Tuning in to the Voices: A Multisite fMRI Study of Auditory Hallucinations

Judith M. Ford[1–4], Brian J. Roach[2–4], Kasper W. Jorgensen[2,3], Jessica A. Turner[5], Gregory G. Brown[6], Randy Notestine[6], Amanda Bischoff-Grethe[6], Douglas Greve[7], Cynthia Wible[8], John Lauriello[9], Aysenil Belger[10], Bryon A. Mueller[11], Vincent Calhoun[2,9], Adrian Preda[5], David Keator[5], Daniel S. O'Leary[11], Kelvin O. Lim[12], Gary Glover[13], Steven G. Potkin[5,14], FBIRN, and Daniel H. Mathalon[2–4]

[2]Yale University, West Haven, CT; [3]University of California, San Francisco; [4]San Francisco VA Medical Center; [5]University of California: Irvine; [6]University of California: San Diego; [7]Massachusetts General Hospital, Charlestown, MA; [8]Brigham and Women's Hospital, Boston, MA; [9]University of New Mexico, Albuquerque, NM; [10]University of North Carolina, Durham, NC; [11]University of Iowa, Iowa City, IA; [12]University of Minnesota, Minneapolis, MN; [13]Stanford University, Stanford, CA; [14]Functional Imaging Biomedical Informatics Research Network

Introduction: Auditory hallucinations or voices are experienced by 75% of people diagnosed with schizophrenia. We presumed that auditory cortex of schizophrenia patients who experience hallucinations is tonically "tuned" to internal auditory channels, at the cost of processing external sounds, both speech and nonspeech. Accordingly, we predicted that patients who hallucinate would show less auditory cortical activation to external acoustic stimuli than patients who did not. *Methods:* At 9 Functional Imaging Biomedical Informatics Research Network (FBIRN) sites, whole-brain images from 106 patients and 111 healthy comparison subjects were collected while subjects performed an auditory target detection task. Data were processed with the FBIRN processing stream. A region of interest analysis extracted activation values from primary (BA41) and secondary auditory cortex (BA42), auditory association cortex (BA22), and middle temporal gyrus (BA21). Patients were sorted into hallucinators (*n* = 66) and nonhallucinators (*n* = 40) based on symptom ratings done during the previous week. *Results:* Hallucinators had less activation to probe tones in left primary auditory cortex (BA41) than nonhallucinators. This effect was not seen on the right. *Discussion:* Although "voices" are the anticipated sensory experience, it appears that even primary auditory cortex is "turned on" and "tuned in" to process internal acoustic information at the cost of processing external sounds. Although this study was not designed to probe cortical competition for auditory resources, we were able to take advantage of the data and find significant effects, perhaps because of the power afforded by such a large sample.

Key words: schizophrenia/auditory hallucinations/fMRI/ auditory cortex

Introduction

Auditory hallucinations or voices are experienced by 75% of people diagnosed with schizophrenia. These voices range from random and/or muffled words to complete sentences and conversations. Patients can describe them as either internal (coming from inside their head) or external, and they are often reported as real despite evidence to the contrary.[1] With hemodynamic and electrophysiological brain imaging, we have the opportunity to understand both the neural origin of the voices and the neural mechanisms underlying them.

Different neurobiological strategies have been used to assess the pathophysiology of auditory hallucinations in schizophrenia. Some investigators have had success using a naturalistic "symptom capture" approach where neurobiological data are collected as patients experience hallucinations. While this approach is conceptually simple, it is difficult in practice because it relies not only on the timely occurrence of an elusive subjective experience but also on the ability of the patient to reliably report its initiation and completion. Symptom capture requires patience from the research team as well as cooperation and insight from the patient. Nevertheless, 4 groups have been successful at comparing brain activations during periods when hallucinations were present and absent. One found no activation in auditory cortex during periods of hallucinations,[2] 2 found auditory cortical activity but no primary auditory cortex activity,[3,4] and 1 found activation in primary and secondary auditory cortex.[5] The lack of consistency may be due to small sample sizes (*n* ≤ 6) used in these studies.

A more mechanistic approach that does not rely on timing, patience, and cooperation is the "fundamental deficit" approach.[6] Following the writings of Feinberg[7] and Frith,[8] we used electroencephalography-based methods to test the hypothesis that there is a fundamental dysfunction

---

[1]To whom correspondence should be addressed; tel: 415-221-4810 x4187, fax: 415-750-6622, e-mail: judith.ford@yale.edu.

of the efference copy/corollary discharge mechanism, whereby old memories, preoccupations, and thoughts, that are not identified as self-generated, are interpreted as coming from an external source (ie, hallucinations).[9,10]

The "probe approach" is yet another method used to study auditory hallucinations. With this approach, auditory stimuli, which might compete for resources with auditory hallucinations, are presented to patients while hearing voices[11] or to patients likely to be hearing voices.[12,13] Hubl et al[11] combined symptom capture and probe approach. They asked psychotic patients who frequently hallucinated to signal periods of hallucinations while simultaneously probing cortical responsiveness with pure tones. They found that the N1 component of the auditory event-related brain potential to the tones was reduced, especially on the left, during periods of auditory hallucinations compared with periods without hallucinations. Woodruff et al[12] did not ask patients to signal hallucinations but instead studied the same patients during episodes of severe hallucinations (state positive) and about 3 months later when not actively hallucinating (state negative). He also studied schizophrenia patients who never hallucinated (trait negative) and healthy controls. Regardless of hallucination propensity, patients with schizophrenia responded less to speech probes than did controls in BA42 and BA22 on the left. This effect was exaggerated in patients likely to be hearing voices, suggesting that external sounds were competing with voices for left hemisphere resources. Similarly, Plaze et al[13] found a strong negative relationship between activation in BA22 on the left to sentences and severity of auditory hallucinations in 16 schizophrenia patients who hallucinated daily.

Current Approach and Hypothesis

We have adopted the probe approach in this article. We presumed that the auditory cortex of schizophrenia patients who recently experienced hallucinations is tonically "tuned" to the internal channels in which hallucinatory stimuli are typically broadcast. In this way, the auditory cortex is always in a state of readiness to process internally generated auditory signals whenever they are spontaneously emitted. The auditory processing "bandwidth" devoted to internal verbal dialogues is posited to be particularly costly from the standpoint of auditory processing resources, diminishing the capacity of the auditory cortex to process external sounds. Based on this framework, we predicted that patients who hallucinate would show less auditory cortical activation to external acoustic stimuli than patients who did not. While it is certainly possible that patients who hallucinated during the previous week were more likely to be actively hallucinating during the experiment, our predictions did not strictly depend on this being the mechanism of diminished auditory cortical activation.
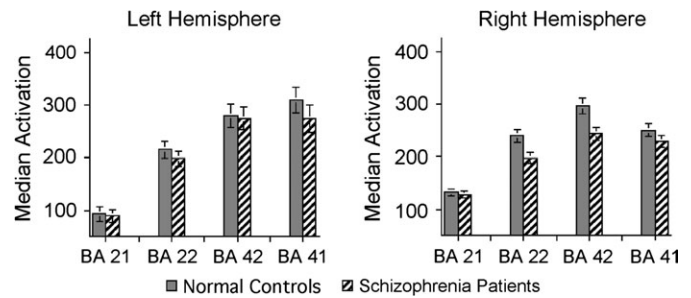

Fig. 1. Median Activations for Each Region of Interest are Plotted for Healthy Controls and Patients With Schizophrenia (Those Who Did and Did Not Hallucinate in the Prior Week). Activations are plotted separately for left and right hemisphere.

We adopted a region of interest (ROI) analysis approach in our analysis. This was based on our observation that hallucinations may be generated from different subregions within a cortical area, as noted in figure 1 of Dierks et al.[5] Compared with the more traditional voxel-wise group analysis approach, the ROI approach allows us to extract activations from within a region rather than relying on consistent activation of a cluster of voxels. Although areas other than auditory have been implicated in the experience of auditory hallucinations (eg, anterior cingulate, supplementary motor area, Broca's area), we focused our analysis on cortical areas directly related to auditory processing to test the theory that voices would compete with external sounds for auditory processing resources. We inspected activations in 4 auditory cortical regions: primary auditory cortex (BA41), which is also called anterior transverse temporal gyrus; secondary auditory cortex (BA42), which is also called posterior transverse temporal gyrus; auditory association cortex (BA22); and middle temporal gyrus (BA21). Because language perception[14] and voices[15] may involve right hemisphere structures, we included both left and right hemisphere structures in our analysis.

We predicted that external sounds would primarily compete for auditory cortex resources on the left because of the left lateralization of language. Specifically, we predicted that schizophrenia patients endorsing auditory hallucinations would have less activation to sounds in left auditory cortex compared with right in comparison to patients who did not endorse auditory hallucinations. Although patients and controls were balanced for age within each site, there were age differences across sites; consequently, age was included as a factor in the analysis. Also, because there were different magnet strengths and manufacturers at the different sites, site was also considered in the analyses.

Methods

Participants

All 9 Functional Imaging Biomedical Informatics Research Network (FBIRN) sites received local Institutional
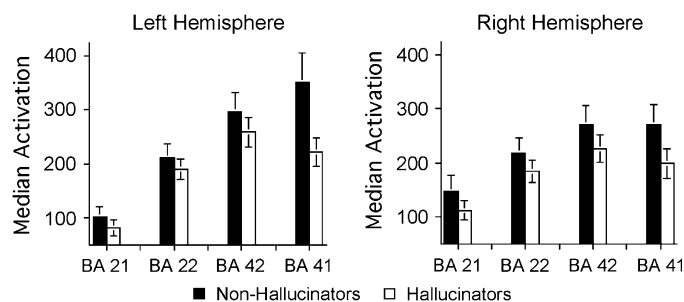
Fig. 2. Same as Figure 1, but for hallucinators and nonhallucinators, separately.

Review Board approval for this study, and all participants provided written informed consent. Data from healthy men and women ($n = 111$) and from people with schizophrenia or schizoaffective disorder ($n = 106$) were included. All subjects had normal hearing (no more than a 25 dB loss in either ear) and were able to perform the task.

Control subjects were interviewed with Structured Clinical Interview *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV)* for normal persons. They were excluded if they had a current or past history of a major neurological, psychiatric, medical illness; substance or alcohol dependence; head injury; and IQ less than 75 (as measured by the North American Adult Reading Test [NAART]); if they were using migraine treatments; or if a first-degree family member had a diagnosis of a psychotic illness.

Patients meeting the Structured Clinical Interview *DSM-IV* criteria for schizophrenia or schizoaffective disorder participated in the study. Subjects were excluded if they had a current major medical illness; previous head injury or prolonged unconsciousness; or current or past substance and/or alcohol dependence. Patients were also excluded if they had an IQ less than 75 as measured by the NAART, migraine treatments, and significant tardive dyskinesia (measured by the Global section of the Abnormal Involuntary Movement Scale). Subjects were required to be clinically stable with no significant changes in their psychotropic medications in the previous 2 months.

Subjects were asked to have a normal night's sleep the night before each scan, no more than one alcoholic drink the night before, and abstain from drinking coffee within 2 h prior to lying down in the scanner. Subjects who smoked refrained from smoking starting 40 min before lying down in the scanner.

Clinical Measures Collected

Many demographic data were collected from patients and controls; those relevant to this report are the Edinburgh Handedness Inventory and the Socioeconomic Status Questionnaire. In addition, all patients received a full complement of symptom ratings, but only the Scale for the Assessment of Positive Symptoms (SAPS) is relevant to this report.

For the purposes of the analysis presented here, patients were split into 2 groups: hallucinators (SAPS item #36 $\geq$ 1) and nonhallucinators (SAPS item #36 = 0). There were 66 hallucinators and 40 nonhallucinators. Demographic characteristics of this sample appear in table 1. In addition, we performed a control analysis based on thought disorder (SAPS item #69—global rating of positive thought disorder). For this analysis, patients were split into 2 groups: thought disordered (SAPS #69 $\geq$ 1) and nonthought disordered (SAPS #69 = 0).

Task

Subjects heard a sequence of standard (95%; 1000 Hz) and target (5%; 1200 Hz) 100-ms duration tones every 500 ms. They were instructed to press a button to the oddball tone. A black fixation cross in the middle of a gray screen was presented for the duration of each run. There were 2 practice runs and 4 experimental runs each lasting 280 s (4.67 min). Before and after the 4 experimental runs, there was a fixation block lasting 15 s.

Each subject adjusted the volume of a test stimulus to the left and right ears so that it could be heard comfortably over the noise of the scanner during an echo planar image (EPI) scan.

Responses were monitored for performance accuracy.

Imaging Parameters

Scan parameters relevant to this article are described here.

The numbers of subjects included in the final analysis from each site are listed here, as well as the type of scanner used. DUKE-UNC, $n = 29$, GE LX 4T; BWH, $n = 14$, GE Signa 3T; MGH, $n = 7$, Siemens 3T Trio; UCLA, $n = 20$, Siemens 3T Trio; UCI, $n = 34$, Picker 1.5T Eclipse; UNM, $n = 29$, Siemens 1.5T Sonata; UI, $n = 27$, Siemens 3T Trio; UMN, $n = 29$, Siemens 3T Trio; Yale, $n = 28$, Siemens 3T Trio.

The scanning session consisted of a localizer scan as needed to identify the anterior commissure-posterior commisure (AC-PC) axis; any shimming that a site used (higher order when possible); B_0 field mapping scans were acquired, and dewarping was used in the analysis, except at sites using 1.5T scanners or spiral acquisitions.

The functional scans were T2*-weighted gradient echo EPI sequences, with relaxation time = 2000 ms, echo time (TE) = 30 ms (UCI used TE = 40 ms. UNM used TE = 39 ms), flip angle 90° (acquisition matrix 64 × 64, 22 cm field of view, 27 slices (UCI collected 21 slices), 4 mm thick with 1 mm gap, oblique axial AC-PC aligned.

Each scan session consisted of a brief training session to familiarize the subject with the paradigms, placement in the scanner for about 1½ h during which structural and functional images were collected. At least 24 h later and

Table 1. Demographics of Populations Studied

Variable	Healthy Controls (n = 111)				Nonhallucinating Patients (n = 40)				Hallucinating Patients (n = 66)				P Value
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	
Age (y)	36.33	11.71	19	65	39.58	13.10	19	65	38.47	11.60	19	58	.32
Education (y)[a]	15.9	2.43	5	24	13.97	2.11	11	18	13.17	1.87	10	18	.0001
SES[b] based on education of primary caretaker before age 18 y[c]	2.85	1.38	1	7	3.32	1.49	1	7	3.00	1.48	1	7	.22
SES based on occupation of primary caretaker before age 18 y[d]	3.3	1.81	1	7	3.97	1.83	1	7	3.80	1.83	1	7	.08
Mean symptom scores from SAPS[e]													
Item #36 auditory hallucinations									3.27	1.37	1	5	
Item #37 voices commenting									1.85	1.85	0	5	
Item #38 voices conversing									1.47	1.73	0	5	
Handedness	100 right 7 left 4 ambidexterous				35 right 4 left 1 ambidextrous				61 right 5 left				
Gender	43 women 68 men				10 women 30 men				20 women 46 men				

[a]Data missing from 6 controls, 5 nonhallucinators, and 12 hallucinators.
[b]Scale for the Assessment of Positive Symptoms.
[c]Data missing from 2 controls, 2 nonhallucinators, and 5 hallucinators.
[d]Socioeconomic status, Hollingshead and Redlich, 1958.
[e]Data missing from 7 controls, 3 nonhallucinators, and 2 hallucinators.

no more than 3 weeks later, the subject repeated the entire session; however, only data from the first session are included here.

Data Analysis: Preprocessing

Images were processed with a developmental version of the FBIRN Image Processing System (FIPS), an image analysis pipeline primarily using routines from the FMRIB Software Library (FSL) (http://www.fmrib.ox. ac.uk/). Preprocessing steps were separated from the remainder of the FIPS pipeline, with XML and related files developed to track provenance information. The preprocessing scripts used FSL's MCFLIRT to motion correct the time series of each subject (usually aligning to the middle volume), PRELUDE and FUGUE to B_0 correct images at sites where field maps were collected, and "slice-timer" to correct images for slice-timing differences (http://www.fmrib.ox.ac.uk/). To equilibrate images for potential site differences in the blood oxygen level dependent (BOLD) signal due to spatial smoothness, we smoothed all 3-D volumes to 8 mm full-width-half-max (FWHM).[16] The smooth-to-script used FSL's "betfunc" program to skull-strip the functional magnetic resonance imaging (fMRI) dataset, then Freesurfer's "mri_fwhm" program (http://surfer.nmr.mgh.harvard. edu/) and FSL's "ip" program to spatially smooth the fMRI dataset to the prescribed smoothness.

Image Quality Assurance Screening

Upload scripts included a wide range of image quality measures aimed at identifying image sets with poor temporal stability, in-plane intensity distortion, and abnormal smoothness, among other characteristics. We excluded 1 control and 2 patients for coregistration failures, 6 controls and 3 patients for poor performance (target detection accuracy < 50%), and 4 controls and 7 patients for not having 4 complete runs on the first session. None of the excluded subjects are included in table 1.

ROI Analysis Approach

WFU Pickatlas was used to generate masks in MNI space for auditory cortex (left and right Brodmann areas 41, 42, 22, and 21) and for primary visual cortex (BA17) as a control ROI. The median activation in each ROI was extracted. This analysis focused on the contrast between targets and standards.

Two main analyses of variance (ANOVAs) with contrasts were run to assess group effects, hemisphere, and ROI; in one ANOVA, we compared healthy controls with all patients, and in the other ANOVA we compared patients who endorsed recent hallucinations (hallucinators) with those who did not (nonhallucinators). The data were entered to allow a focused assessment of pri-

mary auditory cortex (BA41) compared with all the other regions (BA41 + BA22 + BA21; contrast 3), planum temporale (BA42) compared with superior temporal gyrus (STG) + middle temporal gyrus (MTG) (BA22 + BA21; contrast 2), and STG (BA21) compared with MTG (BA22; contrast 1). The analysis is evident in table 2 where the results from both ANOVAs are presented.

To assess the specificity of the effects to hallucinations, we performed a similar analysis comparing nonthought disordered and thought disordered patients. To assess the specificity of effects to auditory cortex, we performed an analysis of group effects (nonhallucinators vs hallucinators) and hemisphere for activation in BA17.

Performance accuracy differences between the groups were assessed in 2 *t* tests, healthy controls vs all patients, and nonhallucinators vs hallucinators.

Results

The results of the ANOVAs comparing auditory cortical activations of healthy controls to schizophrenia patients (left) and of hallucinators to nonhallucinators (right) appear in table 2. In this table, all modeled effects are presented. Those involving effects of noninterest (site and age) are shaded. Significant effects of interest are bolded. The results of the other analyses are detailed below.

Healthy Controls (n = 111) vs Patients (n = 106)

As can be seen in table 2 and figure 1, there was a main effect of group, with healthy controls having greater activation in the temporal lobe ROIs than the patients, a main effect of hemisphere, with left hemisphere having more activation than right hemisphere, and a main effect of ROI, with BA42 having greater activation than BA21 and BA22, and BA22 having greater activation than BA21.

There was a group × ROI interaction involving the contrast between BA22 and BA21. This was parsed by inspecting the contrast separately for each group. Although the effect of BA22 > BA21 was larger in the controls than in the patients, it was significant for both groups (controls, $P < .0001$; patients, $P < .0001$).

There was an ROI × hemisphere interaction involving the contrast between BA42 and BA21 + BA22. This was parsed by inspecting the contrast separately for left and right hemispheres; BA42 had more activation than BA21 + BA22 in both left ($P < .0001$) and right ($P < .0001$) hemispheres.

Controls missed fewer targets (7.3%) than patients (9.3%), but this difference was not significant ($P = .16$).

Hallucinators (n = 66) vs Nonhallucinators (n = 40)

As can be seen in table 2 on the right, and in figure 2, there was a main effect of ROI, with BA42 having greater activation than BA21 and BA22 and BA22 having greater activation than BA21. Most important, there was a

Table 2. ANOVA Results for Median Activations in Auditory Cortex Regions of Interest (ROIs): BA21, BA22, BA42, BA41

Source	Contrasts for ROI	Contrast for Hemisphere	Healthy Controls (111) Vs Schizophrenia Patients (106)			NonHallucinators (40)Vvs Hallucinators (66)		
			df	F	Significant	df	F	Significant
Group			1, 206	3.76	**.05**	1, 95	2.99	.09
Hemisphere		Right vs left	1, 206	3.79	**.05**	1, 95	2.43	.12
Hemisphere × group		Right vs left	1, 206	1.23	.27	1, 95	0.00	.96
Hemisphere × age		Right vs left	1, 206	3.92	.05	1, 95	2.04	.16
Hemisphere × site		Right vs left	8, 206	1.34	.23	8, 95	0.79	.61
ROI	BA22 vs BA21		1, 206	59.76	**.0000**	1, 95	21.33	**.0000**
	BA42 vs (BA22 + BA21)/2		1, 206	46.39	**.0000**	1, 95	31.46	**.0000**
	BA41 vs (BA22 + BA21 + BA42)/3		1, 206	2.07	.15	1, 95	0.48	.49
ROI × group	BA22 vs BA21		1, 206	4.40	**.04**	1, 95	0.03	.87
	BA42 vs (BA22 + BA21)/2		1, 206	1.18	.28	1, 95	1.50	.22
	BA41 vs (BA22 + BA21 + BA42)/3		1, 206	1.61	.21	1, 95	8.14	**.01**
ROI × age	BA22 vs BA21		1, 206	9.56	.00	1, 95	4.05	.05
	BA42 vs (BA22 + BA21)/2		1, 206	6.73	.01	1, 95	8.67	.00
	BA41 vs (BA22 + BA21 + BA42)/3		1, 206	0.82	.37	1, 95	0.68	.41
ROI × site	BA22 vs BA21		8, 206	3.89	.00	8, 95	0.82	.59
	BA42 vs (BA22 + BA21)/2		8, 206	3.08	.00	8, 95	0.77	.63
	Level 4 vs Previous		8, 206	4.05	.00	8, 95	2.19	.04
ROI × hemisphere	BA22 vs BA21	Right vs left	1, 206	1.49	.22	1, 95	0.18	.67
	BA42 vs (BA22 + BA21)/2	Right vs left	1, 206	6.89	**.01**	1, 95	3.18	.08
	BA41 vs (BA22 + BA21 + BA42)/3	Right vs left	1, 206	1.38	.24	1, 95	0.01	.91
ROI × hemisphere × group	BA22 vs BA21	Right vs left	1, 206	2.30	.13	1, 95	0.03	.86
	BA42 vs (BA22 + BA21)/2	Right vs left	1, 206	2.02	.16	1, 95	0.11	.75
	BA41 vs (BA22 + BA21 + BA42)/3	Right vs left	1, 206	0.31	.58	1, 95	6.79	**.011**
ROI × hemisphere × age	BA22 vs BA21	Right vs left	1, 206	0.00	.97	1, 95	0.28	.60
	BA42 vs (BA22 + BA21)/2	Right vs left	1, 206	3.42	.07	1, 95	1.03	.31
	BA41 vs (BA22 + BA21 + BA42)/3	Right vs left	1, 206	0.05	.83	1, 95	1.01	.32
ROI × hemisphere × site	BA22 vs BA21	Right vs left	8, 206	1.23	.28	8, 95	0.74	.65
	BA42 vs (BA22 + BA21)/2	Right vs left	8, 206	1.37	.21	8, 95	1.42	.20
	BA41 vs (BA22 + BA21 + BA42)/3	Right vs left	8, 206	1.98	.05	8, 95	2.03	.05

group × hemisphere × ROI interaction involving the contrast between BA41 and the other 3 ROIs. The group × ROI interaction involving this contrast was stronger on the left ($F_{1,95}$ = 12.40, $P < .001$) than on the right ($F_{1,95}$ = 0.753, $P = .39$). Specifically, nonhallucinators had greater activation in left BA41 than hallucinators ($F_{1,95}$ = 8.34, $P < .005$). This was not true for right BA41 ($F_{1,95}$ = 2.68, $P = .11$).

In addition, we calculated the correlation between activation in left BA41 and hallucination severity in the group of hallucinators. The correlation was not significant ($r = 0.02$, $P = .86$), suggesting that whether a patient tends to hallucinate or not is a better predictor of BA41 activation to sounds than is hallucination severity.

Nonhallucinators had significantly ($P = .028$) fewer missed targets (5.5%) than hallucinators (9.9%); nevertheless, poor performance was not significantly related to decreased activation in left BA41 ($r = -0.20$, $P = .11$) in the hallucinators. In addition, we ran the main ANOVA with accuracy as a covariate. The group × hemisphere × ROI interaction involving the contrast between BA41 and the other 3 ROIs changed in significance from $P = .011$ to $P = .014$.

A comparison of thought disordered ($n = 58$) and non-thought disordered ($n = 44$) patients revealed a different pattern of results (symptom ratings for thought disorder were missing for 4 patients). While thought disordered patients had less activation in the auditory cortical structures than the thought disordered ones ($F_{1,91}$ = 4.99, $P = .028$), the group × hemisphere × ROI interaction involving the contrast between BA41 and the other 3 ROIs was not significant ($F_{1,91}$ = 0.772, $P = .38$).

The analysis of BA17 revealed a main effect of group with nonhallucinators having greater activation that hallucinators ($F_{1,95}$ = 7.80, $P = .006$). The group × hemisphere interaction was not significant ($F_{1,95}$ = 2.10, $P = .15$), but there was a tendency for a larger group difference over the right than left hemisphere.

Discussion

Using the probe method of studying auditory hallucinations, we found that patients who hear voices have less activation to probe tones in left primary auditory cortex than patients who do not hear voices. This effect was not seen on the right. That is, in patients who hallucinate, resources for processing external sounds were compromised on the left relative to the right, perhaps because of the linguistic content of voices. This effect might be due to both functional and structural reasons.

Functional

Although we had no direct evidence that people were hearing voices while listening to tones in the scanner, our finding of reduced responsiveness to tones in the left auditory cortex in hallucinators is consistent with a study using event-related potentials (ERPs) to tones.[11] Using the symptom capture + probe approach, Hubl et al[11] asked patients to signal the start of hallucinations and sorted ERP trials according to the presence or absence of voices, allowing them to compare state-positive to state-negative periods. In the 7 patients studied, they found that the N1 ERP component from left auditory cortex to tone probes was reduced during state-positive periods. Because N1 is likely to emanate from primary auditory cortex,[17,18] these ERP findings are similar to our findings of reduced left primary auditory cortex responsiveness in hallucinators. In spite of the fact that we both used pure tones, which are processed by both the right and left primary auditory cortex, both our findings were distinctly left-sided. Perhaps the linguistic nature of the internal acoustic experience ("voices") competes for general auditory resources on the left.

Our findings are also consistent with fMRI probe studies of Woodruff et al[12] and Plaze et al.[13] Although neither study asked patients to signal the presence of hallucinations, it is possible that the patients were hallucinating while hearing the external acoustic stimuli. We have no evidence that patients in our study were hallucinating while listening to the sounds. Instead, we presumed that the auditory cortex of patients with recent hallucinations is tonically poised to process internally generated voices at the expense of processing external sounds. Accordingly, we predicted that patients who tend to experience hallucinations would show less auditory cortical activation to externally delivered acoustic stimuli and less capacity to engage cortical resources to perform auditory tasks, such as an auditory oddball task, than patients who do not experience hallucinations. This prediction was borne out. Thus, while we did not do a symptom capture study, the power of our analysis to capture group differences in hallucinations was clearly enhanced by the large sample collected by the 9 FBIRN data collection sites. Our sample included 66 hallucinators and 40 nonhallucinators.

While the ERP probe study suggested the involvement of primary auditory cortex,[11] neither of the fMRI probe studies pointed to the involvement of BA41.[12,13] This difference may be due to the different probes used. We used tones and found reductions in primary auditory cortex, BA41; the other fMRI probe studies used speech sounds and found reductions in speech processing regions, BA42 and BA22.[12,13] Because we used pure tones, it is not surprising that the effects were seen in primary auditory cortex, as the main processing region for pure tones. If we had used speech sounds, we may have found robust competition for resources in the auditory association cortex in posterior portion of the temporal cortex (BA22).

It is important to consider the possible contribution of attention to the main finding described here, the interaction between Group, Hemisphere, and ROI (BA41 vs the other areas). If patients were hearing voices and

attending to them, their attention may have been diverted from the task. However, controlling for performance accuracy did not affect this effect, in spite of the fact that patients who tended to hallucinate performed the task less accurately.

Also, the reduction of left hemisphere primary auditory cortical activation in hallucinators is not seen in thought disordered patients, nor is left hemisphere reduction seen in visual cortex in patients who tend to hallucinate. Although other symptoms and other regions were not subjected to the same analysis, these effects may be relatively specific to hallucinations and auditory cortex.

Structural

It is also possible that a reduction in gray matter volume of the left auditory cortex in hallucinators is responsible for their reduced responses to sounds on the left. MRI studies suggest that auditory hallucinations are associated with reduced gray matter volumes in the temporal lobe, especially in the STG including the primary auditory cortex.[15] Although the topic of another article from the FBIRN, structural MR data were available from 20 nonhallucinators and 39 hallucinators. The volume of gray matter for each subject's transverse temporal gyrus was measured using a semi-automated method (Freesurfer version 3.05, http://surfer.nmr.mgh.harvard. edu/).[19–21] We found no differences in gray matter volume between hallucinators and nonhallucinators. Perhaps a more focused inspection of BA41 alone would have revealed some group differences because this is the region in our data that was sensitive to group differences. However, we have no evidence that our group effects are due to structural brain differences.

In summary, patients who tended to hallucinate had less activation to target tones in left primary auditory cortex (BA41) than did nonhallucinators. This suggests that even though "voices" are the anticipated sensory experience, a nonspeech area of auditory cortex (eg, Heshcl's gyrus) is also "turned on" and "tuned in" to process internal acoustic information at the cost of processing sounds in general. Although this study was not designed to probe auditory cortical competition for processing resources, we were able to take advantage of the data and find significant effects perhaps because of the power rendered by such a large sample.

Acknowledgments

References

1. Nayani TH, David AS. The auditory hallucination: a phenomenological survey. *Psychol Med*. 1996;26:177–189.
2. Silbersweig DA, Stern E, Frith CD, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature*. 1995; 378:176–179.
3. Shergill S, Brammer M, Williams S, Murray R, McGuire P. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2000;57:1033–1038.
4. Lennox BR, Park SB, Medley I, Morris PG, Jones PB. The functional anatomy of auditory hallucinations in schizophrenia. *Psychiatry Res*. 2000;100:13–20.
5. Dierks T, Linden D, Jandl M, et al. Activation of Heschl's gyrus during auditory hallucinations. *Neuron*. 1999;22:615–621.
6. Silbersweig D, Stern E. Functional neuroimaging of hallucinations in schizophrenia: toward an integration of bottom-up and top-down approaches. *Mol Psychiatry*. 1996;1:367–375.
7. Feinberg I. Efference copy and corollary discharge: implications for thinking and its disorders. *Schizophr Bull*. 1978;4: 636–640.
8. Frith CD. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychol Med*. 1987;17:631–648.
9. Ford JM, Mathalon DH. Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. *J Psychiatr Res*. 2004;38:37–46.
10. Mathalon DH, Ford JM. Corollary discharge dysfunction in schizophrenia: evidence for an elemental deficit. *Clin EEG Neurosci*. 2008;39:82–86.
11. Hubl D, Koenig T, Strik WK, Garcia LM, Dierks T. Competition for neuronal resources: how hallucinations make themselves heard. *Br J Psychiatry*. 2007;190:57–62.
12. Woodruff PW, Wright IC, Bullmore ET, et al. Auditory hallucinations and the temporal cortical response to speech in schizophrenia: a functional magnetic resonance imaging study. *Am J Psychiatry*. 1997;154:1676–1682.
13. Plaze M, Bartres-Faz D, Martinot JL, et al. Left superior temporal gyrus activation during sentence perception negatively correlates with auditory hallucination severity in schizophrenia patients. *Schizophr Res*. 2006;87:109–115.
14. Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci*. 2007;8:393–402.

15. Allen P, Laroi F, McGuire PK, Aleman A. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev*. 2008;32:175–191.

16. Friedman L, Glover G, Krenz D, Magnotta V. Reducing inter-scanner variability of activation in a multicenter fMRI study: role of smoothness equalization. *Neuroimage*. 2006;32:1656–1668.

17. Pantev C, Bertrand O, Eulitz C, et al. Specific tonotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. *Electroencephalogr Clin Neurophysiol*. 1995;94:26–40.

18. Pantev C, Hoke M, Lehnertz K, Lutkenhoner B, Fahrendorf G, Stober U. Identification of sources of brain neuronal activity with high spatiotemporal resolution through combination of neuromagnetic source localization (NMSL) and magnetic resonance imaging (MRI). *Electroencephalogr Clin Neurophysiol*. 1990;75:173–184.

19. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000;97:11050–11055.

20. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage*. 1999;9:179–194.

21. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31:968–980.