0.927 (0.497–1.357)	Right middle/inferior frontal gyrus (45/46)
–42	–16	10	4.10*	0.916 (0.486–1.346)	Left transverse temporal gyrus (Heschl) (41)
–44	–50	32	3.90*	0.871 (0.441–1.301)	Left inferior supramarginal gyrus (40)

*$P < 0.001$; spatial extent $k = 55$ voxels.
Coordinates (given in millimetres) refer to the template space and correspond approximately to the space of the Talairach atlas. The effect size *d* indicates to what extent the volume decrease is related to hallucination score.

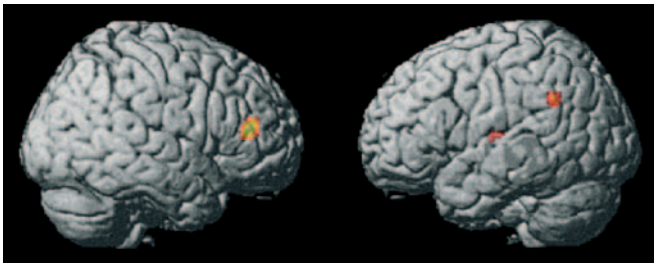

Figure 2. Relationship between volume decrease and severity of hallucinations: The resulting *t*-map is superimposed on the rendered surface of the single template brain ($P < 0.001$). Only clusters consisting of at least 55 voxels are displayed corresponding to a spatial extent threshold of $P < 0.01$. A correlation between volume decrease and severity of hallucinations was found the right prefrontal cortex (partially the region homologue to Broca's area), in the left inferior supramarginal gyrus and in the transverse temporal gyrus (Heschl's gyrus).

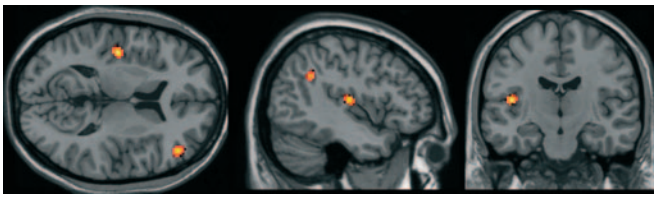

Figure 3. Orthogonal sections of spatial location of the findings (same thresholds used as in Fig. 2. Heschl's gyrus can be best identified by its omega-like shape in coronal and sagittal planes. Significant clusters are shown in axial, sagittal and coronal planes, superimposed on the template brain. Section coordinates conform to space of this template and refer only approximately to Talairach space: $x = -44$ mm, $y = -16$ mm, $z = 10$ mm.

–0.011), or SAPS total score without auditory hallucinations ($r = 0.245$).

Discussion

In this study, we find strong support for the hypothesis that auditory hallucinations in schizophrenia are indeed related to selective subtle changes in brain morphology. We find these deficits to be distributed over left superior temporal, left temporoparietal and right prefrontal regions, affecting both sensory and heteromodal cortical areas. These structural abnormalities go beyond the findings of functional imaging studies, showing a persistent abnormality rather than transient phenomena. It is not unlikely that previous approaches to detect structural alteration and to relate them to particular symptoms have been hampered by a modest sensitivity of conventional volumetric methods in assessing relatively subtle deficits. Therefore, DBM might have enabled the detection of these small changes, combining higher sensitivity with the option of whole-brain analysis rather than analyzing only predefined regions.

The main finding of our study is that structural changes associated with auditory hallucinations include the gyrus of Heschl, an area mostly coinciding with the primary auditory cortex (Liegeois-Chauvel *et al.*, 1991). Previous studies on temporal lobe pathology in positive symptoms have suggested the posterior portions of the superior temporal gyrus (STG) to be relevant for formal thought disorder (Shenton *et al.*, 1992; Menon *et al.*, 1995). Another study has suggested a relation to STG morphology and auditory hallucinations (Barta *et al.*, 1990), but since a coarse resolution (including gaps between MRI slices) was used, no precise localization within STG cortical fields was possible. Our results show that in auditory hallucinations, the preferentially affected area appears to be located in the primary auditory cortex, rather than the secondary or association areas of the posterior planum temporale. Thus, these two major symptoms of schizophrenia both appear related to localized shrinkage in the left superior temporal cortex, but with slightly different anatomical localization. However, the difference in localization of changes might be relative, since other areas around the gyrus of Heschl's appeared at lower thresholds on post-hoc inspection and the previous studies on formal thought disorder (Shenton *et al.*, 1992; Menon *et al.*, 1995) did not include specific delineation of the gyrus of Heschl. Recent cognitive studies, however, give further support for the assumption of regional separation. These studies have shown distinct profiles of cognitive dysfunction to be associated with particular positive symptoms (Kerns and Berenbaum, 2002). Formal thought disorders and auditory hallucinations appear to be associated with different profiles of cognitive deficits, for example in word production (Kerns *et al.*, 1999).

The cross-sectional design of our study does not allow inference on the timing of these alterations and possible changes during the course of the disorder. Recent studies in first-episode schizophrenia, however, underline that STG pathology is often present at the onset of schizophrenia (Hirayasu *et al.*, 2000) and it is therefore unlikely to be simply an effect of medication or hospitalization, even though some brain regions might show progressive reduction in some patients on follow-up after several years (Mathalon *et al.*, 2001).

Another area of volume loss was located in the left supramarginal gyrus. Temporoparietal and inferior parietal cortical areas have been difficult to measure in conventional morphometric approaches. However, these areas are central for the processing of language. The supramarginal gyrus in particular is a key module of the auditory/phonological loop, a circuitry mediating the short-term storage and processing of auditory information and especially language (Paulesu *et al.*, 1993). Although the phenomenology of auditory hallucinations can be heterogeneous, many (if not most) patients present with verbal hallucinations, such as voices conversing or commenting on the patient (David and Busatto, 1998). This second cluster in our results is therefore suggestive of a pathology involved in higher aspects of language. Also, schizophrenia patients with auditory hallucinations show selective deficits in speech perception (Hoffman *et al.*, 1999), underlining the intimate relation to disturbed anatomical substrates of speech. Both temporal and temporoparietal clusters show an overlap with the functional neuroanatomy of physiological processing of auditory information and language (Silbersweig and Stern, 1998).

Beside these two areas, which were included in our anatomical hypothesis, we found an effect in the right prefrontal cortex, a major target of previous imaging studies in schizophrenia. Although the maximum voxels in this cluster were in fact more significant than in the STG clusters, this finding can only be reported as a trend, as in the absence of a previous anatomical hypothesis it was encountered at a threshold uncorrected for multiple comparisons. Nevertheless, this finding deserves attention in the light of studies emphasizing frontotemporal interplay of regions in volitional (and involitional)

auditory perception (Silbersweig and Stern, 1998). While several studies indicate prefrontal cortical abnormalities in schizophrenia (Wible *et al.*, 2001), there are relatively few studies relating specific symptoms to this region. This study provides a first link of auditory hallucinations in schizophrenia to a discrete prefrontal structural change. Interestingly, this alterations partially includes the right hemisphere homologue of Broca's area. As with temporal cortical changes, deficits in frontal gray matter are also detectable in first-onset patients (Hirayasu *et al.*, 2001). Further studies might be warranted to investigate the relation of prefrontal to temporal function in auditory hallucinations.

Our results implie that auditory hallucinations are not associated with a single regional deficit. Rather, several nodes of a more complex circuitry might be involved. Changes in primary auditory cortex and temporoparietal areas might be at the core of this abnormality, and together with prefrontal deficits this could result in deficient frontotemporal interaction. Recent functional imaging studies have elucidated the function of frontotemporal networks on conscious volitional auditory perception and sensory awareness (Frith, 1996; Silbersweig and Stern, 1998). These results emphasize an interaction between auditory temporal areas and the prefrontal cortices, which constantly modulate the superior temporal areas, therefore enabling facilitation or inhibition of the processing of sensory information. In schizophrenia, this frontotemporal network appears to be affected, either through local structural deficits or due to compromised connectivity of regions, which might lead to the emergence of positive symptoms such as auditory hallucinations. In neuropsychological terms, dysfunction of this network could be understood as a failure to inhibit and attribute internal speech, as suggested previously in theories relating to 'inner speech' (McGuire *et al.*, 1995; Johns and McGuire, 1999).

So far, there are few data on the relation of specific symptoms to regional neuropathology in schizophrenia. Our method only allows inference on volume changes. Thus, it does not disclose the type of microscopic pathology underlying these changes. While alterations on the cellular level might be held responsible at least for part of the effects, there might be other factors, such as changes in local blood flow or blood volume, that contribute to the MRI volumetric structural measurements.

Another general problem in assessing the relation of symptoms to structural changes is the transient nature of most symptoms, particularly hallucinations. Similar to post-mortem studies, it is difficult to obtain valid scores of a person's lifetime experience of auditory hallucinations. For our study psychopathology scores were chose to cover at least 1 week before scanning. Our results therefore also rely on the assumption of a correlation between the stability of auditory hallucinations (possibly a persistent predisposition for experiencing them) and underlying brain structure.

In conclusion, our results can be interpreted as a symptom-specific distributed structural deficit, comprising multiple nodes of a more complex frontotemporal circuitry. The particular anatomical distribution of changes is associated with the emergence of the specific symptom of auditory hallucinations. Arising from both prefrontal and superior temporal cortical pathology, this abnormality predisposes patients to transient auditory hallucinations with its most pertinent characteristics: its involitional nature (inability to suppress these perceptions), the predominantly verbal phenomenology of 'voices' and, finally, the co-occurrence with other positive symptoms arising from prefrontal and/or superior temporal pathology in schizophrenia. Novel morphometric techniques might open further avenues to segregate localized abnormalities and specific symptoms or syndromes in schizophrenia.

Notes

This work was supported by the VKF Clinical Research Council of the University of Jena, Germany.

Address correspondence to Christian Gaser, Department of Psychiatry, Friedrich-Schiller-University of Jena, Philosophenweg 3, 07743 Jena, Germany. Email: christian.gaser@uni-jena.de.

References

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd revised edn. Washington, DC: American Psychiatric Association.

Andreasen NC (1983) The scale for the assessment of negative symptoms (SANS). Iowa City: The University of Iowa.

Andreasen NC (1984) The scale for the assessment of positive symptoms (SAPS). Iowa City: The University of Iowa.

Ashburner J, Friston KJ (1999) Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254–266.

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

David AS (1994) The neuropsychological origin of auditory hallucinations. In: Neuropsychology of schizophrenia (David AS, Cutting J, eds), pp. 269–313. Hove: Lawrence Erlbaum.

David AS, Busatto G (1998) The hallucination: a disorder of brain and mind. In: Disorders of brain and mind (Ron M, David AS, eds), pp. 336–362 Cambridge: Cambridge University Press.

Dierks T, Linden DE, Jandl M, Formisano E, Goebel R, Lanfermann H, Singer W (1999) Activation of Heschl's gyrus during auditory hallucinations. Neuron 22:615–621.

Frith CD (1996) The role of the prefrontal cortex in self-consciousness: the case of auditory hallucinations. Philos Trans R Soc Lond B Biol Sci 351:1505–1512.

Gaser C, Volz HP, Kiebel S, Riehemann S, Sauer H (1999) Detecting structural changes in whole brain based on nonlinear deformations — application to schizophrenia research. Neuroimage 10:107–113.

Gaser C, Nenadic I, Buchsbaum BR, Hazlett EA, Buchsbaum MS (2001) Deformation-based morphometry and its relation to conventional volumetry of brain lateral ventricles in MRI. Neuroimage 13:1140–1145.

Gurtin ME (1987) An introduction to continuum mechanics. Boston, MA: Academic Press.

Hirayasu Y, McCarley RW, Salisbury DF, Tanaka S, Kwon JS, Frumin M, Snyderman D, Yurgelun-Todd D, Kikinis R, Jolesz FA, Shenton ME (2000) Planum temporale and Heschl gyrus volume reduction in schizophrenia: a magnetic resonance imaging study of first-episode patients. Arch Gen Psychiatry 57:692–699.

Hirayasu Y, Tanaka S, Shenton ME, Salisbury DF, DeSantis MA, Levitt JJ, Wible C, Yurgelun-Todd D, Kikinis R, Jolesz FA, McCarley RW (2001) Prefrontal gray matter volume reduction in first episode schizophrenia. Cereb Cortex 11:374–381.

Hoffman RE, Rapaport J, Maazure CM, Quinian DM (1999) Selective speech perception alterations in schizophrenic patients reporting hallucinated 'voices'. Am J Psychiatry 156:393–399.

Ishii R, Shinosaki K, Ikejiri Y, Ukai S, Yamashita K, Iwase M, Mizuno-Matsumoto Y, Inouye T, Yoshimine T, Hirabuki N, Robinson SE, Takeda M., (2000) Theta rhythm increases in left superior temporal cortex during auditory hallucinations in schizophrenia: a case report. Neuroreport 11:3283–3287.

Johns LC, McGuire PK (1999) Verbal self-monitoring and auditory hallucinations in schizophrenia. Lancet 353:469–470.

Kerns JG, Berenbaum H (2002) Cognitive impairments associated with formal thought disorder in people with schizophrenia. J Abnorm Psychology 111:211–224.

Kerns JG, Berenbaum H, Barch DM, Banich MT, Stolar N (1999) Word production in schizophrenia and its relationship to positive symptoms. Psychiatry Res 87:29–37.

Lennox BR, Park SB, Medley I, Morris PG, Jones PB (2000) The functional anatomy of auditory hallucinations in schizophrenia. Psychiatry Res 100:13–20.

Liddle PF, Friston KJ, Frith CD, Hirsch SR, Jones T, Frackowiak RS (1992) Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160:179–186.

Liegeois-Chauvel C, Musolino A, Chauvel P (1991) Localization of the primary auditory area in man. Brain 114:139–151.

Line P, Silberstein RB, Wright JJ, Copolov DL (1998) Steady state visual evoked potential correlates of auditory hallucinations in schizophrenia. Neuroimage 8:370–376.

McGuire PK, Shah GM, Murray RM (1993) Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. Lancet 342:703–106.

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

Mathalon DH, Sullivan EV, Lim KO, Pfefferbaum A (2001) Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 58:148–157.

Menon RR, Barta PE, Aylward EH, Richards SS, Vaughn DD, Tien AY, Harris GJ, Pearlson GD (1995) Posterior superior temporal gyrus in schizophrenia: grey matter changes and clinical correlates. Schizophr Res 16:127–135.

Noga JT, Aylward E, Barta PE, Pearlson GD (1995) Cingulate gyrus in schizophrenic patients and normal volunteers. Psychiatry Res 61:201–208.

Paulesu E, Frith CD, Frackowiak RSJ (1993) The neural correlate of the verbal component of working memory. Nature 362:342–345.

Schröder J, Buchsbaum MS, Siegel BV, Geider FJ, Lohr J, Tang C, Wu J, Potkin SG (1996) Cerebral metabolic activity correlates of subsyndromes in chronic schizophrenia. Schizophr Res 19:41–53.

Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M, McCarley RW (1992) Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Engl J Med 327:604–612.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001) A review of MRI findings in schizophrenia. Schizophr Res 49:1–52.

Silbersweig DA, Stern E (1998) Towards a functional neuroanatomy of conscious perception and its modulation by volition: implications of auditory neuroimaging studies. Philos Trans R Soc Lond B Biol Sci 353:1883–1888.

Silbersweig DA, Stern E, Frith C, Cahill C, Holmes A, Grootoonk S, Seaward J, McKenna P, Chua SE, Schnorr L, Jones T, Frackowiak RSJ (1995) A functional neuroanatomy of hallucinations in schizophrenia. Nature 378:176–179.

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Stuttgart: Georg Thieme.

Volz HP, Gaser C, Sauer H (2000) Supporting evidence for the model of cognitive dysmetria in schizophrenia — a structural magnetic resonance imaging study using deformation-based morphometry. Schizophr Res 46:45–56.

Weiss AP, Heckers S (1999) Neuroimaging of hallucinations: a review of the literature. Psychiatry Res 20:61–74.

Wible CG, Anderson J, Shenton ME, Kricun A, Hirayasu Y, Tanaka S, Levitt JJ, O'Donnell BF, Kikinis R, Jolesz FA, McCarley RW (2001) Prefrontal cortex, negative symptoms, and schizophrenia: an MRI study. Psychiatry Res 108:65–78.

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET (2000) Meta-analysis of regional brain volumes in schizophrenia. Am J Psychiatry 157:16–25.