

Aberrant Localization of Synchronous Hemodynamic Activity in Auditory Cortex Reliably Characterizes Schizophrenia

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Background: Among the most prominent features of schizophrenic brains are abnormalities in auditory cortex structure and function, particularly in the superior temporal gyrus (STG). In this study, we attempted to examine auditory cortex function using an intrinsic, task-uncorrelated measure.

Methods: Using functional magnetic resonance imaging data, we calculated synchronous hemodynamic independent maps (SHIMs) of auditory cortex in patients with schizophrenia and matched healthy control subjects while they performed an auditory oddball task.

Results: Patient SHIMs revealed greater synchrony in ventral and medial STG regions (including auditory association Brodmann area [BA] 42); control SHIMs had greater synchrony in dorsal and lateral STG regions (which did not include BA 42). A within-participant subtractive comparison of these two sets of regions differentiated schizophrenic from healthy control subjects with 97% accuracy initially (further validated by a retest of the healthy control subjects) and performed with 94% accuracy in a confirmatory study of new subjects scanned at a different site.

Conclusions: These results shed new light on STG functional differences in schizophrenia, suggest that aberrant patterns of coherence in temporal lobe cortical regions are a cardinal abnormality in schizophrenia, and have the potential to provide a powerful, quantitative clinical tool for the assessment of schizophrenia.

Key Words: Functional magnetic resonance imaging, schizophrenia, auditory, independent component analysis, superior temporal gyrus, synchrony

Schizophrenia, currently diagnosed on the basis of a constellation of psychiatric symptoms, has been associated with both structural and functional abnormalities in neocortical networks, including frontal, parietal, and temporal regions. Temporal lobe neuroanatomic abnormalities were described in early work by Flechsig (1896) and Southard (1915). To date, structural findings include evidence for mild, widespread deficits in cortical gray matter volumes, and more specific regional reductions in heteromodal association cortex and temporolimbic structures (Pearlson and Marsh 1999). Volumetric changes reported in superior temporal gyrus (STG) correlate with severity of auditory hallucinations (Barta et al 1990) and of formal thought disorder (Shenton et al 1992). It has been proposed that structural and functional STG pathology represents a local example of a more general disruption in schizophrenia of neocortical networks (Ross and Pearlson 1996). The STG is an essential part of several such networks, and thus disruptions in its structure and function are potentially of great importance (Pearlson 1997).

Functional brain disturbances in patients with schizophrenia have been studied with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (Lennox et al

1999; Woodruff et al 1997). It has been demonstrated that auditory cortex shows abnormal fMRI activity in speech-related areas (Penfeld and Perot 1963). Activation of primary auditory cortex, a subset of Heschl's gyrus, has also been shown in patients experiencing active hallucinations (Dierks et al 1999). Source localization measurements have demonstrated anatomic and laterality shifts of function in auditory cortex. For example, data from magnetoencephalography (MEG) have shown anomalous asymmetry of the 100-msec latency (M100) auditory abnormalities, compatible with neuronal generators located in the transverse gyri of Heschl on the superior temporal gyri, in patients with schizophrenia and schizoaffective disorder (Teale et al 2000). Using MEG, Rojas et al (2002) showed that auditory cortex tonotopy is not linear in schizophrenia, as it is in healthy individuals.

One of the most robust abnormalities in schizophrenia is a deviant P3 event-related potential (ERP) to low-probability auditory target stimuli (Blackwood et al 1991; Ebmeier et al 1990; McCarley et al 1993). McCarley et al (1993) link the abnormal P3 ERP response to decreased STG gray matter volume. Some studies indicate that P3 reductions in schizophrenia are greater over left than right temporal lobe sites (McCarley et al 1991; Salisbury et al 1998; Turetsky et al 1995), whereas other studies have found equal hemispheric P3 reductions (Ford et al 1994; Kiehl and Liddle 2001; Pfefferbaum et al 1995). Similarly, Kiehl and Liddle (2001) showed that, during performance of an auditory oddball task, schizophrenic patients relative to control subjects exhibit diffuse aberrant hemodynamic activity, particularly in the temporal lobes. The utility of task-uncorrelated functional processes has been suggested previously. Work by Fletcher et al (1998) replicated earlier work showing, in patients with schizophrenia, a lack of deactivation of superior temporal regions that was independent of memory-task performance, possibly reflecting a core abnormality of the condition.

Despite evidence indicating functional disturbances of the auditory cortex, there has been no intrinsic, task-free study of auditory cortex function in schizophrenia. With fMRI, functional connectivity (two regions are considered functionally "connected" if they are temporally correlated with one another) in the

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“resting state” has been demonstrated for healthy individuals in functionally similar cortical regions, such as primary motor, visual, language, or auditory cortex (Biswal et al 1995, 1997; Cordes et al 2001; Lowe et al 1998; Xiong et al 1999). Functional connectivity of, for example, the primary motor cortex to other areas can be assessed with fMRI by taking a seed point (voxel) from within the motor cortex and correlating the fMRI time course from this voxel to all the other fMRI time courses within the brain (typically after low-pass filtering to remove high-frequency noise) (Xiong et al 1999). Voxels from ipsilateral cortex correlate highly with the seed point, as do the contralateral motor cortical areas. One of the disadvantages of such connectivity studies is the requirement of a seed voxel (because it induces a bias, depending on which voxel is chosen) and the choice of the filtering parameters. To have more control over the participant’s cognitive activities compared with “resting” acquisitions, functional connectivity maps can also be generated from data in which a task is used (Arfanakis et al 2000). Recent work by Leopold et al (2003) in monkey visual cortex suggests that these fMRI signals might be related to low-frequency fluctuations in local field potential.

Recently, methods based on independent component analysis (ICA) have been applied to measure functional connectivity; they have the advantage of not requiring a seed voxel or temporal filtering (Calhoun et al 2001, 2002; McKeown et al 1998). Independent component analysis was developed to solve problems similar to the “cocktail party” scenario, in which individual voices must be resolved from microphone recordings of many people speaking at once (Bell and Sejnowski 1995). The algorithm, as applied to fMRI, assumes a set of nonsystematically overlapping (spatially independent) brain networks, each with associated time courses. The model used constrains the fluctuations of each voxel in a given component to have the same time course and thus the resulting components are appropriately defined as synchronous hemodynamic independent maps (SHIMs). Independent component analysis is particularly useful when the temporal form of the activation is not known a priori, for example, in a naturalistic behavior, such as simulated driving (Calhoun et al 2002).

Independent component analysis has been previously used on fMRI data sets to identify auditory cortex temporal fluctuations (Seifritz et al 2002). We hypothesized that this synchronous cortical activation inclusive of auditory cortex would be abnormal in patients with schizophrenia. In particular, we hypothesized that localized intrasubject differences in STG synchrony would be present in schizophrenia. In addition, we predicted that these measures would provide reliable discrimination criteria for schizophrenia. We used ICA to calculate spatially independent, temporally synchronous regions; and we selected (using the Talairach and Tournoux [1988] coordinates of primary and association auditory cortex) the auditory SHIM for each healthy control and for each patient with schizophrenia. We then examined the spatial characteristics within and between the two groups.

The goal of this study was thus to use ICA to identify task-uncorrelated coherent auditory cortex activity and to characterize its spatial location in healthy control subjects and patients with schizophrenia while they performed an auditory oddball task. The auditory oddball task was used to allow more control over participant’s behavior beyond just “resting.” Three analyses were performed. In the first, subregions of the auditory SHIMs were automatically determined, such that maximal separation between patients and control subjects was realized. We

then examined a subset of the same healthy control subjects on a different day, using the regions determined from the first analysis to determine the reliability of the measure for this group. Finally, we tested the robustness of the detected differences in auditory cortex synchrony by testing an independent sample of patients and control subjects scanned on a different MRI scanner.

Methods and Materials

Participants

Data were collected from two locations. The first cohort (CH1), from Vancouver, British Columbia, consisted of 17 outpatients with chronic schizophrenia, currently in complete or partial remission, and 17 screened healthy control subjects. Each gave written, informed, institutional review board (IRB)-approved consent at the University of British Columbia and was compensated for their participation. A subset of eight healthy control subjects from CH1 returned 2 weeks later for a second scan session. The second cohort (CH2), from Hartford, Connecticut, consisted of eight patients and eight control subjects, each of whom gave written, informed, IRB-approved consent at Hartford Hospital. Patients were diagnosed according to DSM-IV criteria for schizophrenia on the basis of a structured clinical interview and review of the case file (mean \pm SD duration of illness = 11.2 ± 6.3 years) (First et al 1995). All participants had normal hearing (assessed by self-report) and were able to perform the oddball task successfully (to discriminate between the tones) during practice before the scanning session. Healthy participants (and their first-degree relatives) were free of any DSM-IV Axis I disorder (assessed by asking if there was any history of psychosis in their first-degree relatives). All but one patient (and one for whom medications were not recorded) with schizophrenia were receiving stable treatment with atypical antipsychotic medications (CH1: olanzapine [8], risperidone [6], clozapine [1], loxapine [1]; CH2: olanzapine [4], risperidone [4]). There were equal numbers of men and women in the patient and control groups (CH1: 13 men, four women; CH2: seven men, one woman) and all but two participants were right-handed. There were no significant differences between-group differences in age (CH1: patients 36 ± 9.9 years, control subjects 30 ± 9.5 years; CH2: patients 33 ± 14.3 years, control subjects 33 ± 14.2 years) or premorbid and current intelligence as assessed, respectively, with the National Adult Reading Test (Nelson and O’Connell 1978) (CH1: patients = 114 ± 6 , control subjects = 118 ± 5 ; CH2: patients = 112 ± 7 , control subjects = 115 ± 6) and the Quick Test (Ammons and Ammons 1962) (CH1: patients = 103 ± 13 , control subjects = 110 ± 13 ; CH2: patients = 103 ± 12 , control subjects = 107 ± 10). Hollingshead criteria for socioeconomic status (CH1: patients = $2.4 \pm .9$, control subjects = 2.9 ± 1.3 ; CH2: patients = 2.5 ± 1.0 , control subjects = 3.0 ± 1.2) were not significantly different between the groups, as assessed by *t* tests. Reality distortions (7.3 on a scale of 1–25) and psychomotor poverty (3.5 on a scale of 1–10) were assessed in patients. With respect to hallucinations, only nine of 13 patients (for whom this information was available) endorsed this symptom within the past week.

Experimental Design

The auditory oddball task consisted of two runs of 244 stimuli presented to the participant with a custom visual and auditory presentation package (<http://nilab.psychiatry.ubc.ca/vapp/>) with an MRI-compatible auditory sound system (Magnacoustics, Atlantic Beach, New York) with noise-attenuating (25 dB) head-

Table 1. Regions Activated in Auditory Cortex SHIMs for Healthy Control Subjects and Patients with Schizophrenia

Region	Brodmann Area	Control		Patient	
		Volume (cm ³)	Peak Location	Volume (cm ³)	Peak Location
L/R Superior Temporal Gyrus	22, 41, 38, 13, 42, 21, 29	5.7/5.4	5.3 (−51, −19, 5)/5.9 (48, −4, −3)	5.4/5.2	5.0 (−48, −15, 4)/5.2 (48, −4, 0)
L/R Middle Temporal Gyrus	21, 22	.3/.5	3.8 (−59, −4, −3)/4.4 (55, 0, −7)	.4/.2	3.8 (−59, −31, 5)/4.2 (55, 0, −7)
L/R Transverse Temporal Gyrus	41, 42	.6/.5	5.1 (−55, −23, 9)/4.7 (44, −23, 9)	.6/.6	4.8 (−55, −23, 9)/4.7 (55, −23, 9)
L/R Inferior Frontal Gyrus	47	.2/1.2	3.6 (−44, 11, −4)/5.3 (44, 11, −7)	.1/.7	3.5 (−44, 11, −4)/4.7 (44, 11, −7)
L/R Insula	13	.8/1.9	4.5 (−44, −15, 4)/5.6 (44, −4, −3)	.8/1.6	4.6 (−44, −15, 4)/5.1 (44, −4, 0)

Regions identified in the mean activation maps. Coordinates of peak activation (ICA voxel weight) and volume of suprathreshold regions as delineated by the Talairach atlas are indicated.

SHIMs, synchronous hemodynamic independent maps; L, left; R, right; ICA, independent component analysis.

phones and insert ear phones. The stimulus runs consisted of nontarget stimuli (1.5-kHz tones, 80% probability), target stimuli (1-kHz tones, 10% probability), and nonrepeating random digital noises (e.g., tone sweeps, whistles, 10% probability). The stimulus duration was 200 msec with an 1800-msec interstimulus interval. The intervals between stimuli of interest were allocated in a pseudorandom manner in the range 6–10 sec so as to ensure that these stimuli had an equal probability of occurring 0, 1, or 2 sec after the beginning of the 3-sec acquisition period. Participants were instructed to respond as quickly and accurately as possible with their right index finger every time the target tone occurred and not to respond to nontarget tones or novel stimuli. An MRI-compatible fiber-optic response device (Lightwave Medical, Vancouver, British, Columbia) was used to acquire behavioral responses in all studies. Before entry into the scanning room, each participant performed a practice block of 10 trials. The stimulus paradigm data acquisition techniques and stimulus-related activation are described more fully in Kiehl and Liddle (2001).

Image Acquisition

Scans at both the University of British Columbia and Hartford Hospital were acquired on GE 1.5-Tesla scanners (General Electric Medical Systems, Milwaukee, Wisconsin) fitted with a horizon echo-speed upgrade. Functional scans consisting of two runs of gradient-echo echoplanar scans (repetition time = 3 sec, echo time = 40 msec, field of view = 24 cm, matrix = 64 × 64, slice thickness = 5 mm, gap = .5 mm, 29 slices) were obtained consistently over an 8-min 20-sec period for a total of 167 scans per run. Four “dummy” scans were performed at the beginning to allow for longitudinal equilibrium, after which the paradigm began.

Preprocessing

Data were preprocessed with statistical parametric mapping software package, SPM99 (Worsley and Friston 1995). Data were motion corrected, spatially smoothed with a 12-mm³ full width at half-maximum Gaussian kernel, spatially normalized into the standard Montreal Neurologic Institute space, and then converted to the standard space of Talairach and Tournoux (1988) with an algorithm developed by Matthew Brett. The data were slightly subsampled to 4 mm³, resulting in 40 × 48 × 34 voxels. Group spatial ICA was used to decompose the data for each group into 15 components (Calhoun et al 2001). For each participant, the two runs were concatenated and then reduced from 334 to 30 temporal dimensions with principal component analysis on all in-brain voxels within a subset of axial slices inclusive of auditory cortex. Data from all subjects were then concatenated and this aggregate data set reduced to 15 temporal dimensions with principal component analysis, followed by an

independent component estimation with a neural network algorithm that attempts to minimize the mutual information of the network outputs (Bell and Sejnowski 1995). Calibrated time courses and spatial maps were then reconstructed for each subject. More details on the specifics of the method are described by Calhoun et al (2001). For each individual, the component or SHIM (and its corresponding time course) with maximal values in the superior temporal lobe was identified. Group average maps were then converted to *Z* values and thresholded at *Z* > 3.1; suprathreshold regions are presented in Table 1. Because individual analysis was the goal, *Z* thresholding was used as a convenient way to examine the largest weights (voxel values) for the mean SHIM (as opposed to the statistical *t* test approach used when group inference is the goal [Calhoun et al 2001]). Thus, voxels that have high mean value but are highly variable across participants will not be penalized for the high variability. Because the mean map was used for deriving our discrimination criterion, we show this map in Figure 1. We subsequently performed analysis of the auditory cortical maps.

Region Identification

Difference maps from CH1 were compared by subtracting the average control SHIM from the average patient SHIM and identifying a set of voxels within the suprathreshold regions. Regions were automatically selected by thresholding the mean SHIM difference (control–patient) maps to determine voxels with the greatest (most positive) and the least (most negative) values. Identified regions in the auditory cortex divided into ventromedial (AVM) and dorsolateral (ADL), respectively, as indicated by the yellow-and-green bordered regions in Figure 2. For each individual, we then averaged within each region separately and applied the discrimination function $AVM \langle \rangle ADL$ (a measure that is invariant to interindividual fMRI magnitude [scaling] difference).

We then evaluated the discrimination function values. Formulating the problem as a hypothesis test in which healthy control subjects constituted the null hypothesis provides four possible results: false negative (labeling a patient a control), false positive (labeling a control a patient), true negative (labeling a control a control), and true positive (labeling a patient a patient). The two thresholds were then optimized from the first experiment (CH1), such that maximum separability (minimum error) was obtained with the Neyman-Pearson criterion (Lehmann 1968). These regions were then used in the second (retest of healthy control subjects from CH1) and third (confirmatory study on a new set of patients and control subjects [CH2]) studies.

Results

On the auditory oddball task, there were no significant accuracy differences between groups (or between cohorts) for

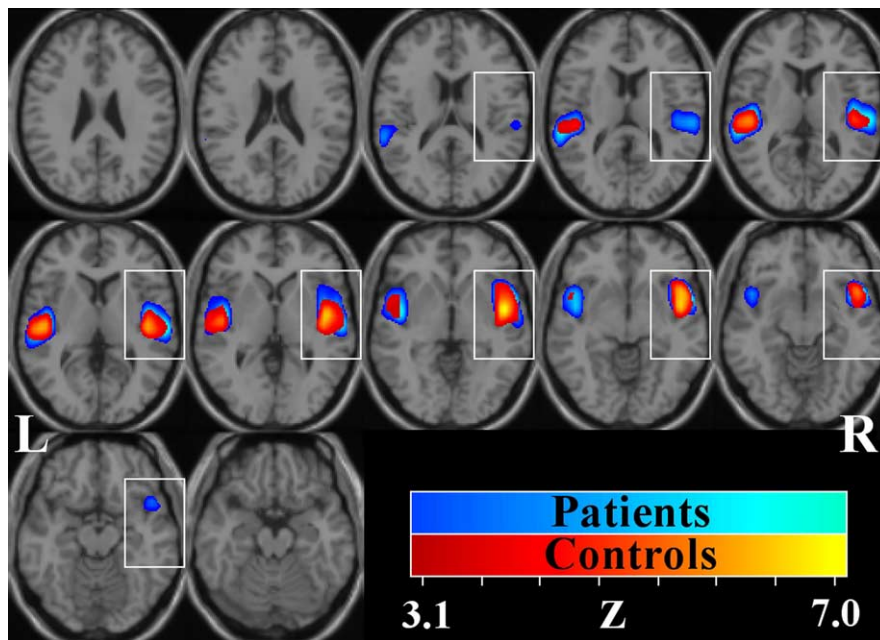


Figure 1. Auditory cortex mean activation maps. Mean activation maps from patients with schizophrenia (blue) and superimposed healthy control maps (orange), both thresholded at $Z > 3.1$. Control subjects tended to activate more posteriorly and medially, whereas patients activated more anteriorly and laterally. The right auditory cortex demonstrated the greatest difference (white box). R, right; L, left.

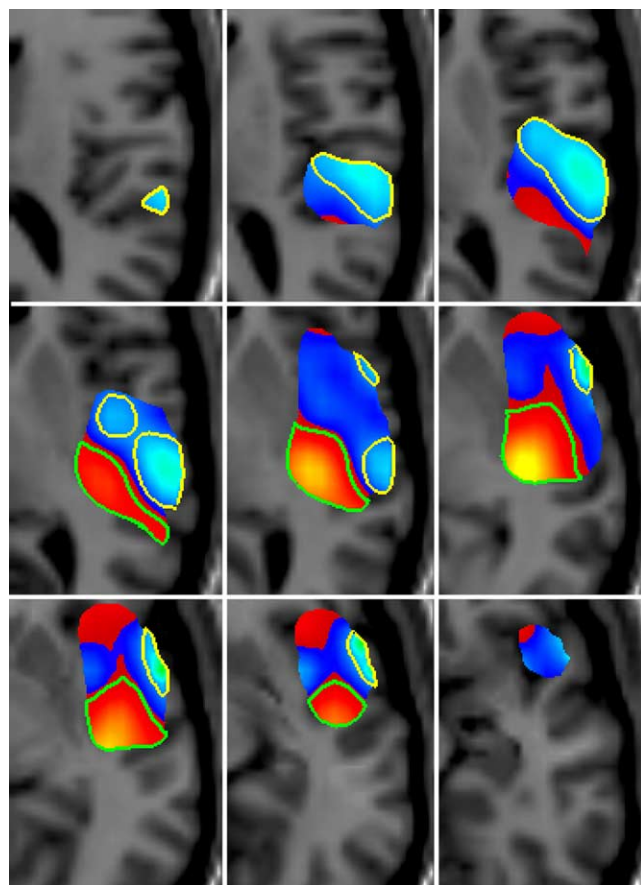


Figure 2. Difference maps and discrimination regions. Right auditory cortex difference maps indicated regions where control subjects are greater than patients (orange) and where patients are greater than control subjects (blue). Also indicated are boundaries depicting intraindividual comparison regions determined by thresholding the difference maps, such that individual categorization was optimized.

percentage of correct hits (patients 98.5 ± 2.8 ; control subjects $99.8 \pm .9$), errors of omission (patients $.6 \pm 1.14$, control subjects $.6 \pm .8$), or errors of commission (patients $.2 \pm .4$, control subjects $.1 \pm .3$). Behavioral results are reported as grand averages across all cohorts. Control subjects responded to target stimuli faster than did patients ($p < .001$). The reaction times were 539 ± 155 msec and 375 ± 83 msec for patients and control subjects, respectively.

Group-averaged auditory cortex SHIMs for the first analysis of 34 subjects (CH1) are presented in Figure 1 for the schizophrenia patients (orange) and healthy control subjects (blue). Functional maps were similar between groups, but patients demonstrated more dorsolateral synchrony than control subjects, and control subjects demonstrated more ventromedial synchrony (especially on the right side) than patients.

To investigate group differences in the CH1, the average patient SHIM was subtracted from the average control SHIM (see Figure 2). On average, orange regions are more active in control subjects and blue regions are more active in patients. The figure also depicts (automatically determined) boundaries surrounding voxels subtracted in a subsequent comparison of dorsolateral and ventromedial temporal lobe regions.

Table 1 describes regions identified in Figure 1, and Table 2 summarizes regions within the boundaries delineated in Figure 2 by green and yellow lines. Coordinates of peak activation (mean ICA voxel weight) and volume of suprathreshold regions as delineated by the Talairach atlas are also indicated.

Patient data revealed greater auditory cortex synchrony dorsolaterally (ADL) than in healthy control subjects; healthy control subjects on the other hand, demonstrated more synchrony ventromedially (AVM) than did patients. Regions of patient increases included primary auditory cortex (Brodmann's area [BA] 41) and auditory association areas BA 42 and 22, whereas control increases included BA 41 and 22, but not BA 42. The discrimination function was, for each individual, the sign of the average of the area bounded in yellow minus the average of the area bounded in green (regions delineated in Figure 2). The right

Table 2. Discrimination Regions in Right Auditory Cortex Difference SHIMs

Region	Brodmann Area	Volume (cm ³)	Peak Location
Orange Areas (Greater in Control Subjects)^a			
Insula	13, 22	.4	4.8 (44, -16, 1)
Superior temporal gyrus	22, 38, 41	.3	4.2 (48, -19, 1)
Clastrum		.1	4.4 (36, -16, 1)
Blue Areas (Greater in Patients)^a			
Superior temporal gyrus	42, 22, 41, 38	.8	3.8 (59, -26, 16)
Transverse temporal gyrus	42, 41	.3	2.4 (59, -19, 12)
Insula	13	.1	3.4 (48, -15, 12)

Regions within minimum error discrimination boundaries (indicated in Figure 3). Volumes of suprathreshold regions as delineated by the Talairach atlas are indicated.

SHIMs, synchronous hemodynamic independent maps.

^aSee Figure 2.

hemisphere distinguished schizophrenic patients (ADL > AVM) from healthy control subjects (AVM > ADL) with 97% accuracy. These scores from the discrimination function were not correlated with the report of hallucinations (in the prior week) as assessed from 11 patients in CH1 for whom this information was available. Next, to assess the reliability of the model, nine healthy control subjects were rescanned in a second session on a different day and tested with the regions and discrimination function from CH1. For these data, similar results (all but one demonstrated AVM > ADL) were revealed. Figure 3 depicts the right AVM–ADL value for each of the 17 schizophrenia patients and 17 healthy control subjects. Finally, the same test (previously optimized on CH1) was applied to an independent sample of patients and control subjects meeting the same criteria as before but scanned on a different scanner. Results indicated 94% accuracy and suggest that these differences are robust and a cardinal abnormality in schizophrenia. The left temporal lobe also demonstrated a significant group difference in regional synchrony, but with considerable control subject/patient overlap.

To examine the amount to which the auditory cortex SHIMs were task dependent, we calculated the correlation of the ICA time courses with hemodynamic models for the target and the novel stimuli of the oddball task (calculated by convolving the ideal timing of the events with a canonical hemodynamic response used in the SPM99 program). In all cases, the correlations were low (control subjects: targets = .091, novels = .057; patients: targets = .025, novels = .008). In addition, in both groups other ICA time courses (not the selected auditory component) were found to be more highly correlated to the novels

and/or the targets (although correlation values were also very low). These nonauditory SHIMs were not examined because the goal of our study was to develop a discrimination test by using an intrinsic measure of auditory cortex fluctuations, not to probe regions correlated with the task. These data suggests that the identified auditory cortex activations are largely task independent (uncorrelated), though to what degree this activity can be modulated by the oddball task is unknown.

Discussion

Synchronous hemodynamic independent maps of auditory cortex activity during an auditory oddball task were identified with spatial ICA. The time courses of the SHIMs were uncorrelated with the auditory oddball task, which was used as a convenient control condition in which patient and control performance was similar. Results revealed a novel and interesting finding, which relates to prior work implicating temporal lobe dysfunction in schizophrenia and subdivides the auditory cortex into several regions. Patients with schizophrenia were reliably differentiated from healthy control subjects in two independent samples by comparing differences, for each individual, in dorso-lateral and ventromedial synchronous right hemisphere auditory cortical activity.

Regional boundaries were defined functionally (not anatomically) according to the average activation maps optimized from CH1, thus providing a measure of regions exhibiting a high degree of temporal synchrony. The largest group difference was on the right hemisphere, though the left hemisphere had a lesser but still significant difference. The difference in laterality is consistent with several prior studies. Barta et al (1990) demonstrated volumetric changes in STG, in particular reversals of the usual left > right volume asymmetry in the planum temporale, posterior to the primary auditory cortex, in patients with schizophrenia, which were correlated with severity of auditory hallucinations. A subsequent replication study found that the planum temporale gray matter thickness on the right side was 50% less in patients with schizophrenia (Barta et al 1997). A recent longitudinal and cross-sectional analysis of subjects who later developed psychosis demonstrated significant gray matter loss in right STG (Pantelis et al 2003). Jacobsen and Rapoport (1998), in a study of childhood-onset schizophrenia, showed significantly greater decreases in right temporal lobe, bilateral STG, posterior STG, and right anterior STG volumes.

Some ERP studies suggest that the left hemisphere might be more compromised than the right in schizophrenia during performance of auditory oddball tasks (McCarley et al 1993). Other studies have found that similar deficits in hemodynamic mea-

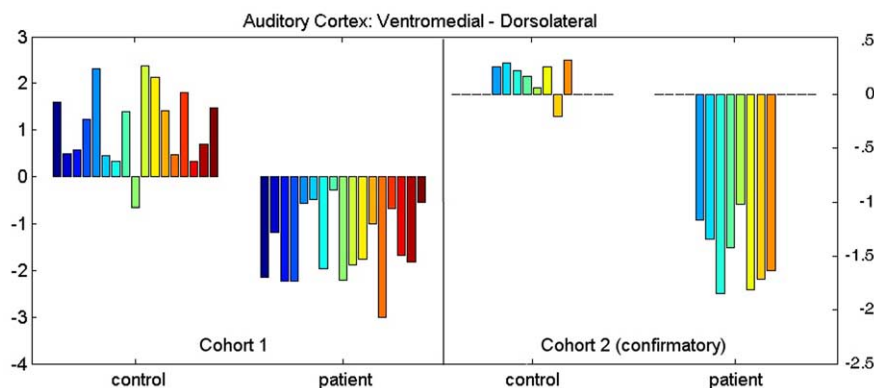


Figure 3. Right auditory cortex discrimination results. Single-subject regional differences for cohort 1 (at University of British Columbia) and cohort 2 (at the Institute of Living) are shown. Ordinate values are the average of independent component analysis values in voxels in auditory cortex ventromedially (AVM) subtracted from the average of voxels in auditory cortex dorsolaterally (ADL) (i.e., AVM – ADL). All but one control subject in each cohort have values greater than zero (AVM > ADL), whereas all schizophrenic patients have values less than zero (AVM < ADL).

asures of oddball processing were found in schizophrenia in both right and left temporal lobe structures (Kiehl and Liddle 2001). In the current study, the effect was bilateral, with the greatest effect on the right side, though the observed abnormalities were not correlated with the task-induced measures of oddball processing; thus, these abnormalities seem to be independent of phase-locked oddball processing.

Analogous lateral differences in fMRI and PET signal have also been observed. Woodruff et al (1997) found that right-handed patients with schizophrenia (both with and without a history of hallucinations) showed excess activation in right middle temporal gyrus and less fMRI activation in left posterior auditory cortex while listening to speech, compared with normal control subjects. Results of a single photon emission computed tomography study suggested reduced right ear (left hemisphere) advantage for dichotic word perception in schizophrenia and also that right temporal lobe over-activity and positive symptoms are related (Malaspina et al 2000).

One difficulty in studying schizophrenia with the use of cognitive tasks is that performance deficits can confound activation patterns. The current study attempted to mitigate this problem by identifying largely task-uncorrelated activity with a data-driven approach and by using a task in which patients perform as well as do control subjects. The fMRI activation correlated with the auditory oddball task has been reported in a previous study (Kiehl and Liddle 2001). For the schizophrenic patients, selective deficits were observed in both the extent and magnitude of activation associated with target processing in bilateral anterior STG, among other areas. These deficits, though statistically significant, are unable to discriminate patients at the level of the individual (overlap is 30% for the largest reported effect, with an intergroup separation of just over 1 SD). Event-related potential data from the subjects reported in the current study revealed a magnitude difference of just over 1 SD in the magnitude of the P300 response. The current fMRI analysis approach, in contrast, examined an intrinsic measure of auditory cortex function, which was uncorrelated with the task, resulting in an intergroup separation of more than 3 SDs.

It is interesting to consider the implications of auditory activity that is uncorrelated with the task. Two possibilities arise. The first is that the auditory cortical function is task-independent (not related to the oddball task at all). This would then imply that a resting-state scan could ascertain a similar result. A second possibility is that the auditory cortex function is uncorrelated with the oddball task but reflects some measure of auditory processing that is modulated to some degree by the oddball task. The second explanation seems possible, because the oddball paradigm involves auditory processing; however, the first explanation would be consistent with recent work demonstrating that low-frequency synchrony in electroencephalogram of monkey visual cortex might contribute significantly to the fMRI signal and was not modulated by the visual task (Leopold et al 2003). To answer this question fully, additional data should be collected. It is clear that task-uncorrelated processes provide a powerful probe for studying the brain and would benefit from additional studies (Arfanakis et al 2000).

Two sub-areas of the superior temporal lobe cortex seem to be affected differently in patients with schizophrenia and healthy control subjects. Although both regions are exhibiting synchronous activation, dorsolateral synchrony increases relative to ventromedial in patients with schizophrenia. The dorsolateral region (patient increases) seems to be centered on primary

auditory cortex (Heschl's gyrus) and to extend into BA 42, whereas the ventromedial region (control increase) seems to be centered at the junction between the temporal lobe and the insula and does not include BA 42 (although it is important to remember that the BA provided by the Talairach atlas for the fMRI data are not definitive). Cytoarchitectonic evidence has demonstrated reduced BA 42 pyramidal volume in schizophrenia (Sweet et al 2003). In the human, cortex specialized regions for speech or nonspeech (analogous to the visual "what" and "where" systems) have been reported (Belin et al 2002). In particular, speech or object-related auditory regions were found to exist in more anterior regions of the STG, and nonspeech or pattern-related regions were found to be in more posterior and lateral portions of STG and also to exhibit laterality differences (Belin et al 2002; Hart et al 2003). The current study reveals more anterior and medial STG synchrony in control subjects and more posterior and lateral STG synchrony in patients, with a stronger distinction on the right side, and is consistent with functional specialization of the auditory cortex. One possible explanation is that patients exhibit excessive elaboration, which results in speech processing of nonspeech stimuli by speech-related and additional auditory association areas. Further studies involving multiple imaging modalities will be necessary for ultimately understanding the biological mechanisms.

Structural changes in patients, as previously mentioned, are thought to be present in temporal lobe regions. Individual examination of functional maps was used to verify that the reported patterns were clearly present and not an artifact of spatial normalization differences between patients and control subjects. In addition, changes in synchrony (and in particular the definition of the regions of interest) will likely benefit from the use, for example, of high-resolution functional mapping combined with spatial normalization localized to the auditory cortex. Such measures might better capture individual differences and correspondences between functional and structural information, thereby further highlighting specific differences in auditory cortex function.

The reported methods, which reliably discriminated schizophrenic patients from healthy control subjects in two separate samples, might also be useful for differentiating other types of neuropsychiatric disorders that share clinical phenomenology with schizophrenia (e.g., bipolar disorder). Additional studies will be required to answer this question and to determine whether long-term neuroleptic exposure could produce changes in synchronous activity in auditory cortex. Previous work has indicated structural (McDonald et al 2002; Pantelis et al 2003) and functional (Braus et al 2002) abnormalities in nonpharmacologically treated at-risk relatives of patients; thus, it is not clear at this point whether measures of synchrony will be affected by medications.

Strengths of our approach include generating a connectivity map of synchronous auditory cortex voxels with ICA, a method that does not require a seed voxel or filtering parameters. We have also used an optimization method and defined criteria to attack the problem of discriminating patients from control subjects. Our method involved intrasubject criteria and was sensitive enough to classify at the level of the individual. Limitations of our approach include the possibility of task-dependent activity affecting the resulting SHIMs (although the same problem exists for resting-state data but cannot be measured at all in this case). The current study also does not compute a direct correspondence between functional and structural changes (and relies on the Talairach label provided by a low-resolution fMRI study). In

addition, there are many other potential optimizations to be performed (e.g., optimization of thresholding, choice of maps [T-maps, mean-maps], the use of individualized regions vs. group-defined regions). Finally, the impact of potential (subtle) gender differences was not examined in the current study. In future studies, we will be exploring the possibility of a more subtle effect by increasing the number of female patients and control subjects.

In conclusion, we used ICA, a multivariate statistical approach, to identify aberrant localization of hemodynamic coherence in schizophrenia. Individual auditory cortex SHIMs (maps of task-uncorrelated synchronous fMRI activity) of patients with schizophrenia and matched healthy control subjects were calculated and analyzed according to the sign of a difference between two sets of regions in auditory cortex. Patient SHIMs revealed greater synchrony in dorso-lateral regions; healthy control subjects had greater synchrony in ventromedial regions of right auditory cortex. These SHIMs 1) categorized schizophrenic and healthy control subjects with 97% accuracy initially; 2) similarly categorized a subset of the same healthy control subjects scanned in a different session; and 3) categorized, with 94% accuracy, a study of new patients and control subjects scanned on a different scanner. Left auditory cortex also demonstrated a significant effect, but there was overlap between the groups. These data suggest that aberrant task-uncorrelated auditory cortex function is a cardinal abnormality in schizophrenia, sheds new light on STG dysfunction, and might provide a powerful quantitative biologic measure for the assessment of schizophrenia.

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