Chronic Auditory Hallucinations in Schizophrenic Patients: MR Analysis of the Coincidence between Functional and Morphologic Abnormalities[1]

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Purpose: To prospectively evaluate if functional magnetic resonance (MR) imaging abnormalities associated with auditory emotional stimuli coexist with focal brain reductions in schizophrenic patients with chronic auditory hallucinations.

Materials and Methods: Institutional review board approval was obtained and all participants gave written informed consent. Twenty-one right-handed male patients with schizophrenia and persistent hallucinations (started to hear hallucinations at a mean age of 23 years ± 10, with 15 years ± 8 of mean illness duration) and 10 healthy paired participants (same ethnic group [white], age, and education level [secondary school]) were studied. Functional echo-planar T2*-weighted (after both emotional and neutral auditory stimulation) and morphometric three-dimensional gradient-recalled echo T1-weighted MR images were analyzed using Statistical Parametric Mapping (SPM2) software. Brain activation images were extracted by subtracting those with emotional from nonemotional words. Anatomic differences were explored by optimized voxel-based morphometry. The functional and morphometric MR images were overlaid to depict voxels statistically reported by both techniques. A coincidence map was generated by multiplying the emotional subtracted functional MR and volume decrement morphometric maps. Statistical analysis used the general linear model, Student *t* tests, random effects analyses, and analysis of covariance with a correction for multiple comparisons following the false discovery rate method.

Results: Large coinciding brain clusters ($P < .005$) were found in the left and right middle temporal and superior temporal gyri. Smaller coinciding clusters were found in the left posterior and right anterior cingular gyri, left inferior frontal gyrus, and middle occipital gyrus.

Conclusion: The middle and superior temporal and the cingular gyri are closely related to the abnormal neural network involved in the auditory emotional dysfunction seen in schizophrenic patients.

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Schizophrenia is a heterogeneous disorder affecting almost 1% of the world's population (1). Currently, there is no magnetic resonance (MR) imaging finding specific to or strongly suggestive of schizophrenia.

Understanding the neural network hypothetically responsible for the pathogenesis of schizophrenia requires a precise determination of the extent and distribution of abnormalities in brain anatomy and function (2). Functional imaging has been informative for understanding individual symptoms: Negative symptoms correlate with decreased activity in the dorsolateral prefrontal cortex (3,4), and auditory hallucinations correlate with an increased blood flow in the Broca area in the left hemisphere (5).

The use of brain activation maps to detect brain areas with a different functional response is heavily dependent on the stimulus itself. Although a wide range of paradigms, including different senses (mainly visual but also olfactory) with distinctive features for each paradigm, has been used to study the emotional response with functional MR imaging, most of the studies in psychoses have used the visual sensory modality through the recognition of facial emotions (6–9). However, language impairment is one of the "core" phenomenological characteristics of patients with schizophrenia, emphasizing the depth of the evaluation, so auditory stimuli with and without emotional charge seem more adequate in this context. Furthermore, schizophrenic patients have a reduction in size in different cortical areas, as demonstrated with the morphologic analysis of T1-weighted MR images (10).

Although many brain regions have been implicated in schizophrenia by means of MR, no single region has been consistently reported as abnormal to date. Differences between samples (clinical heterogeneity) and in methods among studies (sequences, paradigm, and postprocessing heterogeneity) may explain the lack of consistency in the results obtained in this field. Developing a clear understanding of the pathologic details of specific schizophrenic phenotypes is one of the greatest challenges in psychiatry. The purpose of our study was to prospectively evaluate if MR functional abnormalities associated with auditory emotional stimuli coexist with focal brain reductions in schizophrenic patients with chronic auditory hallucinations.

Advances in Knowledge

- Functional MR imaging abnormalities associated with auditory emotional stimuli coexist with focal brain density reductions in schizophrenic patients experiencing chronic auditory hallucinations.
- Large coinciding brain clusters were found in the left and right middle temporal and superior temporal gyri; smaller coinciding clusters were found in the left posterior and right anterior cingular gyri, left inferior frontal gyrus, and middle occipital gyrus; these areas are related to the abnormal neural network involved in the auditory emotional dysfunction seen in these patients.

Materials and Methods

Patient and Control Participant Characteristics

All patients and control participants gave written informed consent to participate in the research, which was approved by the local ethics committee. The ability of psychiatric patients to provide informed consent to participate in clinical research applies more to patients with conceptual disorganization and poor attention than to those experiencing mainly hallucinations (11). All patients in our series were experiencing hallucinations; however, all participants could read and understand the consent form, none were admitted to the hospital or underwent outpatient commitment at the time, and all were legally competent.

A group of 21 right-handed male patients with schizophrenia and persistent hallucinations (according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition) were studied. Right-handed men were selected to avoid bias due to differences in brain structure and because schizophrenia affects men and women differently. Their ages ranged from 21 to 51 years (mean ± standard deviation, 39 years ± 10); all had a secondary school education level. These patients were selected from a sample of 160 patients with auditory hallucinations confirmed by their psychiatrist and clinical assessment (12).

All 21 patients in our series met the following selection criteria for persistent hallucinations: persistence of hallucinations despite pharmacologic treatment was present in all patients. Two antipsychotic drugs were tried at doses equivalent to at least 600 mg/d of chlorpromazine in the last year, but the voices heard were not modified in any way by treatment and were present at least once per day in the past year. All patients were being treated with antipsychotic medications at time of evaluation, 16 with second-generation and five with combined first- and second-generation antipsychotic drugs. The duration of treatment was 14.3 years ± 6.9. All patients heard voices during the functional MR data acquisition.

Schizophrenic patients began to hear hallucinations at a mean age of 23 years ± 10 (range, 15–43). The mean duration of illness was 15 years ± 8. All patients were clinically assessed by two

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Abbreviations:
3D = three-dimensional
VBM = voxel-based morphometry

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of the authors (E.J.A. and J.S., each with more than 16 years experience in clinical psychiatry) by consensus. Scores from both the Positive and Negative Syndrome Scale (13) and Psychotic Symptom Rating Scales were obtained during the 24-hour period before MR examination (14).

Ten healthy control participants were selected by matching the schizophrenic patients with respect to ethnic group (white), age (35 years ± 7 for controls vs 39 years ± 10 for patients), and education level (secondary school). Control participants were also right-handed men. None of them had a personal or family history of mental disorders or perceptual abnormalities, as assessed with a brief mental health questionnaire. No individual in either group had from hearing loss.

MR Acquisition

Both functional and morphologic MR images were acquired with a 1.5-T scanner (Intera; Philips Medical Systems, Best, the Netherlands) with a quadrature volume head coil. The imaging plane was transverse and oriented parallel to the inferior limit of the rostrum and the genu of the corpus callosum.

The functional MR images were obtained by means of blood oxygen level dependent contrast material–enhancement. An emotional auditory stimulation-response paradigm was designed to replicate those emotions related to the patient's hallucinatory experiences (15). Words were grouped into two classes, one with highly emotional and the other with neutral content, and recorded on a compact disc. The same set of emotional and neutral Spanish words was used for each patient. Given that the stimuli pattern of functional MR lasts 20 seconds for each block, the most relevant 13 words were selected. The emotional words were defined according to the words most frequently heard by psychotic patients with auditory hallucinations. A total of 65 words were chosen based on their frequency and meaning. The words were classified according to the qualitative analysis of their content in five categories: negative content and imperative tone, insult, imperative tone, exclamation related to emotional state, and positive content. Neutral words were selected from a Spanish emotional valence database (15). At the end of the trial every participant was asked to score their level of anxiety. Emotional and neutral words were significantly different in both groups as shown by using a paired Student t test (P = .001).

Patients had earphones adjusted to their heads and connected by a pair of air tubes to an external audio compact disc player. All participants underwent two functional MR studies, one session with the high-emotion and the other with the neutral-emotion content words. Neutral and emotional content sessions were randomly presented to avoid habituation confounding effects. For each session, the voice stimuli consisted of four periods of activation alternated with four periods of rest with a block design. Both sessions were separated by no less than 40 seconds.

A dynamic echo-planar T2*-weighted functional MR sequence (repetition time msec/echo time msec, 2000/50; section thickness, 5 mm, with no intersection gap; matrix, 96 × 128; field of view, 220 mm; flip angle, 65°) was obtained in each session. The pixel size was 3.27 × 1.72 × 5 mm, with a voxel volume of 28.12 mm^3. Each dynamic acquisition consisted of 24 contiguous sections covering the whole brain. The emotional and neutral functional MR session order was randomized for both patients and controls.

For the morphologic analysis, a high spatial resolution three-dimensional (3D) spoiled gradient-echo T1-weighted MR sequence (96 partitions, 7/1.9; section thickness, 1.25 mm, with no intersection gap; matrix, 256 × 256; field of view, 220 mm; flip angle, 8°) was acquired after the functional MR examinations. These anatomic images of the whole brain had a voxel size of 0.86 × 0.86 × 1.25 mm, giving a voxel volume of 0.9245 mm^3.

During the acquisition, patients were under direct observation by psychiatrists and interviewed about their experiences immediately after the MR procedure.

Postprocessing Analysis

Whole-brain postprocessing analysis, including functional MR, voxel-based morphometry (VBM), and maps of coincidence, was performed jointly by three of the authors (J.J.L., G.G., and L.M., more than 5 years experience in MR postprocessing each).

Functional MR methods.—MR images were realigned with a subvoxel movement correction to avoid spurious signals (16). Functional and morphologic images were coregistered and transformed into a standard space named MNI152 (Montreal Neurological Institute, Montreal, Canada). Voxels were resampled to 2 × 2 × 2 mm and spatially smoothed with a 3D Gaussian 6 × 6 × 6-mm kernel filter to increase the signal-to-noise ratio, reduce the anatomic variability between participants, and approximate the voxel distribution to the normal distribution (17).

SPM2 (Statistical Parametric Mapping, Functional Imaging Laboratory, London, England) analysis was performed for each patient and control participant and by comparing groups. In the individual analysis, a design matrix was defined for each participant. Both an ideal hemodynamic response function and the mean value of each functional MR session were included in the design matrix.

Images of subtraction between emotional and nonemotional content words (both against the rest task) were then extracted for every schizophrenic patient and control subject. These images were considered to be maps of emotional activation associated with the auditory response. A paired sample t test map was calculated by using the control participants and patients to test the differences in activation between emotional and nonemotional sessions. t Tests were performed by means of the general linear model (16), applying a random effects analysis that accounts for within- and between-subject differences. Common features were extracted by using the general linear model over the subtraction of contrasts.

VBM method.—SPM2 was used to perform the structural image processing and the comparison analyses. Statistically significant anatomical differences in gray matter volume among patients and control volunteers were explored

by means of optimized VBM (18), which involves using specific gray matter templates to warp the gray matter segmented maps. Although *volume loss* is a more familiar term to radiologists, we will use *gray matter density* because neuropathlogic studies in schizophrenia have found not neuronal loss or gliosis, but smaller neurons, dendrites with a lower density of spines, and less extensive arborization (19).

Custom templates were created to avoid the presence of errors due to differences in the contrast of the images and to specific nonuniformities of each MR acquisition and demographic differences in the sample. The process involved the translation of each image into the same Talairach stereotactic space, applying a 12-parameter affine transformation by using the standard MNI 152 (Montreal Neurological Institute) template as a reference. The normalized images were averaged and smoothed by using a 3D 8 mm^3 Gaussian kernel to obtain the custom template used in the next step. In addition, a priori gray matter, white matter, and cerebrospinal fluid probabilistic maps were obtained at this stage by averaging and smoothing the segmentation output of normalized images.

The VBM process started with the normalization of the T1-weighted images (with affine functions) to the self-generated template, obtaining a set of images in the same stereotaxic space, and applying a trilinear interpolation with a final voxel size of $1 \times 1 \times 1$ mm. These images were segmented into gray matter, white matter, and cerebrospinal fluid. In addition, a cleaning process was performed, removing nonbrain tissue such as scalp, skull, and dural venous sinus (20). Estimation parameters from nonlinear spatial normalization (21) between segmented images and a priori probabilistic maps were created and employed to reconstruct a normalized version in MNI space of the original T1-weighted images. Finally, warped T1 images were segmented by obtaining gray matter maps, which were smoothed by using a $12 \times 12 \times 12$ mm 3D Gaussian filter.

A parametric map was created to help show the differences between schizophrenic patients and control subjects for the gray matter in the whole brain.

Functional MR and VBM: Maps of coincidence.—Activation clusters identified on the functional MR parametric map with an uncorrected *P* of less than .005 uncorrected were selected with a small extent threshold ($\kappa > 5$). Differences in structural images were given a threshold of *P* less than .005 corrected for multiple comparisons and a large extent threshold ($\kappa > 200$). Both threshold maps were overlaid to depict the common differences found by using both techniques.

The coincidence map was then generated voxel-by-voxel by multiplying the emotional subtracted functional MR images by the gray matter concentration differences. Both contrasts are defined as positive since both represent *t* values. The sign of the product was maintained. The coincidence analysis showed high activity in low gray matter density areas: the higher the activity, the higher the *t* value; the lower the density, the higher the *t* value. Therefore, the higher activation area and concentration decrease allowed more highlighted area to appear. Clusters of coincidence were grouped into large ($\geq$100 voxels) and small (<100 voxels) clusters; larger clusters are probably more relevant to the phenomenologic analysis.

To allow the direct overlay of the different data sets, both functional and morphometric MR images were normalized to the same space by means of the MNI template and coordinates, which are also in the Talairach space. VBM volumes were normalized to the MNI space by creating a self-generated template to avoid segmentation artifacts.

Functional MR and VBM need different assumptions to minimize important missing findings. Functional MR imaging techniques indirectly measure brain activity. Both individual emotional and neutral versus rest responses are comparisons measuring emotional and neutral content words related to activation. To detect group differences between emotional and neutral words, a new comparison was generated by testing emotional as larger than the neutral comparison. VBM technique does not test for individual intrasubject variations but for between-subject variations instead. Our approach to functional, morphometric, and coincidence multiparametric comparison analysis was designed to select only those differentiated areas between patients and control subjects under the particular paradigm.

Statistical Analysis

Both functional MR and VBM statistical measurements were made under the general linear model framework and *t* tests were carried out to acquire the difference maps. Additionally, random effects analyses were applied to obtain functional maps. The statistical model included a group condition (patient vs control) and a covariate of interest (age). Since age is known to be a cause of change in brain structure (20,22), a regression study was performed to evaluate the relationship between this effect and the amount of gray matter.

A regression study showed linear correlation between age and brain tissue volume. Therefore, age was modeled in order to minimize its effect on the results maps.

Statistical parametric maps were acquired by performing independent *t* tests for each voxel across groups, using SPM2 one-tailed comparisons to measure the gray matter difference (patients < controls) and minimize the age effect in probabilistic maps by using analysis of covariance. A *P* of less than .005 was used to establish a significance threshold and a correction for multiple comparisons by using the false discovery rate method (23). Additionally, a cluster filtering (κ) was applied only for reporting clusters with 200 or more voxels.

Anatomic areas that showed changes among study groups were labeled with the Talairach coordinates and Broadman areas by using Automated Area Labeling software (Cyceron; Centre d'Imagerie Cerebrale et de Recherche en Neurosciences, Paris, France) (24). Coordinates for identifying each area were determined by using the maximum *t* value in the corresponding area.

Results

Clinical Evaluation

The Positive and Negative Syndrome Scale mean score was 71 (range, 53–94; standard deviation [SD], 10) while the Psychic Symptom Rating Scale mean score was 30 (range, 24–36; SD, 4), reflecting a homogeneous sample of schizophrenic treatment–resistant patients with persistent auditory hallucinations.

MR Evaluation

MR image analysis revealed that the most relevant areas with an increase in the auditory-triggered emotional activation were (Talairach coordinates x, y, and z, in millimeters) the right temporal middle (52, 2, −18; $t = 7.59$), left temporal middle (−60, −48, 6; $t = 6.03$), right superior temporal and Heschl (54, −18, 8; $t = 5.35$), right superomedial frontal (2, 50, 34; $t = 5.36$), right angular (44, −66, 28; $t = 5.63$), right posterior cingulum (10, −36, 28; $t = 5.44$), left middle cingulum (−8, −14, 44; $t = 5.31$), and right thalamus (4, −12, 4; $t = 4.89$).

The morphometric analysis showed a main local density reduction in the left insula (−42, 16, −9; $t = 7.19$), right lingual (13, −45, −2; $t = 7.02$), left postcentral (−60, −11, 24; $t = 6.82$), right precuneus (12, −50, 5; $t = 6.52$), right insula (47, 15, −6; $t = 6.52$), right superomedial frontal (10, 59, −1; $t = 6.38$), left lingual (−11, −52, 1; $t = 6.29$), and left middle temporal (−62, −62, −3; $t = 6.17$).

Coincidence Map Evaluation

The coincidence analysis selected different regions (Table) and showed that the regions had either large or small clusters of both emotional activation and volume loss (Figure). As shown, larger clusters were found in the left and right middle temporal and left and right superior temporal gyri. Smaller clusters were found in the left posterior and right anterior cingular gyri, left inferior opercular frontal gyrus, and right middle occipital gyrus.

Discussion

A recent meta-analysis of 15 VBM studies found that the left superior temporal gyrus and the left medial temporal lobe are the key regions of structural difference between patients with schizophrenia and control subjects (10). The human voice contains in its acoustic structure information on the speaker's emotional state which is easily perceived with remarkable accuracy. The neural basis of the perception of speaker-related vocal features was found bilaterally in the upper bank of the superior temporal sulcus (25).

The coexistence of functional and morphologic abnormalities behaves as a filter selecting areas that could be specifically related to the schizophrenic phenotype under study. Our data confirm the left middle temporal gyrus as the most important structural and functional area implicated in the pathogenesis of auditory hallucinations.

Auditory hallucinations activate the left and right superior and middle temporal gyri. Structures activated during the perception of external voices are also activated during auditory hallucinations with the additional activation found in areas responsible for the processing of emotion (26). A clear overactivation of the temporal cortex, frontal lobe, insula, cingulate, and amygdala was found in patients when hearing emotional words compared with control subjects. However, when studying the effect of the auditory-triggered emotion on schizophrenic patients with chronic auditory hallucinations, an overactivation of both middle temporal, right superior temporal, and Heschl gyri; left frontal superomedial and right angular; cingulum; and thalamus is depicted. This overactivation of the limbic and frontal brain areas in persistent hallucinatory patients using a specific auditory emotional paradigm may partially reflect the dysfunction of the emotional response to auditory stimuli in schizophrenia. Some of these activated areas may reflect a true hemodynamic abnormality related to functional changes, while others may express the adoption of a modified strategy to perform adequately by using different cognitive skills and engaging different brain regions. The coexistence of gray matter deficits with activated areas may differentiate a true abnormality from an adopted strategy.

Voxel-based gray matter reduction implies a decrease in the optical density of a region. Although no neural loss has been found in patients with schizophrenia, a decreased cortical volume due to smaller neurons and dendrites with a lower density of spines and less extensive arborization is observed in pathologic studies (19). Postmortem studies in patients with schizophrenia have shown a substantial frontal gray matter volume reduction when compared with

Most Relevant Regions Showing Differences in Schizophrenic Patients with Chronic Auditory Hallucinations

Coincidence Area	Functional MR *t* Value	Morphologic MR *t* Value	Talairach Coordinates (mm)	Brodman Areas
Left temporal middle	4.81	4.98	−54, −30, 0	21–22
Left temporal superior	4.26	4.92	−57, −16, 9	48
Right temporal middle	4.47	4.30	60, −15, −12	21
Right temporal superior	3.96	4.07	57, 3, −11	38
Left frontal inferior opercular	4.54	4.18	−50, 10, 14	44
Right anterior cingulate	3.96	4.35	5, 45, 12	33
Left posterior cingulate	4.62	4.01	−3, −42, 31	23
Right occipital middle	3.91	4.04	41, −70, 10	37

Note.—As observed in functional, voxel-based morphometry, and coincidence MR analysis.

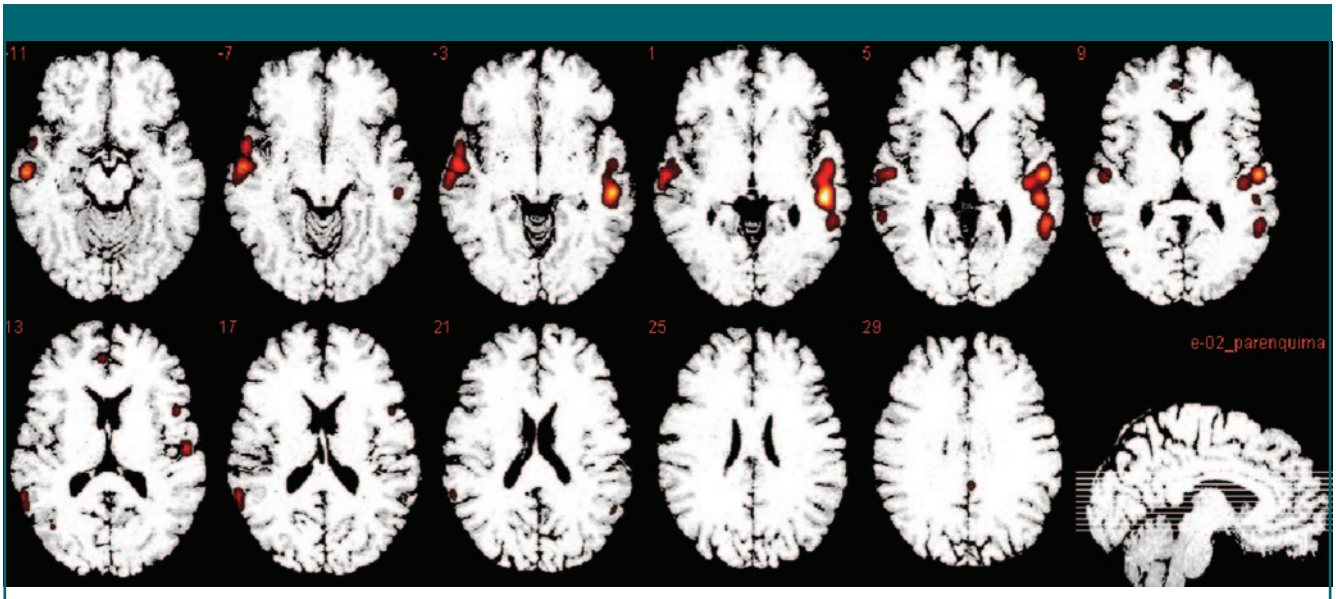
controls (27), the magnitude of the volumetric decrease is proportional to the functional deficits. In vivo studies involving whole-brain morphometric analysis performed by using nonlinear deformation functions have also shown a reduction in the hippocampus, cingulate, orbitofrontal, frontotemporal, parietotemporal, and occipital areas near the lingual gyrus (10,28,29). Other studies have reported a reduced gray matter volume in the ventral and medial prefrontal regions; the orbitofrontal, superotemporal, and occipitotemporal regions; the right medial frontal lobe; and the left middle and left superior temporal gyri (28,30). Areas of gray matter volume reduction that correlated negatively with hallucinations were found in the left superior (transverse) temporal gyrus, left thalamus, and left and right cerebellum (31). In our series, we have been able to demonstrate a gray matter volume reduction mainly in the right precentral, left rolandinc gyrus, left inferior opercular frontal, left superomedial frontal, bilateral orbitomedial frontal, right posterior cingular, bilateral anterior cingular, both medial temporal gyri, both superior temporal gyri, right parahippocampus, right insula, and right precuneum regions.

The ventromedial prefrontal cortex and the amygdala are involved in the normal processing of emotional signals. The temporolimbic and fronto-orbital network have also been implicated in regulating emotion, and the medial limbic system, specifically, has been related to the emotion-processing deficits of schizophrenia. The lingual gyrus at the inferior occipital region was observed to be reduced in these patients (28). Although the reduced volumes in the temporal regions were more marked on the left side (28), we observed a quasi-symmetrical pattern of neuronal reduction. Our different depiction of abnormalities may be related to differences in the phenomenology of schizophrenia studied, the homogeneous series evaluated, the whole-brain morphometric approach, and the appropriate analysis of the confounders (ie, age, gender, handedness and education level).

The VBM approach provides details regarding the specific points of maximal density change. However, many of the morphologic structural abnormalities are relatively subtle and have pronounced interindividual variability, making their use as diagnostic markers of schizophrenia less sensitive.

A neurophysiologic interaction among psychopathology (auditory hallucinations), brain function (increased hemodynamic response in the temporal lobe) and structure (gray matter deficits) has been previously hypothesized (26). It is generally accepted that areas of decreased perfusion parallel decreases in gray matter concentration. An example of this is the age-related brain reduction most probably associated with a decrease in blood flow and metabolism in those areas (32). However, our findings show that in schizophrenic patients abnormal activation may be found in specific areas of maximal neural density decrement. These areas of coincidence where the same voxels have hemodynamic functional changes associated with the emotional auditory-triggered response and focal decreased volume could possibly express a compensation phenomenon in which regions with decreased volume need a larger hemodynamic dysfunctional response to a defined paradigm.

The different areas found in the results of the coincidence maps have rela-



Functional MR coincidence maps. Highlighted areas indicate increased activation associated with emotional auditory stimuli and decreased gray matter volume. Yellow areas represent greater values for functional and morphometric statistical source images. Selected clusters can appear in white matter by means of partial volume effects after spatial smoothing.

tionships with both emotion and schizophrenia, and are probably part of the auditory hallucination phenotype. The bilateral middle temporal gyri are also being involved in emotion (33). The right superior temporal gyrus is mainly involved with hearing, emotion, and changes in the aural sensory environment (34,35). The posterior cingular gyrus is involved with the association of recognized words (36), the threat of emotional words, and unpleasant words (37). The anterior cingular gyrus is involved with attention, while the opercular frontal gyrus has traditionally been affected in schizophrenic patients (orbital prefrontal cortex) and involved with decision-making (38).

The study had study limitations. As all patients had auditory hallucinations at MR, a subtraction strategy was developed to depict only those voxels activated during the emotional stimuli but not from the neutral voices. This way, emotion-related auditory activation areas can be better delineated.

The voxel size of the functional and morphometric MR images was approximately 30 times larger than the functional voxel (28.12 vs 0.9245 mm^3). Since partial volume effect may exist, it is possible that one functional MR voxel will not be activated while part of it is depicted during the morphometric analysis. This means that our approach is conservative, depicting only the coincidence voxels at the price of losing small contributions, making the results easily reproducible. Changes in the volume and activation of these brain areas can result from the medication, not just the symptoms, in schizophrenic patients. However, smaller volumes of gray matter in similar regions as those observed in this study have also been found in neuroleptic-naive patients and in first-episode schizophrenic patients, thus giving more relevance to the disease than to medication (9,29).

As schizophrenia affects men and women differently, the selected population consisted only of men to avoid this bias in the analysis of the temporolimbic structures (39). Also, factors of ethnicity, gender, hand dominance, age, and education level were minimized. We recognize that the results obtained from a defined homogeneous sample, only including schizophrenic patients with chronic resistant auditory hallucinations, can not be generalized to schizophrenia as a whole. The clinical heterogeneity of schizophrenia is beyond the scope of this paper.

Also, we have used a 1.5-T imager with high (>99%) mean specificity in our study, and we recognize that field magnets with higher specificity will probably produce better results by increasing the signal-to-noise and reproducibility in the functional MR study. This also allows a decrease in the voxel size (40). These improvements deserve further evaluation.

In summary, coincidence analysis grouping functional MR abnormalities with focal brain density reductions in schizophrenic patients with chronic auditory hallucinations are largely depicted at the middle, superior temporal, and cingular gyri. The possibility that coincidence maps could be used for follow-up of these patients after treatment should be evaluated.

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