Most functional imaging studies of the auditory system have employed complex stimuli. We used positron emission tomography to map neural responses to 0.5 and 4.0 kHz sine-wave tones presented to the right ear at 30, 50, 70 and 90 dB HL and found activation in a complex neural network of elements traditionally associated with the auditory system as well as non-traditional sites such as the posterior cingulate cortex. Cingulate activity was maximal at low stimulus intensities, suggesting that it may function as a gain control center. In the right temporal lobe, the location of the maximal response varied with the intensity, but not with the frequency of the stimuli. In the left temporal lobe, there was evidence for tonotopic organization: a site lateral to the left primary auditory cortex was activated equally by both tones while a second site in primary auditory cortex was more responsive to the higher frequency. Infratentorial activations were contralateral to the stimulated ear and included the lateral cerebellum, the lateral pontine tegmentum, the midbrain and the medial geniculate. Contrary to predictions based on cochlear membrane mechanics, at each intensity, 4.0 kHz stimuli were more potent activators of the brain than the 0.5 kHz stimuli.

Introduction
Numerous functional imaging studies have employed complex acoustic stimuli such as speech and language (Frackowiak et al., 1997). However, we are unaware of any systematic efforts to define the responses of the human auditory system to simple, non-cognitively oriented stimuli that vary over a broad range of frequencies and intensities.

Much of what we know about the functional characteristics of the auditory system has been derived from physiological and anatomical studies of anesthetized animals. These studies have provided a wealth of information about the basic anatomical and functional properties of excitatory and inhibitory neurons, patterns of decussation, structural characteristics of the brainstem, thalamic and cortical regions, and the tonotopic organization that is characteristic of most of the central auditory nervous system. Many of these studies have used recording methods that are restricted in their spatial extent and have thus provided information about activity in a limited portion of the brain, rather than the responses in the entire auditory system. Positron emission tomography (PET) is well suited to studies of dispersed systems since it is possible to sample the entire brain many times in a single experimental session. Limitations in spatial resolution can be overcome, partially, by the use of multiple subjects and contemporary image analysis techniques (Fox et al., 1988; Frackowiak et al., 1997) Thus, detailed data about neural systems that are distributed throughout the brain are likely to emerge from studies using this technology.

Early physiological mapping studies of the auditory system were conducted on patients during the course of surgical treatment for epilepsy or other diseases of the brain (Penfield and Jasper, 1954). Noninvasive methods have been focused on the temporal lobe, and have provided evidence for a tonotopic organization in brain regions with cytoarchitectonic characteristics of primary and associative auditory cortex. Lauter et al. (1985) found evidence for a tonotopic cortical organization in an early study of the cerebral blood flow (CBF) response to tones. They used 0.5 and 4.0 kHz stimuli presented at 50 dB sensation level. Their analysis was restricted to the predicted location of the primary auditory cortex in the superior portion of the left temporal lobe. They found evidence that lower-frequency tones stimulated a brain region that corresponds to the lateral, more superficial portion of the transverse temporal gyrus, or Heschl’s gyrus, whereas the higher-frequency stimuli activated a site that was more medially located on this gyrus. The maximum changes were always located in the temporal lobe contralateral to the stimulated ear. Some investigators have used scalp electrodes to record event-related potentials and to map electrical fields (Bertrand et al., 1991; Pantev et al., 1995), while others have used magnetoencephalography to study the auditory system (Pantev et al., 1995). Again, responses to low-frequency stimuli originated closer to the surface of the brain, whereas responses to higher frequencies were found at sites deeper in the Sylvian fissure. As a part of a study of tinnitus, we mapped responses to 2.0 kHz tones in normal subjects and tinnitus patients and found activation of both temporal lobes (Lockwood et al., 1997). Several reports describe the effects of auditory stimuli on CBF, as measured by single-photon emission computed tomography (Le Scao et al., 1991, 1993). In general, these are preliminary, non-quantitative studies that lack many details in the description of the methods and are thus difficult to interpret.

We designed the present study to map the human auditory system in a systematic manner. We hypothesized that specific neural sites responsive to tonal stimuli could be identified by changes in CBF (Posner et al., 1988) and used PET to measure the CBF changes produced by the stimuli. We chose pure sine-wave stimuli to avoid cognitive task elements that are characteristic of more complex stimuli, such as speech. The frequencies of 0.5 and 4.0 kHz were chosen to achieve a three-octave separation of stimuli in the range of speech and music. The four different stimulus intensities, ranging from 30 to 90 dB HL (hearing level), are in the range of those encountered daily. We presented the stimuli to the right ears of young adults with normal hearing. The results of this study have been presented in abstract form (Salvi et al., 1998).

Materials and Methods

Subjects
Right-handed subjects with normal hearing, free of tinnitus and neurological disease, were recruited. Written informed consent was obtained from all subjects in accord with the Declaration of Helsinki. All procedures were approved by the Human Subjects, Radiation Safety, and Radioactive Drug Research Committees.

Cerebral Cortex Jan/Feb 1999;9:65–76; 1047–3211/99/$4.00
Auditory
Standard audiometric measures were obtained from all subjects prior to the PET scans. Subjects were tested in a double-walled audion sound room using a Grason-Stadler audiometer (GS 10) and TDH-49 head-phones. Air-conduction thresholds were measured at 0.25, 0.5, 1, 2, 4 and 8 kHz. Speech reception thresholds were assessed by live voice using the CID W-1 spondaic word list. Speech discrimination scores were evaluated using a phonetically balanced word list (CID Auditory Test W-22) on compact disk. Tympanograms and contralateral middle ear reflex measurements were made with a Grason-Stadler Middle Ear Analyzer (GSI 35).

Acoustical Survey of PET Environment
Environmental noise levels in the PET camera were measured with a Larson Davis 800B sound-level meter equipped with a 0.5 in. condenser microphone (ACO 7017) calibrated with a Larson Davis Ca250-0146 calibrator. Measurements were taken with the microphone located at the center of the field of view of the PET camera.

Positron Emission Tomography
Subjects were positioned in a Siemens ECAT 951/31R tomograph so that the inferior image plane coincided with the cantho-medial line. Etymotic ER3A insert earphones were placed in the external auditory meatus of both ears. To reduce ambient noise even further, Cabot Safety Model 3000 earmuffs were placed over both ears. Head position was maintained throughout by means of an individually fitted thermoplastic mask. After a 20 min transmission scan, nine emission scans were obtained. Each scan began with the slow i.v. injection of a bolus (15 s injection followed by a 15 s flush) of 260 MBq or less of [15O]H2O as a tracer of CBF. Activation procedures began at the beginning of the injection and continued throughout the scan. The initial 60 s of emission data, timed from the arrival of the [15O]H2O in the brain, were used for image reconstruction (random coincidence correction, measured attenuation, Hanno filter, cutoff frequency 0.4 cycles/pixel) and analysis.

PET studies were performed with the eyes open. One resting-state scan (no auditory stimulation) and eight active-state scans were obtained. Auditory stimuli were delivered to the right ear only using a Neuroscan Stim system. The choice of the right ear was arbitrary, but maintained throughout the study to assure uniformity among subjects. To avoid potential cognitive biases, subjects were told only to, 'Listen to the tones'. To prevent subsequent bias and to assure correct operation of the equipment, post-stimulus debriefing consisted of verification that the tones were heard. During active stimulation, sine-wave tones (500 ms on, 500 ms off, digitization rate 120 000 Hz, 50 ms Blackman rise/fall time) were presented at 30, 50, 70 and 90 dB HL at 0.5 and 4.0 kHz, the same frequencies used by Lauter et al. (1985). The rise and fall time was shaped with a Blackman function in order to minimize the spread of acoustic energy from the frequency of the tone burst. To avoid the effects of stimulus habituation and anticipation, the order of presentation of the stimuli was randomized as follows: first, the frequency was chosen, then the intensity order. Thus, subjects were tested with either the 0.5 or 4.0 kHz stimuli presented in random order of intensity followed by a random-order presentation of the remaining stimuli. Tasks were separated by 12-15 min to permit subjects to rest and for tracer activity to decay to near background levels.

PET Data Analysis
Images were converted to the Analyze format and a threshold was set at a level to include all pixels that would be recognized by the additional image-processing steps. Images were edited, using visual inspection, on a slice-by-slice basis to remove extracerebral activity (such as scalp, great vessels, muscles and sinuses) and analyzed by statistical parametric mapping (SPM) using SPM 1995 (Friston and Frackowiak, 1991; Friston et al., 1995) Unless otherwise specified, all analyses were performed using a Z threshold of 3.09 corresponding to \( P = 0.001 \) (uncorrected for multiple comparisons) with an extent threshold of 0.5. This threshold is widely used and provides an assurance that activation sites identified are unlikely to be due to chance (Frackowiak et al., 1997). Andreasen et al. (1996) have shown that the probability of a type II error with the sample size we used is acceptably low.

The public version of SPM that we used for our analyses yields two \( P \) values for SPM(\( Z \)) maxima that are detected. For one value, the program applies a correction factor, based on the number of independent data points or resolution elements (RESELS), in the entire data set to calculate the probability that an activation site is due to chance alone. The second \( P \) value is uncorrected for multiple comparisons. There is ample evidence that tonotopically organized brain regions are confined to the auditory system. The largest of these regions exists in the transverse temporal gyrus and possibly the medial geniculate body. Since these regions are only a small fraction of the whole brain, we believe that the whole-brain default correction used by SPM is excessively restrictive when a tonotopic effect is sought. In keeping with earlier studies we restricted the volume of the brain when statistical tests related to tonotopy were applied (Lauter et al., 1985; Wassinger et al., 1997; Mühlnickel et al., 1998).

The detailed justification and explanation for this is as follows. The 1985 atlas that forms the referential basis for anatomical localization in the SPM analytical process shows that the transverse temporal gyrus is \(-45 \text{ mm in length and } -10 \text{ mm in width and height (4.5 cm3); the nearby medial geniculate occupies a volume of } <1 \text{ cm3} \) (Talairach and Tournoux, 1988). These data are consistent with others, and indicate that the structures of interest occupy \(<1\% \) of the entire brain (Campain and Minckler, 1976; Penhune et al., 1996; Mühlnickel et al., 1998). Because these two regions of probable tonotopic organization occupy a small fraction of the entire brain, a whole-brain correction is excessive. The SPM(\( Z \)) image from the contrast comparing 4.0 kHz 90 dB HL to the 0.5 kHz 90 dB HL contains 293 RESELS. Since the resolution of the SPM(\( Z \)) image smoothed with the 10 mm filter was 13.7, 16.6, 13.9 mm in the \( x, y, z \) dimensions respectively, 10 RESELS should be more than adequate to include the region of interest. Therefore, a multiple comparison adjustment for 10 RESELS (~1/30th or ~3% of the whole brain) should produce a reasonable and conservative \( P \) value. Therefore, we believe that it is reasonable, for this analysis only, to multiply the uncorrected \( P \) values produced by SPM by 10. Finally, software for correcting small volume analyses in SPM has been disseminated on the internet (matthew.brett@physiol.ox.ac.uk). This method is based on work of Worsley et al. (1996). We used this software to correct for volumes of interest restricted to the medial geniculate body and to the medial portion of the primary auditory cortical region, defined for this purpose as the medial portion of the brain region within the 50% probability contour defining auditory cortex (Penhune et al., 1996). For this analysis, we used SPM files produced with the 10 mm smoothing kernel.

Results

Subjects
Data were obtained from 12 subjects: six men and six women. The average age (mean \( \pm \) SD) was 24.1 \( \pm \) 2.6 years (range 21–28). One subject was Asian-American, one was black, one was Hispanic and the remainder were Caucasian.

Audometric Examinations
All subjects had normal hearing (\( \leq 15 \text{ dB HL, 0.5–8 kHz} \)). Speech discrimination, tympanograms and acoustic reflex thresholds were within normal limits, bilaterally, for all subjects.

Acoustical Properties of the PET Environment
The overall sound level in the PET camera was 71 dB sound pressure level (SPL). Octave band SPLs were 58 dB at 32 Hz, rising to a peak of 66 dB at 125 Hz, and falling to 32 dB at 8 kHz. The insert earphones attenuate room noise by 25–30 dB (Berger and Killion, 1989). This attenuation was further augmented by the Cabot Safety model 3000 earmuffs. Under these conditions, fan and room noises are barely audible. Thus, the background octave band sound levels experienced by subjects during the study are expected to provide little shift in hearing thresholds for the frequencies used in our study.
**Comparison with Resting State**

**General Features**

We found significant results at the $P = 0.001$ threshold for SPM contrasts that compared each frequency and each stimulus intensity with the resting state. Most of the regional maxima and most of the pixels in these images were found in brainstem, thalamic and cortical regions, which are classically associated with the auditory system (Webster, 1992). Subcortical sites were largely confined to the left side of the brainstem, i.e. contralateral to the stimulated ear. Surprisingly, none of our stimuli activated the cochlear nucleus complex ipsilateral to the stimulated ear at any of the stimulus intensities, even when the analytical threshold was reduced to $Z = 1.0$. Two additional generalizations can be made from the eight contrasts that compare the resting state with active stimulation. First, as shown in Figure 1, the total number of pixels in auditory system loci increased as the intensity of the stimuli increased (*vide infra* for rigorous statistical tests). Second, also shown in this figure, the number of pixels activated by the 4.0 kHz stimulus at a given intensity was always greater than the number activated by the 0.5 kHz stimulus. This is further illustrated by the SPM$Z$ projections.

**Figure 1.** Activation of the auditory system by 0.5 and 4.0 kHz tones at different intensities. The total number of pixels exceeding the $P = 0.001$ threshold, excluding the posterior cingulate, are shown.

**Figure 2.** SPM$Z$ projections comparing the activations by 0.5 kHz stimuli at 90 dB HL versus rest are shown on the left and 4.0 kHz stimuli at 90 dB HL versus rest are shown on the right. The threshold for the analysis was set at $Z = 3.09$, $P = 0.001$, uncorrected for multiple comparisons. See Materials and Methods for explanation of the orientation of the projections.
For this tabulation, the SPM\(Z\) threshold was set to \(Z = 1.0\) to facilitate identification of maxima at low stimulus intensities. Note the relatively constant \(z\) location for the foci in the left temporal lobe and the progressive increase from \(z = -8\) mm to \(z = 0\) mm in the right temporal lobe, as the stimulus intensity increases.

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Left lateral temporal</th>
<th>Left medial temporal</th>
<th>Right temporal</th>
</tr>
</thead>
<tbody>
<tr>
<td>x y z</td>
<td>Z score</td>
<td>x y z</td>
<td>Z score</td>
</tr>
<tr>
<td>0.5 kHz, 30 dB HL -58 -26 8</td>
<td>2.90 -46 -32 4</td>
<td>2.46 40 -16 -8</td>
<td>4.04</td>
</tr>
<tr>
<td>0.5 kHz, 50 dB HL -60 -36 12</td>
<td>3.10 -48 -24 8</td>
<td>1.78 40 -16 -8</td>
<td>3.85</td>
</tr>
<tr>
<td>0.5 kHz, 70 dB HL -60 -30 12</td>
<td>3.86 -48 -24 12</td>
<td>3.21 42 -26 4</td>
<td>4.12</td>
</tr>
<tr>
<td>0.5 kHz, 90 dB HL -56 -32 12</td>
<td>4.29 no maximum</td>
<td>1.21 40 -16 -8</td>
<td>4.66</td>
</tr>
<tr>
<td>4.0 kHz, 30 dB HL -60 -30 12</td>
<td>2.82 -46 -32 8</td>
<td>1.21 40 -16 -8</td>
<td>4.66</td>
</tr>
<tr>
<td>4.0 kHz, 50 dB HL -60 -30 12</td>
<td>2.56 -46 -32 8</td>
<td>2.57 42 -20 -4</td>
<td>3.44</td>
</tr>
<tr>
<td>4.0 kHz, 70 dB HL -56 -28 12</td>
<td>4.63 -48 -30 12</td>
<td>3.95 40 -16 -4</td>
<td>5.08</td>
</tr>
<tr>
<td>4.0 kHz, 90 dB HL -56 -32 12</td>
<td>3.99 -42 -26 8</td>
<td>4.63 42 -20 0</td>
<td>5.05</td>
</tr>
</tbody>
</table>

Note that the pixel size in the SPM\(Z\) images is \(2 \times 2 \times 2\) mm in the \(x\) and \(y\) planes, and \(4\) mm in the \(z\) plane. Thus, the sites of maxima are identified in increments of \(2\) or \(4\) mm, in spite of the fact that the SPM\(Z\) images themselves have a resolution of 17.8, 21.2 and 18.0 mm in the three planes respectively (after a 15 mm smooth).

| Coordinates for this maximum were -40, -46, -36. |
| Coordinates for this maximum deviated by 2 mm from specified location in one or two planes. |
| Coordinates for this maximum were 40, -22, 0. |
| Coordinates for this maximum deviated by 4 mm from specified location in one or more planes |
| Coordinates for this maximum were 42, -20, 0. |

Thus, the sites of maxima are identified in increments of \(2\) or \(4\) mm, in spite of the fact that the SPM\(Z\) images themselves have a resolution of 17.8, 21.2 and 18.0 mm in the three planes respectively (after a 15 mm smooth).
Figure 3. Anatomical sites activated by 4.0 kHz stimuli at 90 dB HL are shown in the top portions of this figure. (A) Transaxial SPM(Z) images superimposed on auditory cortex probability maps (Penhune et al., 1996). The pixels exceeding the $P = 0.001$ threshold are shown in colors, ranging from red (threshold) to yellow. Pixels below this threshold are shown in grey. The contours depict the probability that the region within is the locus of primary auditory cortex. Within the outer red contour the probability that the site contains primary auditory cortex is 25% or greater, within the inner green contour the probability is 50% or greater, and within the inner magenta contour the probability is 75% or greater. Note that the activated sites are within and immediately adjacent to the primary auditory cortex. See also Figure 2. (B) SPM(Z) data superimposed on $T_1$-weighted MRI images at various levels below the commissural plane. This illustrates the site of a 878 pixel region containing nine discrete SPM(Z) maxima at the $P = 0.001$ threshold. These sites include the lateral cerebellum and extend from lateral pontine tegmentum, the anatomical site of the superior olivary nuclear complex, to the level of the medial geniculate body. This is further illustrated by a parasagittal plane 16 mm to the left of the midline, shown in (C). (D) Anatomical sites activated by 0.5 kHz stimuli at 30 dB. The SPM(Z) images in transaxial plane $z = 28$ and right parasagittal plane $x = 10$ mm are superimposed on $T_1$-weighted MRI images for the 500 Hz, 30 dB HL versus rest contrast. The activated region contains 630 pixels with two maxima and corresponds with Brodmann area 23. See text for additional details.
Figure 4. Notched box plots depicting CBF values at three locations (A) lateral cerebellum (Talairach coordinates –44, –48, –36), (B) superior olivary nucleus region in left pontine tegmentum (Talairach coordinates –20, –36, –28), (C) right posterior cingulate gyrus (Talairach coordinates 4, –38, 24). Markers show the location of CBF values from each subject for 0.5 and 4.0 kHz stimuli at rest and during stimulation at 30, 50, 70 and 90 dB HL. The boxes are notched (narrowest) at the median and return to full width at the 95% confidence limit (note that in some cases, this return to full width is beyond the hinge). If the confidence limits do not overlap, the two population medians are different at the 95% confidence level. The edges of the box (hinges) are placed at the boundaries of the first and third quartiles and define the range (Hrange). The Hrange includes 50% of all observations. The ends of the whiskers show boundaries of points that fall within ±1.5 times the Hrange.
dependent responses were found. The mean CBF responses at two sites where frequency-cerebellar site, shown in Figure 4 differed. In the lateral limits, the graphs are presented as notched box plots). Four different CBF response patterns were found: (i) in the lateral cerebellar site, shown in Figure 4A, we found a rapid increase to a near-maximum at 30 dB HL, with little change associated with additional increments in the intensity of the stimuli; (ii) in the pontine site, shown in Figure 4B, we observed a steady increase throughout the range of stimuli; and (iii) in the posterior cingulate, shown in Figure 4C, particularly at 0.5 kHz, we found an increase to maximal values at 30 dB with a subsequent decrease at the higher intensities. In all three examples shown in Figure 4, the largest increments in the CBF response were seen in the intensity interval between rest and the 30 dB HL stimulus intensity. For each of those intervals, there is non-overlap of the 95% confidence limits, whereas considerable overlap exists among the other intensity intervals. In Figure 5A, B, we illustrate the mean CBF responses at two sites where frequency-dependent responses were found.

Cingulate Activations
In addition to activations in brain regions classically associated with the auditory system, we also observed activation of the middle and posterior portions of the right cingulate gyrus. These activations were most prominent for the 0.5 kHz frequency at the lowest stimulus intensity (30 dB HL). At the P = 0.001 threshold, and under those conditions, compared to rest, we observed a 630 pixel region with two maxima (at 4, -38, 24, Z = 4.69, and more anteriorly at 10, -6, 32, Z = 4.48). This region is shown in Figure 5C, depicting transaxial plane z = 28 and parasagittal plane x = 10 mm. This site corresponds almost exactly to Brodmann area 23 (Talairach and Tournoux, 1988). In the 0.5 kHz, 50 dB HL contrast, we found two discrete sites including 142 pixels with similarly positioned maxima. Contrasts at 70 and 90 dB HL yielded no results at the default threshold. The 4.0 kHz stimulus was a less potent activator of the cingulate. The 50 dB HL contrast was the only one of the four that yielded results at the default threshold. At that intensity, two sites containing a total of 99 pixels were identified in the posterior cingulate (at 18, -52, 32, 3.89, and at 2, -36, 24, Z = 3.61).

Tonotopic Differences in CBF Responses to Stimuli
We employed three approaches to determine whether our paradigm demonstrated tonotopic differences in neural activation. In the first of these, we considered the differences in the active versus the resting states using an analytical strategy that considered the whole brain. In the 0.5 kHz, 90 dB HL versus rest contrast, we found a single SPM(Z) maximum in the lateral left superior temporal plane: at -56, -32, 12, Z = 4.29. The identical pixel was also the site of an SPM maximum for the 4.0 kHz, 90 dB HL versus rest contrast (Z = 3.99). In this contrast, a second, more medially and posteriorly located maximum was also found: at -42, -26, 4, Z = 4.63. Thus, 0.5 kHz tones activated a single site, whereas the 4.0 kHz tone (three octaves higher) activated two discrete sites.

In the second approach, we sought additional evidence for a tonotopic organization of the auditory system by comparing the CBF responses to the 90 dB HL stimuli with two SPM contrasts: 4 kHz at 90 dB versus 0.5 kHz at 90 dB, and 0.5 kHz at 90 dB versus 4 kHz at 90 dB. As indicated in Materials and Methods, we expected that any tonotopically dependent spatial differences would appear in the region of the transverse temporal gyrus or, because of the intensity of the CBF response, in the medial geniculate body. In addition, because tonotopically dependent spatial differences might be small, a 10 mm smoothing kernel was applied. Only the first of these contrasts yielded sites with 25 or more pixels at an analytical threshold of P = 0.01. One focus was near the Talairach coordinates for the medial geniculate nucleus, contralateral to the stimulated ear (at -12, -26, -8, Z = 2.91). At that site, the P value, uncorrected for multiple comparisons was 0.002. A Bonferroni-like correction for 10 REELS in the 293 RESEL set would increase the P value from P = 0.002 to P = 0.02. This P value is within the usual limits for rejection of the null hypothesis. The second region was in the primary auditory cortex, contralateral to the stimulated ear, at a locus that was virtually identical to the more medially positioned maximum in the 4.0 kHz, 90 dB HL versus rest contrast (at -40, -26, 8, Z = 2.67). At that site, the uncorrected P value was P = 0.004. An extension of the previously advanced argument would lead to a readjustment of the value to P = 0.04. The Brett approach also yielded P values that were <0.05. Graphical representations of the mean CBF responses to all conditions at

Figure 5. The mean CBF responses to 0.5 and 4.0 kHz tones in (A) primary auditory cortex (Talairach coordinates –40, –28, 8), and (B) medial geniculate (Talairach coordinates –12, –28, –8), contralateral to the stimulated ear. Note the greater CBF response to the 4.0 kHz stimuli at 90 dB HL compared to the response at 0.5 kHz at 90 dB HL.
these two sites are shown in Figure 5. Additional details concerning the sites of activation in the temporal lobes are shown in Table 1.

In the third approach, discussed below, we identified sites where the CBF responses at a given frequency were correlated with the intensity of the stimuli.

**Effects of Stimulus Intensity**

We identified sites where the CBF response was correlated with the intensity of the 0.5 and 4.0 kHz stimuli by using the SPM multisubject, covariates-only analytical design. As might be expected, the SPM\(Z\) images showing positive correlations between stimulus intensity and CBF at these two frequencies were similar to those comparing the 90 dB HL intensity to rest. Pixels where \(Z \geq 3.09, P \leq 0.001\) (uncorrected for multiple comparisons) are shown in Figure 6. At 0.5 kHz, a single SPM\(Z\) maximum was identified lateral to the primary auditory cortex contralateral to the stimulated ear (at –58, –30, 12 mm, \(Z = 4.97\)). The \(P\) value at this site, corrected for multiple comparisons, was \(P = 0.001\). At 4.0 kHz, two SPM\(Z\) maxima were identified in contralateral temporal lobe cortex (at –60, –34, 12 mm, \(Z = 4.41\) and at –42, –24, 4 mm, \(Z = 5.09\)). The \(P\) values, corrected for multiple comparisons in this image, were \(P = 0.016\) and \(P = 0.001\) respectively. These data provide additional support, in the context of a whole-brain analysis, for a tonotopic organization of the auditory cortex. Both analyses identified a site in the inferior lateral portion of the thalamus near the Talairach coordinates for the medial geniculate nucleus. The 0.5 kHz correlation analysis yielded a maximum at –14, –22, –8 where \(Z = 4.22\). The \(P\) value corrected for multiple comparisons at this site was \(P = 0.001\). A stronger effect was found in the 4.0 kHz analysis where at –14, –24, –8 mm, \(Z = 5.15\). The \(P\) value corrected for multiple comparisons at this site was \(P < 0.001\).

We also used the individual task versus rest analyses to determine whether there were amplitopictopic differences in the temporal lobe, i.e. whether different intensities of tones of a given frequency activated different brain regions. In this analysis, we tabulated \(x, y, z\) coordinates and \(Z\) scores for CBF maxima in the temporal lobe sites for each contrast. For these analyses, the SPM\(Z\) threshold was reduced so that the lower-threshold sites, shown in Table 1, would be identified. Three foci were identified in all but one of the contrasts. One focus was present in the medial portion of the superior temporal plane on the side ipsilateral to the stimulated ear. Two foci were identified in the contralateral superior temporal plane, as indicated above: one was present laterally close to the surface of the hemisphere while the other was deeper and corresponds to the presumed site of primary auditory cortex (Penhune et al., 1996). These data are presented in Table 1.

As shown in Table 1, the \(x, y, z\) loci were relatively constant for the two temporal lobe sites contralateral to the stimulated ear across all intensities at a given frequency. However, in the right hemisphere, ipsilateral to the stimulated ear, the \(z\) plane location of the maximal response, i.e. the distance above or below the commissural plane, appeared to vary with the intensity, but not the frequency of the stimulus. For both frequencies, the maxima for the 30 dB HL stimulus intensity was at \(z = –8\) mm, and rose to \(z = 0\) mm for the stimuli presented at 90 dB HL. The \(Z\) scores for these foci also appear to vary in a systematic fashion. They were high at the 30 dB HL intensity, fell at the 50 dB HL intensity and then rose to new maxima at 70 and 90 dB HL. Similar patterns were seen in the data depicted in Figure 5. This observational aspect of our data analysis is thus similar to the vast majority of the reports in the literature that describe the tonotopic and amplitopic organization of the auditory system (for examples see Romani and Kaufman, 1982; Nisevich et al., 1989; Cansino et al., 1994; Pantev et al., 1995).

**Discussion**

We have used PET to examine the whole brain and to identify loci of neural activation in response to 0.5 and 4.0 kHz tones presented at 30, 50, 70 and 90 dB HL in subjects with normal...
The Experimental Environment

For most anatomical sites, our data show that the largest increments in neural activity occurred in the stimulus intensity intervals between rest and 30 dB HL, as shown in Figures 4 and 5. This suggests that low-noise environments are an essential prerequisite in studies of threshold phenomena in the auditory system. This contention is supported by a comparison of the data from this study with the data from our earlier study of patients with tinnitus and normal controls (Lockwood et al., 1998). In our earlier study, we stimulated the right ear of normal subjects with 0.5 and 2.0 kHz stimuli at 80 dB SPL (other stimulus parameters were the same as in the present study). The major responses were in the cortex; none were seen in infratentorial sites. We suspect that a difference in background noise levels in the room may be responsible for our failure to see these subcortical sites. In the present, but not the earlier study, subjects were equipped with sound-suppressing earmuffs in addition to the insert earphones. This additional reduction of environmental noise may be particularly important in brainstem imaging.

The radio frequency generators in MRI systems produce noise that may reach 117 dB SPL (Counter et al., 1997). This noise reaches the subject directly via the ears, and indirectly by vibrations transmitted through the body. These background levels may fully activate many portions of the auditory system and mask increments in neural activity related to specific test stimuli. Although there has been progress in reducing MRI noise levels (Ravicz and Melcher, 1998), ambient noise may be a limiting factor in studies of low-intensity auditory stimuli using functional MRI techniques.

Preliminary, unpublished studies in our laboratory using active noise suppression technology suggest that further reductions in the already-low sound levels in PET systems may be possible. Thus, PET appears to offer a number of advantages over alternative functional imaging techniques. Although the spatial resolution of PET is considerably less than that of modern MRI systems, the spatial resolution of PET is still superior to that of electrophysiological methods. When PET data are analyzed using SPM or similar statistical techniques that identify peaks of activity, it is possible to differentiate between closely positioned anatomical sites (Fox et al., 1987; Mintun et al., 1989; Frackowiak et al., 1997), as in the present study.

Functional Anatomy of the Auditory System

General Considerations

As shown in Figure 1, we found that the number of pixels activated by our stimuli increased as the intensity of the stimuli increased. An alternative and more rigorous approach to this question is shown by the stimulus intensity–CBF correlations shown in Figure 6. This is the response one would predict, based on studies of the visual system (Phelps et al., 1981). In this study we did not explore the possible effect of changing the duration of the stimuli or the interstimulus interval. Data from both the visual and auditory system suggest that these variables will have an impact on the stimulated system (Fox and Raichle, 1985; Harms et al., 1998).

Surprisingly, at a given stimulus intensity, the high-frequency stimuli were more potent activators of the auditory system than the low-frequency stimuli. Low-frequency sounds that are presented at a high intensity produce a traveling wave displacement pattern that activates the apex, middle and base of the cochlea, whereas high-frequency sounds activate neurons in the base of the cochlea (Rhode, 1980). The basilar membrane displacement patterns are also reflected in psychophysical masking patterns. Low-frequency masking tones mask both low- and high-frequency tones, whereas high-frequency masking tones mask high- but not low-frequency tones (Egan and Hake, 1950). That is, low-frequency maskers activate a much broader range of neurons than high-frequency maskers. Thus, on the basis of basilar membrane mechanics and psychophysical masking patterns, one would predict that low-frequency stimuli would produce a greater activation in the central auditory system than high-frequency stimuli. Therefore, we were surprised to find that the 4.0 kHz stimuli were more potent neural activators than the 0.5 kHz stimuli (see Fig. 1).

The explanation for our observation may depend on the nature of the neural activity produced by high- and low-frequency stimuli. It is likely that the level of neural complexity increases as neural impulses travel through the auditory system as more and more excitatory and inhibitory neurons are activated to process even simple stimuli. Thus neural, rather than cochlear factors, appear to dominate and determine the extent of activations produced by sounds.

Subcortical Activations

The spiral ganglion contains the nerve cell bodies that convey afferent impulses from the hair cells of the cochlea to the brain. All fibers from the spiral ganglion travel to the cochlear nuclear complex, ipsilateral to the stimulated ear, via the auditory nerve. On entering this complex, fibers make synaptic connections with neurons in the anterior ventral, posterior ventral and dorsal cochlear nuclei. Although this region receives all of the excitatory input from the stimulated ear and although the Talairach atlas is not completely dependable in the posterior fossa, we were not able to find clear-cut evidence for activation of the cochlear nucleus ipsilateral to the stimulated ear, even when the analytical threshold was lowered to Z = 1.0. This is probably the result of the relative simplicity of the auditory system at this level. However, we are unable to exclude the less likely possibility that this site is already activated maximally at resting sound levels.

As shown in Figures 2, 3 and 6, the subcortical activations are concentrated on the left side of the brainstem and thalamus, the side contralateral to the stimulated ear. The contralateral activation is probably a reflection of the summed responses of excitatory and inhibitory neurons as the auditory system becomes increasingly complex as impulses move from the periphery to more central loci (for a review see Webster, 1992).

In the 4.0 kHz, 90 dB HL versus rest activation, we identified a 878 pixel subcortical site containing nine SPM[Z] maxima. Because of the intersubject averaging technique that we employed and between-subject variations in the loci of structures in this region, it is difficult to associate the subcortical maxima yielded by the SPM analysis with specific sites in the auditory system. This is illustrated by inspection of figures in the 1993...
Temporal Lobe Cortical Activations

Because of the known variations in the gross anatomy of the auditory cortex (Campain and Minckler, 1976), we have related our sites of activation to Penhune et al.'s probabilistic map of the boundaries of the primary auditory cortex (see Penhune et al., 1996). These authors used high-resolution MR images and anatomical criteria to map the auditory cortex. They expressed their results in the Talairach reference system in the form of z axis planes separated by 1.5 mm intervals. They defined contour intervals in each plane to show the probability that a given Talairach coordinate was within primary auditory cortex. They defined three contours: lines within which there was a 25, 50 or a 75% or greater chance that a given location was in the primary auditory cortex. They found that the auditory cortex began at the commissural plane (z = 0 mm) and extended up to a level 16.5 mm above the plane. As seen in the four transaxial sections in Figure 3A, there is a substantial overlap between the neural sites activated by the 4.0 kHz tones presented at 90 dB HL and the contours that define the probable anatomical boundaries of the primary auditory cortex. However, we found that cortical activations, defined in terms of the $P = 0.001$ threshold, extended beyond the region of primary auditory cortex. The activations began as low as 12 mm below the commissural plane (for the 4.0 kHz, 90 dB HL condition in the temporal lobe ipsilateral to the stimulated ear) and extended to 16 mm above the commissural plane contralaterally. We also found that the activations extended laterally and posteriorly to the 25% contour as shown in Figure 3A. [Note: For our purposes, we presumed that the probability maps reported at 4.5 and 7.5 mm were acceptable representations at 4 and 8 mm above the commissural plane, given the fact that the resolution of the smoothed SPM[Z] images was ~17 mm (full width at half maximum) in the z direction.] These data are consistent with a recent magneto-encephalography (MEG) study in which it was found that activations in the right hemisphere were located more anteriorly than those in the left hemisphere (Pantev et al., 1998).

There are at least three possible explanations for our observation that the activated sites extend beyond the anatomical boundaries of the primary auditory cortex. First, it is possible that there are anatomical differences between our subjects and those of Penhune. We cannot exclude this possibility with certainty, since they provide few details about the characteristics of their subjects. However, it seems unlikely that the relatively large differences between our sites and theirs are due to anatomical differences in the study populations. Secondly, since our data are determined by a blood flow response to a stimulus without any anatomical constraint, it is possible that the functional boundaries of the primary auditory cortex do not coincide with anatomical boundaries that are based on the relationships between cytoarchitectonic and gross anatomical features. We do not see any way to address this possibility directly. Third, and most likely, our simple tonal stimuli, devoid of cognitive elements, may have activated regions that extend beyond the primary auditory cortex into associative cortical regions. There is ample evidence that simple visual stimuli activate primary and associative visual cortex (Frackowiak et al., 1997). It is likely that similar considerations apply to the auditory system.

A variety of techniques have shown that primary auditory cortical regions are linked closely to adjacent auditory associative cortical regions (Pandya et al., 1969; Galaburda and Sanides, 1980; Pandya, 1995; Yukie, 1995). Although the anatomical data are not completely consistent, it is likely that neural activity in the primary auditory cortex is conveyed to other brain regions, including auditory association cortex and the cingulate gyrus, where higher-order neural processing is likely to occur.

Cingulate Gyrus Activations

We were surprised to find activations in the right middle and posterior portions of the cingulate gyrus. Although this region is connected to auditory cortical sites, other functional imaging studies have suggested that this site mediates auditory memory. Fletcher et al. (1995), in agreement with an earlier study (Grasby et al., 1993), found that encoding auditory-verbal episodic memory activated the posterior and retrosplenial portion of the cingulate cortex. Patients with lesions in this region may exhibit impairments of auditory memory, strengthening this association (Valenstein et al., 1987; Rudge and Warrington, 1991). Since our tasks did not have an identifiable memory component, the activation we observed is probably due to some other aspect of the paradigm. Because the activations in this region were maximal at low sound intensities and less prominent at higher intensities, as shown in Figure 4C, we suspect that this region may act as a gain or volume control.

This hypothesis would explain several of our observations and may help explain the fact that the auditory system is able to process stimuli that range over nine orders of magnitude in intensity (the stimuli in this study ranged over six orders of magnitude). A gain control system would be expected to be most active at low stimulus intensities. We observed maximal cingulate activations at low stimulus intensities. As the stimulus intensity increased, the need for amplification would be expected to decrease. This would explain the reduction in cingulate CBF that we found with higher stimulus intensities. This hypothesis is buttressed by an examination of the $Z$ scores for activations found in the right temporal lobe site shown in Table 1. The $Z$ scores at 30 dB HL were higher than those at 50 dB HL. This may be a manifestation of a higher gain at the lower intensity.

Alternatively, the activation of the posterior cingulate could be the manifestation of a neural attention system. However, it is...
Multiple brain sites appear to contribute to the development of
into the brain as the stimulus frequency increased and that
single subject again showed that the N1m source moved deeper
brain while higher frequencies were mapped to deeper, more
Again, low frequencies were mapped close to the surface of the
brain and that high-frequency tones had a more medial representation (40 ± 6 mm). Inasmuch as there are differences between the
versions of the Talairach atlas they used and the one employed in
(67 ± 9 mm). Inasmuch as there are differences between the
locations of the two sites responsive to the 4.0 kHz, or some combination of these factors.

Pantev and his associates have reported ampilotopic differences in the location of equivalent current dipoles evoked by 1.0 kHz stimuli of different intensities in the hemisphere contralateral to the stimulated ear (Pantev et al., 1991). As seen in Table 1, the most consistent evidence for ampilotopic variation in our data was found in the medial-inferior portion of auditory cortical areas in the temporal lobe ipsilateral to the stimulated ear. At both frequencies, low-intensity tones had a maximal effect at a site 8 mm below the plane of the commissures. As the intensity of the stimuli increased, this focus rose to the level of the commissural plane.

Since it was our intent to employ simple stimuli and since our
right-handed subjects received stimuli in the right ear, our study only begins to answer many basic questions including those
related to the effects of hemispheric dominance and unilateral
versus bilateral stimulation. We conclude that the conscious
perception of the simple tonal stimuli used in this study activates
a large and complex network of neural elements.

Notes
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Tonotopic and Ampilotopic Organization of the
Auditory System
Abundant evidence from studies of animals indicates that there is
a tonotopic organization at virtually all levels of the central
auditory system (Webster, 1992). Several non-invasive studies
have confirmed the presence of a tonotopic organization of the
human auditory cortex. Lauter et al. (1985) mapped the superior
temporal cortex at a single stimulus intensity, using PET and a
statistical approach that was restricted to this region. They found
that high-frequency tones had a more medial representation (40 ± 6 mm) than was found for lower frequencies
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