fMRI Evidence for Activation of Multiple Cortical Regions in the Primary Auditory Cortex of Deaf Subjects Users of Multichannel Cochlear Implants

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To investigate the activation of the auditory cortex by fMRI, three deaf subjects users of the Ineraid cochlear implant participated in our study. Possible interference between fMRI acquisition and the implanted electrodes was controlled and safe experimental conditions were obtained. For each subject, electrical stimuli were applied on different intracochlear electrodes, in monopolar mode. Stimulation of each electrode was actually producing auditory sensations of different pitches, as demonstrated by psychophysical pitch-ranking measurements in the same subjects. Because deaf subjects did not hear scanner noise, the data were collected in 'silent background' conditions, i.e. as a result of pure auditory sensations. Functional maps showed activation of the primary auditory cortex, predominantly in the left hemisphere. Stimulation of each different intracochlear electrode revealed different clusters of activation. After cluster grouping, at least three regions have been identified in the auditory cortex of each subject, and comparisons with previous architectonic and functional studies are proposed. However, a tonotopic organization could not be clearly identified within each region. These arguments, obtained without interference with unwanted scanner noise, plead in favor of a functional subdivision of the primary auditory cortex into multiple cortical regions in cochlear implant users.

Keywords: electrical stimuli, Heschl's gyrus, pitch ranking, tonotopic organization

Introduction

Cochlear implant systems restore useful hearing to patients suffering from severe to profound deafness (NIH Consensus Conference, 1995). Present cochlear implants are multichannel devices that provide multisite intracochlear stimulation, exploiting the tonotopic organization of the cochlea as well as of the central auditory pathways. Psychophysical experiments have demonstrated that stimulation of different intracochlear electrodes does actually elicit auditory percepts of different pitches (e.g. Eddington, 1980; Tong et al., 1983). Most multichannel cochlear implant systems use a transcutaneous radiofrequency (RF) communication system to send information from an external (body worn) processor to the implanted part of the device (Advanced Bionics Corporation, Sylmar, CA; Cochlear Limited, Melbourne, Australia; Med-El Corporation, Insbruck, Austria). Although the implanted part may not necessarily represent a contraindication to MRI (Teissl et al., 1999), these devices cannot be activated properly in a MRI scanner due to interference between the RF fields accompanying MRI acquisition and their RF communication system.

Functional MRI evidence for activation of the human auditory cortex upon electrical stimulation of the ear was previously reported on deaf subjects (Berthezene et al., 1997; Hofmann et al., 1999; Alwatban et al., 2002; Schmidt et al., 2003) or even on a normal hearing volunteer (Obler et al., 1999). The major motivation for such studies was to develop objective means to assess the integrity of the central auditory system in deaf patients, candidates for cochlear implants. These studies however used acute, transtympanic and extracochlear stimulation of the ear that did not allow for investigation of the effects of the cochlear position of electrical stimulation on cortical activation.

Interestingly, there is one system, the now discontinued Ineraid multichannel cochlear implant system (Eddington, 1980), that does not use implanted electronics nor magnet. Such a system can be in principle used for fMRI if adequately safe experimental conditions are developed. Melcher et al. (1998) were first to report fMRI activation of Heschl's gyrus (HG) in three Ineraid cochlear implant subjects. In one of those, two different intracochlear electrodes were stimulated and 'basal stimulation produced activation on the medial and lateral edges of HG, while apical stimulation produced activation on the superior aspect of HG', suggesting preservation of tonotopic organization in the auditory cortex in a totally deaf subject.

In our center, several profoundly deaf patients were implanted in the 1980s with the Ineraid cochlear implant system (Montandon et al., 1992). We recently developed safe and artifact free experimental methods for fMRI upon intracochlear electrical stimulation (Lazeyras et al., 2002). The deaf volunteer tested in this preliminary experiment did not hear any artifactual noise due to scanner acquisition. This 'silent background' allowed us to use moderate loudness levels for stimulation and resulted in very focused auditory cortex activation.

In this study, we report fMRI evidence for multisite activation of the primary auditory cortex in three deaf subjects using the Ineraid multichannel cochlear implant. On each subject, each intracochlear electrode was stimulated systematically one at a time, and we collected high resolution functional images. To verify that each electrode was actually producing auditory sensations of different pitches, we also conducted psychophysical pitch-ranking measurements in the same subjects.

Materials and Methods

The Ineraid Cochlear Implant

The Ineraid system consists of six intracochlear electrodes (0.5 mm diameter, platinum), separated from each other by a distance of ~3.6 mm. This system does not use implanted electronics. Electrodes are connected to a percutaneous plug and can be activated by external current generators. Low-frequency sounds are coded by electrical stimulation of electrodes located near the apex of the cochlea and high-frequency sounds by stimulation of electrodes located near the base of the cochlea. In this way, the cochlear implant system is able to transmit (at least partially) the spectral information contained in speech

sounds. More details about the Ineraid system can be found elsewhere (Parkin, 1997).

Subjects

Three profoundly deaf subjects (two women, subjects I03 and I29; one man, subject I33) participated to this study after informed consent was obtained. All had been using the Ineraid cochlear implant for at least 6 years at the time of this study and all were good performers with their implant, allowing them to talk freely over the telephone. Table 1 summarizes principal characteristics of subjects. Subject I29 presented an important ossification of the basal part of the cochlea and the implant was inserted in a retro-cochlear way from the apex to the cochlea (Montandon *et al.*, 1994). All the subjects used the continuous interleaved sampling (CIS) sound coding strategy (Boëx *et al.*, 1996) implemented on the Geneva Wearable Processor (Pelizzone *et al.*, 1999). All subjects were right handed.

Position of Electrodes Inside the Cochlea

The exact position of the electrode contacts in the cochlea was determined using a special radiographic procedure, the modified Stenver's view (Marsh *et al.*, 1993). For subjects I03 and I33, their most apical electrodes were found to be inserted by ~430° inside the cochlea, their most basal electrodes by ~45°. For subject I29, her most apical electrode was at ~380° and her most basal electrode was ~125°. Knowing position inside the cochlea, one can estimate the absolute place pitch corresponding to a normal human ear by using a frequency-to-position function (Greenwood, 1990). This estimation yields a range of pitches from ~700 to 10 300 Hz for subjects I03 and I33 (almost 4 octaves) and a smaller range, from ~1300 to 5400 Hz, for subject I29 (>2 octaves).

Psychophysical Pitch-ranking

Pitch-ranking experiments, which indicate relative pitch changes across electrodes, were conducted using a paired comparison procedure to check that electrical stimulation of the different intracochlear electrodes did elicit different auditory percepts. Stimuli were 0.5 s bursts of 1000 Hz sinusoidal current, similar to those used during the fMRI experiment (see below). One burst was presented successively on two different intracochlear electrodes and we asked the subject to indicate which electrode produced the higher pitch sensation (two-alternative, forced-choice procedure). The responses were entered by the experimenter and no feedback was provided. All possible paired combinations of different electrodes were tested four times for subject I33 (six active electrodes, 30 pairs of stimuli), eight times for subject I29 (four active electrodes, 12 pairs of stimuli) and 10 times for subject I03 (five active electrodes, 20 pairs of stimuli). The order of presentation of the different pairs was randomized. Results were analyzed as a percentage of responses in which the more basal electrode was perceived higher than the more apical electrode.

Stimuli and fMRI Paradigm

Stimuli were 0.5 s bursts of 1000 Hz sinusoidal current, presented at a rate of 1 Hz. These electrical stimuli were presented in monopolar mode, at a comfortable loudness level to stimulate successively each intracochlear electrode. The loudness level was chosen to be approximately the same across electrodes within the same subject and similar across subjects to minimize possible sources of variability (Lockwood *et al.*, 1999).

For all fMRI experiments, a block paradigm was applied, which alternated between 'activation' and 'silent control' sequences. Both sequences (20 s each) were repeated five times yielding a total duration

of 3.5 min per stimulation run. Five different intracochlear electrodes were stimulated on subject I03, four on subject I29 and six on subject I33. The order in which electrodes were stimulated was different for each subject.

In a previous study (Lazeyras *et al.*, 2002), our experimental setup was checked for possible interference between fMRI acquisition and the implanted electrodes and a procedure for safe experimental activation was developed with proper shielding of the stimulation cables.

MR Acquisition

Experiments were performed on a 1.5 T whole-body ECLIPSE system (Marconi/Philips Medical Systems, Cleveland, OH). The head was maintained fixed with a vacuum pillow during the whole experiment in order to minimize motion. The acquired multi-slice volume was positioned on sagittal scout images. Functional imaging consisted of an EPI GRE sequence (T_R/T_E/flip = 2 s/40 ms/80°, FOV = 250 mm, matrix = 128 × 128, 15 contiguous 5 mm axial slices). The spatial resolution reached was 1.95×1.95 mm^2 in the plane. Functional scanning was always preceded by 10 s of dummy scans to insure steady-state magnetization of the tissue. We did show previously that the possible signal-to-noise-ratio (SNR) degradation due to the implant connector was very limited for this EPI GRE sequence (Lazeyras *et al.*, 2002).

In addition, anatomical scans were performed. A first GRE T_1-weighted (FOV = 250 mm, T_R/T_E/flip = 162 ms/4.47 ms/80°, matrix = 256 × 256, slice-thickness = 5 mm) was performed to acquire the same volume as in the functional session. Anatomical reference images consisted of a 3D-GRE T_1-weighted sequence (FOV = 250 mm, T_R/T_E/flip = 15 ms/4.4 ms/25°, matrix = 256 × 256, slice thickness = 1.25 mm). During anatomical scans, electrodes were disconnected from the stimulation hardware.

Data Processing

Data processing relied upon cross-correlation analysis (Bandettini *et al.*, 1993) after motion correction (Woods *et al.*, 1992) and removing low-frequency temporal drift of the signal, using MEDx software (Sensor Systems, Sterling, VA). The SNR was sufficient to detect activation and no spatial smoothing has been used, preserving the initial good spatial resolution. The cross-correlation, expressed as a Z-value, was calculated voxelwise between a delayed box-car function and the set of measurements, after auto-correlation correction (4 s) (Friston *et al.*, 1995). Afterwards, the statistical distribution of the Z-values was calculated for each experiment and a corresponding probability was computed (Moser *et al.*, 1996). Inter-scan subject motion was corrected by realigning functional images for each electrode to the first collected data series. The motion correction parameters showed less than one voxel shift. In addition, maps were normalized to the Talairach space (Talairach and Tournoux, 1988), with $2 \times 2 \times 2$ mm^3 size for each voxel.

For voxel counts, a rectangular volume of interest (VOI) containing the auditory cortex (Brodmann's areas 41/42 are identified from the high resolution anatomical volume of each subject, in the level of the transversal and superior temporal gyri) was defined for both hemispheres. The Talairach dimensions of the VOI were: *x* from 0 to ±70 mm, *y* from –50 to 0 mm and *z* from –10 to +24 mm.

Results

Pitch-ranking Results

Subject I33 was able to discriminate the auditory sensation elicited by electrical stimulation of each single electrode from the others. Psychophysical pitch-ranking data were consistent with the natural tonotopic organization of the cochlea (from high to low pitch respectively from the base to the apex of the cochlea). Minor errors occurred for electrode pairs 3–4 and 5–6 (one error out of four trials in each case), the other electrode pairs were perfectly discriminable. For subject I29, each electrode was discriminated from the others, with errors occurring for electrode pairs 1–2 (three errors out of eight trials), 3–4 (two errors out of eight trials) and 2–4 (one error out of eight

Table 1
List of the most relevant characteristics of the three participating subjects

Subjects	Birth date	Deafness etiology	Deafness duration (years)	Implant date	Implant side	Implant insertion	No. of electrodes
I03	1928	Mondini, trauma, 1933	55	1988	Left	Normal	5
I29	1972	Meningitis, 1993	1	1994	Right	Retro	4
I33	1952	Unknown, 1977	18	1995	Right	Normal	6

trials). The other electrode pairs were perfectly discriminable. For subject I03, pitch comparisons were consistent with the natural tonotopic organization of the cochlea for four out of five electrodes. Electrodes 2, 3, 4 and 5 could be discriminated from each other and psychophysical pitch-ranking data among these four electrodes were (almost) perfect. Minor errors occurred only for electrode pairs 2–3 and 4–5 (1 error out of 10 trials). Surprisingly, electrode 1 could not be discriminated from electrode 4, probably due to a cross-turn stimulation of auditory nerve fibers at the level of the spiral ganglion.

FMRI Results

Significantly Activated Voxels

Functional maps of all stimulated electrodes for each subject are shown in Figure 1. For illustration, functional maps were re-sampled using a trilinear interpolation to yield a high voxel spatial definition of ~1 mm^3. Each map summarizes voxels activated by one intracochlear electrode ($P < 0.0005$, uncorrected). All significantly activated voxels fell close to HG, but the location and shape of activated foci varied across subjects and electrodes. Activation of the left hemisphere is more extensive than the right hemisphere.

Significantly activated voxels ($P < 0.0005$, uncorrected) were counted in each hemisphere of each subject (Fig. 2). We found activation in both hemispheres of each subject upon stimulation of each electrode (except in the right hemisphere of subject I29 for stimulation of electrode 3). Activation of the left hemisphere (LH) was systematically stronger than that of the right hemi-sphere (RH) in all these right-handed subjects, independent of the side of stimulated ear. As a consequence, activation was dominant contralateral for subjects I29 and I33, and dominant ipsilateral for subject I03. The degree of lateralization varied across subjects and electrodes.

Cluster Grouping

Since activation was found to be most prominent in LH, we concentrated further analysis on this hemisphere. Figure 3 shows functional maps of the combination of two different electrodes for each subject as well as enlarged projections on high resolution anatomical images of their dominant LH. From this figure, it is clear that stimulation of a single electrode could produce several different clusters of activation. It is also clear that stimulation of different electrodes could produce activation of the same voxels, the degree of overlapping activation being apparently more pronounced for stimulation of neighboring
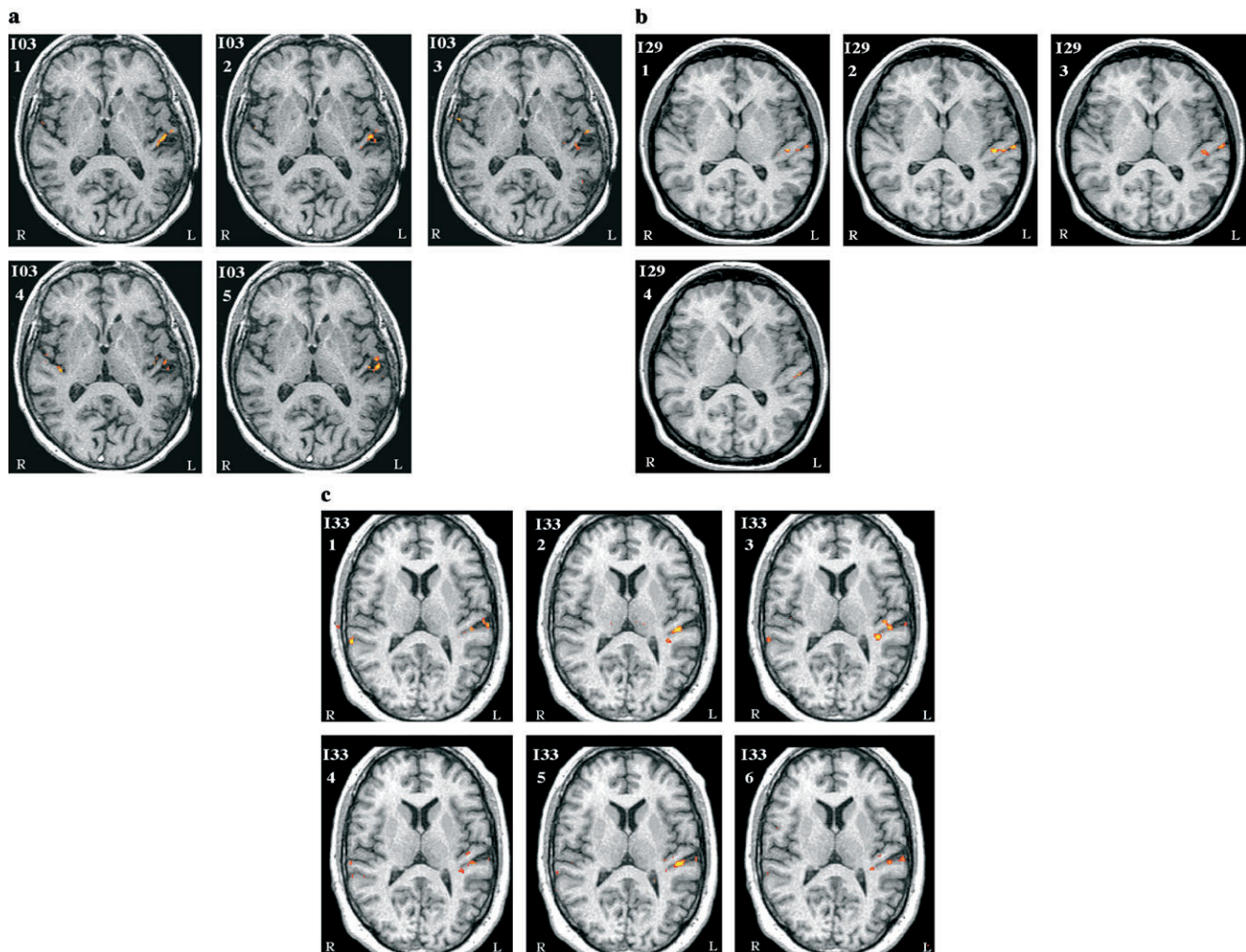
Figure 1. Activated voxels of all electrodes are shown on axial view for (a) subject I03 (Talairach z-plane = +6), (b) subject I29 (Talairach z-plane = +6) and (c) subject I33 (Talairach z-plane = +10). For each stimulated electrode, only the most representative axial slice is illustrated. (statistical threshold $P < 0.0005$, uncorrected).
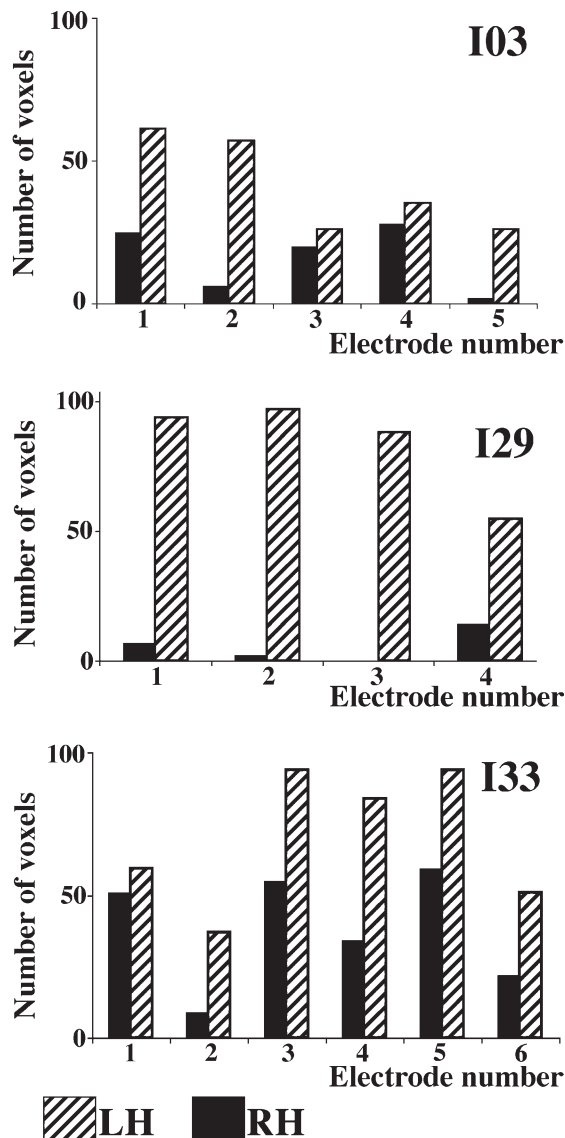
Figure 2. The number of activated voxels in the two hemispheres, for each electrode, is reported for all subjects. This number corresponds to the total number of activated voxels found in the auditory cortex. Black bars correspond to the right hemisphere.

electrodes. However, we did not observe any systematic shift of activation associated with the placement of electrodes inside the cochlea.

To further quantify these observations, clusters of activation for each electrode were defined as to contain at least two contiguous voxels (Forman *et al.*, 1995; Talavage *et al.*, 2000), both being statistically significantly activated ($P < 0.0005$, uncorrected). Using this definition, stimulation of each electrode in each subject elicited several clusters of activation (see Figs 1 and 3). The number of such clusters varied from two to nine for a single electrode and cluster volumes ranged from 16 to 72 mm^3. The locations of these clusters of activation in Talairach z-plane coordinates ranged from –4 mm to +20 mm, i.e. in regions containing the major landmarks of the primary auditory cortex.

To schematically depict the anatomical distribution of these clusters of activation, we projected their mean locations on transverse section at z = +8 mm of Talairach space, centered on HG (Fig. 4). By using methods similar to those used by

Talavage *et al.* (2000) to define frequency-dependent responses regions (FDRRs), we could group adjacent activated clusters for different electrodes into separate regions. This grouping was done in order to have the maximum of stimulated electrodes (at least four electrodes) in each defined region. With this approach, we found separate auditory cortex regions responding to all intracochlear electrodes (subjects I03 and I29), or at least to four out of six single electrodes (subject I33). Four such regions were identified for subjects I29 and I33, and three for subject I03. Table 2 reports the Talairach coordinates of each distinct region, corresponding to the mean location of the activated clusters within the region. Table 2 also indicates the occurrence of electrode responses in each region (i.e. the number of electrodes that produce activation compared to the total number of used electrodes). While these regions were all within the auditory cortex, we did not observe any tonotopic organization of functional responses within one particular region.

Discussion

Electrical stimulation of the ear in deaf subjects can be investigated by fMRI and activation of the auditory cortex has been reported recently in several studies (Berthezene *et al.*, 1997; Melcher *et al.*, 1998; Hofmann *et al.*, 1999; Obler *et al.*, 1999; Alwatban *et al.*, 2002; Schmidt *et al.*, 2003). Methods for safe and artifact free fMRI upon electrical stimulation of the ear were developed previously (Lazeyras *et al.*, 2002). In this study, we used the same experimental conditions to study how the auditory cortex of deaf subjects, users of cochlear implants, responded to monaural stimulation of all possible intracochlear electrodes. During the experiments, the subjects confirmed auditory perception of similar and moderate loudness level upon stimulation of each electrode. None of them heard the imager noise. These experimental conditions, 'soft auditory stimuli on a silent background', helped to minimize possible sources of variability and artifactual interference with MRI noise. Good discrimination across electrodes was demonstrated experimentally with psychophysical pitch-ranking data and was expected since all three subjects were able to conduct free conversations without visual help with their cochlear implant.

We found that stimulation of each single electrode resulted in activation of different cortical clusters, all located within the major landmarks of the human auditory cortex. Furthermore, these clusters were grouped into separate auditory cortical regions responding to stimulation of all (or most) intracochlear electrodes in the same subject. We will now examine these results in regard to architectonic and functional studies of the human auditory cortex.

Comparison with Previous Functional and Architectonic Studies

The human auditory cortex is divided into several areas that can be cytoarchitectonically distinguished, as proposed early in the last century (von Economo and Koskinas, 1925). Later, other investigators reported more subdivisions in the same cortical region (Galaburda and Sanides, 1980; Rivier and Clarke, 1997; Morosan *et al.*, 2001; Rademacher *et al.*, 2001b; Wallace *et al.*, 2002), but with some significant discrepancies across studies due to the use of different experimental methods (Wallace *et al.*, 2002). Generally, the human auditory cortex consists of a primary auditory cortex (PAC) (medial two thirds of the HG; e.g. Morosan *et al.*, 2001; Rademacher *et al.*, 2001b; Wallace
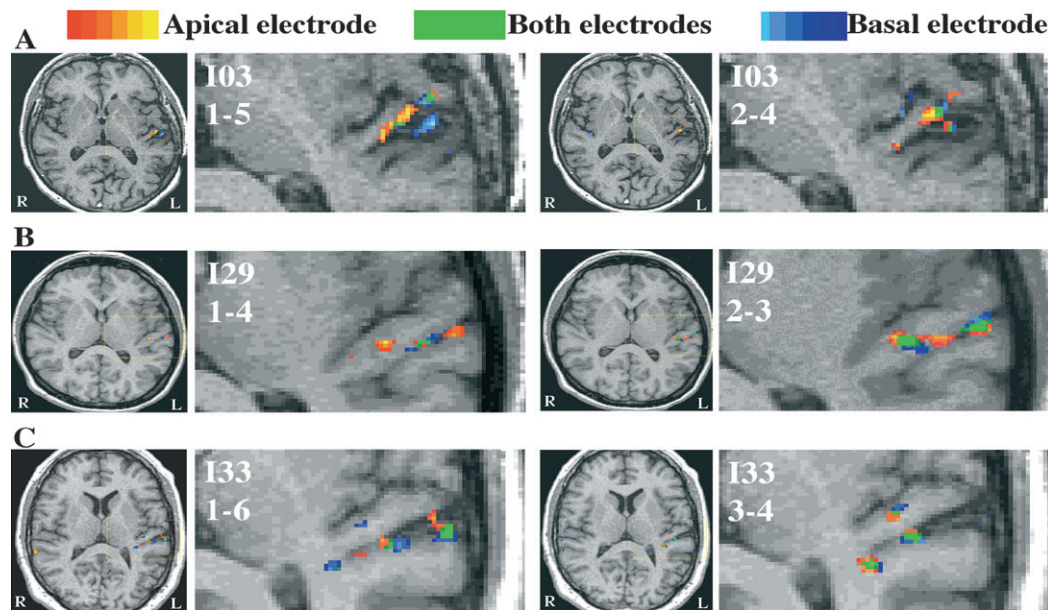
Figure 3. Examples of activated clusters within the auditory cortex upon stimulation of two different electrodes after superposition on high resolution images. For each electrode pair, voxels activated by the apical electrode are indicated in red (and yellow), voxels activated by the basal electrode are indicated in blue. Overlapping voxels activated by both electrodes are indicated in green. (A) subject I03 (Talairach z-plane = +6), (B) subject I29 (Talairach z-plane = +6) and (C) subject I33 (Talairach z-plane = +10).

et al., 2002) and of surrounding multiple non-primary areas that can be defined anatomically (e.g. Galaburda and Sanides, 1980; Rivier and Clarke, 1997). It is also suggested that the PAC itself may be subdivided in two (Galaburda and Sanides, 1980; Wallace *et al.*, 2002) or three regions (Morosan *et al.*, 2001).

Moreover, neuroimaging studies with fMRI suggest a functional parcellation of the auditory cortex into multiple cortical areas (Scheich *et al.*, 1998; Hashimoto *et al.*, 2000; Talavage *et al.*, 2000; Di Salle *et al.*, 2001; Wessinger *et al.*, 2001; Hall *et al.*, 2002; Hart *et al.*, 2002; Schönwiesner *et al.*, 2002). The number of identified auditory areas varied between studies, about three (Di Salle *et al.*, 2001; Hart *et al.*, 2002), four (Scheich *et al.*, 1998; Hashimoto *et al.*, 2000), or seven auditory areas (Talavage *et al.*, 2000; Schönwiesner *et al.*, 2002). Here, the identification of multiple auditory regions (at least three regions) in these subjects users of cochlear implants is consistent with these studies.

Figure 5 summarizes schematically several of the cytoarchitectonic and functional findings described above on an outline of the cortex based on the Talairach z = +12 mm plane. The locations of activated regions responding to stimulation of all (or most) electrodes in the same subject (black circles in Fig. 5) are in excellent agreement with the locations of the different cytoarchitectonic areas (e.g. Rivier and Clarke, 1997; Morosan *et al.*, 2001). The same is generally true for functional results reported by other authors (Hashimoto *et al.*, 2000; Talavage *et al.*, 2000; Di Salle *et al.*, 2001; Schönwiesner *et al.*, 2002) since these regions fall within the limits of the primary auditory cortex (Penhune *et al.*, 1996; Rademacher *et al.*, 2001b). It is, however, difficult to establish a one-to-one relationship between these various cytoarchitectonic and functional areas.

Auditory areas are then defined by grouping adjacent activated regions shown in Figure 4 across subjects and according to their comparable Talairach coordinates proposed in the Table 2. Multiple regions are grouped into an auditory area if the one-to-one Euclidean distance between their respective Talairach coordinates is <10 mm (i.e. a region of one subject is grouped with a region of an other subject into an area if the Euclidean distance between them is <10 mm). This approach has led us to identify five areas that verify these criterions, with areas implicated in all subjects (areas 1 and 2), in two subjects (areas 3 and 4) or in one subject (area 5). Table 3 lists these identified areas and compares them with published architectonic and functional works. We will now propose a correspondence between our auditory areas with those identified in previous studies.

First, the activated area 1 found in all subjects may correspond to the anterior area Te1.0 of Morosan *et al.* (2001). It may be equivalent to area A1 of Rivier and Clarke (1997), area KAm of Galaburda and Sanides (1980) and area AI of Wallace *et al.* (2002). It represents a part of the primary auditory cortex (PAC). Functionally, it seems comparable to previous functional areas, as the area T1a/T1b of Scheich *et al.* (1998), area 1a/1b of Schönwiesner *et al.* (2002), area A1 of Hashimoto *et al.* (2000), area anterior-HG of Di Salle *et al.* (2001) and close to the region FDRR1/FDRR2 of Talavage *et al.* (2000).

Second, the area 2 activated in all subject, more lateral than area 1, may correspond, in view of architectonic data, to the anterior area Te1.2 of Morosan *et al.* (2001) or a part of area KAlt and the exterior extent of area PaAi of Galaburda and Sanides (1980). It seems more anterior than the area LA of Rivier and Clarke (1997) and corresponds well to area ALA of Wallace *et al.* (2002). It corresponds to a more posterior localization than the region FDRR5/FDRR6 of Talavage *et al.* (2000) and area 6 of Schönwiesner *et al.* (2002). It also corresponds well with the proposed area A2l/STa of Hashimoto *et al.* (2000).

Third, the area 3 activated in two subjects (I29 and I33) may correspond to the posterior auditory area Te1.0 of Morosan *et al.* (2001). This region is localized more laterally than the posterior area PA of Rivier and Clarke (1997) and between PaAi and PaAc/d areas of Galaburda and Sanides (1980). It seems that this area is equivalent to area 3 of Schönwiesner *et al.* (2002), area posterior-HG of Di Salle *et al.* (2001), area A2m of
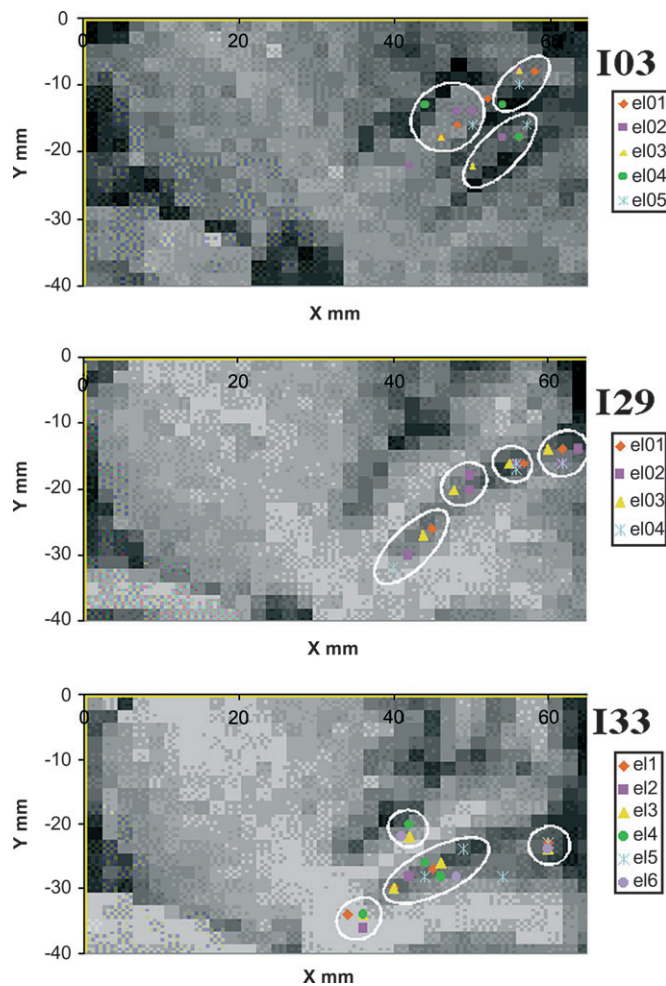
Figure 4. Activated clusters were grouped on the same transverse Talairach plane (z-plane $= +8$ mm) and distinguished groups are considered as different cortical regions, as rounded by white circles. Corresponding colors for all electrodes are given within each graphic.

Hashimoto *et al.* (2000) and more medial than the region FDRR3 of Talavage *et al.* (2000).

Fourth, the area 4, more anterior and lateral, was found in subjects I03 and I29. This area corresponds most closely to the lateral part of area Te1.2 of Morosan *et al.* (2001) and was localized more laterally than area ALA of Wallace *et al.* (2002) and may be a part of the anterior extent of area PaAe of Galaburda and Sanides (1980). It seems to be equivalent to area 6 of Schönwiesner *et al.* (2002) and the region FDRR6 of Talavage *et al.* (2000). Also, it is more anterior than area STa of Hashimoto *et al.* (2000).

Finally, activation has been detected for subject I33 in the area 5 corresponding to the posterior area Te1.1 of Morosan *et al.* (2001) and may represent a part of area PA of Rivier and Clarke (1997) and area PaAc/d of Galaburda and Sanides (1980). This activation is located in area 4 of Schönwiesner *et al.* (2002) and the region FDRR4 of Talavage *et al.* (2000).

What About Tonotopy?

Evidences for a tonotopic organization of the human PAC were reported in magnetoencephalography (Cansino *et al.*, 1994; Lütkenhöner and Steinsträter, 1998), positron emission tomography (PET; Lauter *et al.*, 1985; Lockwood *et al.*, 1999) and fMRI studies (Strainer *et al.*, 1997; Wessinger *et al.*, 1997; Bilecen *et al.*, 1998; Yang *et al.*, 2000; Engelien *et al.*, 2002). At present, the general view is that low frequency signals activate more superficial and lateral regions, while high frequency signals activate more medial and deep regions (but see Pantev *et al.*, 1995; Schönwiesner *et al.*, 2002).

In this study, no spatial shift of activated clusters of the different stimulated electrodes could be observed. Despite the fact that electrical stimulation of different intracochlear electrodes did actually elicit discriminable auditory sensations in good agreement with the tonotopic organization of the cochlea (from high to low pitch respectively from the base to the apex of the cochlea), as assessed in the pitch-ranking experiment, the pattern of functional responses does not show tonotopic organization. For example and according to the tonotopic organization described in previous neuroimaging studies, the most apical electrode could normally produce a separated activated pattern from the most basal electrode (subjects I03 and I33, 4 octaves) with a distance of 12 mm (Romani *et al.*, 1982), 4 mm (Yang *et al.*, 2000; Engelien *et al.*, 2002), or 3–17 mm (Wessinger *et al.*, 1997). In spite of favorable experimental conditions, we observed that different electrodes did generate overlapping functional responses in the three subjects. This absence of tonotopic organization was also observed in other recent fMRI studies with hearing subjects (Ulualp *et al.*, 2000; Hall *et al.*, 2002; Schönwiesner *et al.*, 2002). For example, Ulualp *et al.* (2000) found extensive overlap in functional responses, concluding it was not possible to identify tonotopic organization in spite of the use of five different stimuli frequencies. Schönwiesner *et al.* (2002) came to the same conclusion with four different frequencies and found seven separated regions responding to several of these frequencies. This interpretation of functional maps in terms of parcellation of the PAC rather than the presence of tonotopic organization had been proposed previously with magnetoencephalography (Pelizzone *et al.*, 1985). These findings in hearing subjects are in concordance with our results and can be added to our arguments in favor of the existence of multiple regions in the PAC of deaf subjects users of cochlear implants. On the other hand, despite the fact that tonotopy was not observed, we can not rule out, within each identified auditory region, a possible tonotopic organization. This issue is difficult to address due to the limited spatial resolution of our methods and the confined size of these regions.

Methodological Considerations

First, the EPI sequence used for fMRI acquisition in previous studies determines a consistent activation of the auditory cortex (Ulmer *et al.*, 1998; Shah *et al.*, 1999) and the elimination
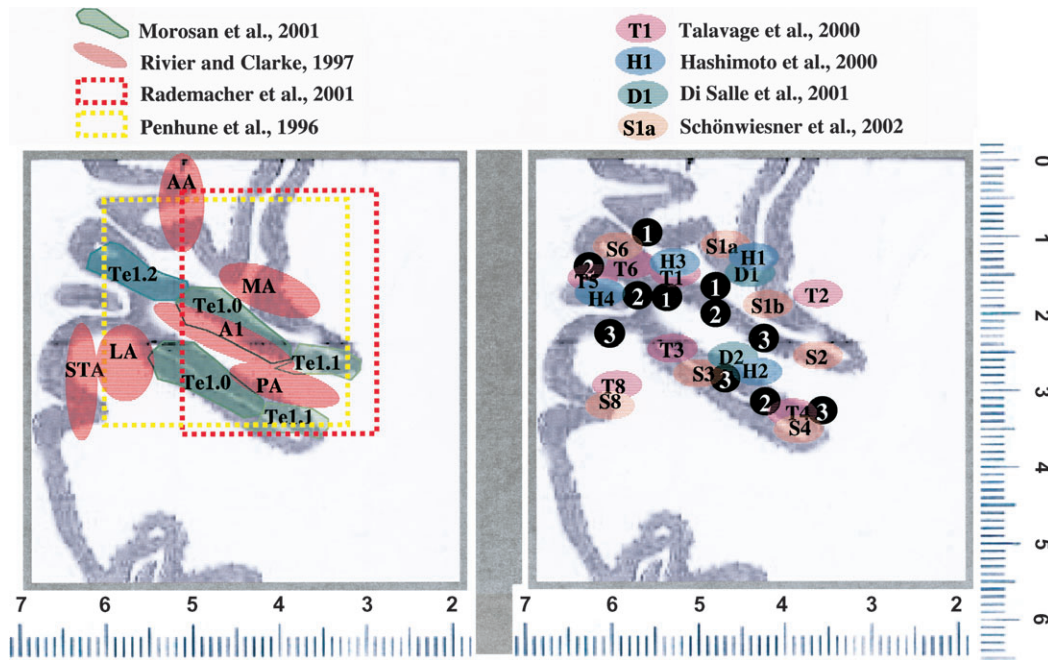
Figure 5. Identified cortical regions, as reported in the Table 2 in the Talairach space, are shown in black color in this figure. Regions for the subject I03 are shown with the number 1, those for the subject I29 with the number 2 and those for subject I33 with the number 3. The limits of the primary auditory cortex are shown in red (Rademacher et al., 2001b) and yellow (Penhune et al., 1996). Auditory areas reported in some previous fMRI studies are shown in the right. Cytoarchitectonic areas, identified by previous architectonic studies are shown in the left. The Talairach slice corresponds to the z-plane = +12 mm.

Table 3

Left: correspondence with previous architectonic studies (Galaburda and Sanides, 1980; Rivier and Clarke, 1997; Morosan et al., 2001, Wallace et al., 2002). Right: correspondence with fMRI studies (Scheich et al., 1998; Hashimoto et al., 2000; Talavage et al., 2000; Di Salle et al., 2001; Schönwiesner et al., 2002)

Areas	Architectonic areas	Functional areas
Area 1	Anterior Te1.0 (Morosan)	T1a/T1b (Scheich)
I03: −48 −16 6	Area A1 (Rivier)	Area 1a/1b (Schönwiesner)
I29: −48 −20 8	Area KAm (Galaburda)[a]	Area A1 (Hashimoto)
I33: −42 −22 10	Area AI (Wallace)	Anterior-HG (Di Salle)
		Between FDRR1/FDRR2 (Talavage)
Area 2	Te1.2 (Morosan)	Posterior than area 6 (Schönwiesner)
I03: −54 −18 6	Anterior than LA (Rivier)	Between STa and A2I (Hashimoto)
I29: −57 −18 8	A part of KAlt and the exterior extent of PaAi (Galaburda)[a]	Posterior than FDRR5/FDRR6 (Talavage)
I33: −60 −24 8	Area ALA (Wallace)	
Area 3	Posterior Te1.0 (Morosan)	Area 3 (Schönwiesner)
I29: −42 −30 6	Lateral than PA (Rivier)	Posterior-HG (Di Salle)
I33: −47 −28 10	Between PaAi and PaAc/d (Galaburda)[a]	Area A2m (Hashimoto)
		Medial than FDRR3 (Talavage)
Area 4	Lateral part of Te1.2 (Morosan)	Area 6 (Schönwiesner)
I03: −56 −10 6	Lateral than ALA (Wallace)	FDRR6 (Talavage)
I29: −62 −14 6	The anterior extent of PaAe (Galaburda)[a]	Anterior than STa (Hashimoto)
Area 5	Posterior Te1.1 (Morosan)	Area 4 (Schönwiesner)
I33: −35 −32 10	Part of PA (Rivier)	FDRR4 (Talavage)
	Part of PaAc/d (Galaburda)[a]	

Talairach coordinates are those given in Table 2.

[a]Talairach coordinates of auditory areas in the study of Galaburda and Sanides (1980) are based upon their figure 1 and adapted from the figure 5a of Talavage et al. (2000).

of the EPI noise-induced activity may be limited by the observed strong non-linearity of the auditory BOLD response (Robson et al., 1998). In our study, auditory activation was measured in 'silent background' conditions as the subject did not perceive

scanner noise. Hence, the detected functional responses in our three subjects reflect perfectly the auditory sensation generated by electrode stimulation.

Second, our pool of subjects was relatively limited (three subjects). The large inter-individual anatomical variability of the temporal gyrus (Rademacher et al., 1993; Westbury et al., 1999) needs to be considered as a major limitation for the precise identification of multiple minuscule auditory regions. Also, gender differences (two women I03 and I29, one man I33) may add variability on our findings, as suggested previously in terms of HG's size, asymmetry and neural density (Witelson et al., 1995; Rademacher et al., 2001a).

Third, the functional delimitation of auditory areas is complicated to assess. Previous studies have attempted to define functional frontiers between auditory areas, in particular for differences between high and low frequencies (Talavage et al., 2000; Schönwiesner et al., 2002), or for stimuli of varying spectral complexities (Wessinger et al., 2001; Hall et al., 2002). Here, with large functional data (from four to six stimulated electrodes), delimitation of auditory regions in each subject was based on the hypothesis that each region could be activated by all (or most) electrodes (i.e. auditory regions that respond to the entire auditory spectrum). Comparison with areas found by architectonic methods was performed to support these functional findings. Nevertheless, it is not clear in this analysis if these are subdivisions of the PAC, as suggested by Morosan et al. (2001), or secondary auditory areas (non-primary) as assumed from Hall et al. (2002).

Another issue concerns the quality of the auditory sensations upon electric stimulation. Cochlear implant patients do not experience perfectly normal acoustic stimulation. They perceive spectrally reduced acoustic information, but with still sufficient selectivity to understand free running speech without lip reading. The evidence for a tonotopic organization of

functional responses might be masked by the monopolar stimulation mode used by the device, which generates a widespread excitation of the auditory nerve fibers, or by the limited pitch range experienced by the patients, 2–4 octaves instead of 6–7 octaves for normal hearing (Engelien *et al.*, 2002). In addition, other factors such as number of active electrodes, side of the implantation and duration of deafness may be sources of the variability within subjects. All these methodological sources should be taken into account in the interpretation of these new results.

Auditory Hemispheric Dominance Following Deafness

Usually in normal hearing persons, monaural stimulation produces bilateral responses of the superior temporal gyrus, with a dominance of the contralateral hemisphere (Lauter *et al.*, 1985; Pantev *et al.*, 1998; Scheffler *et al.*, 1998). In the present study, the laterality of PAC activation was different across patients. We observed in two (I29, I33) out of three subjects a bilateral activation with a dominance of the contralateral auditory cortex in response to monolateral stimuli. Previous fMRI studies in deaf subjects have also found contralateral activation upon electrical stimulation (Berthezene *et al.*, 1997; Obler *et al.*, 1999; Alwatban *et al.*, 2002; Schmidt *et al.*, 2003). Interestingly, in one subject (I03), we observed monolateral responses that were ipsilateral to the stimulation. Previously, this same subject had been tested 20 years ago by recording magnetic fields and had shown stronger responses over the hemisphere ipsilateral to the stimulation (Pelizzone *et al.*, 1986). Ipsilateral dominance had been also observed in an implant cochlear subject by PET (Truy *et al.*, 1995).

Most interestingly, this laterality was found in the favor of the left hemisphere for the three subjects. In previous works, BOLD responses to bilateral pulsed tone stimuli in hearing subjects have shown a lateralization in the left temporal gyrus (e.g. Bilecen *et al.*, 1998) and particularly for high frequencies (Ulualp *et al.*, 2000). A trend towards greater activation in the LH has also been found with band-pass noise stimuli (Wessinger *et al.*, 2001) and with complex auditory tasks (Strainer *et al.*, 1997). This left dominance differs across electrodes, which is in concordance with the different size of activated foci as underlined in previous studies (Talavage *et al.*, 2000; Ulualp *et al.*, 2000). Moreover, our data indicate that cortical activity produced by artificial audition can be preserved in spite of long periods of peripheral deprivation. In particular, cortical activity in subject I03 was found to be similar to two others patients, in spite of the fact she had been totally deaf for > 50 years, in agreement with her good speech and pitch ranking performances.

In conclusion, we have presented fMRI findings in deaf subjects upon electrical stimulation of each of several intracochlear electrodes. These findings were obtained without MRI scanner noise bias and were generally in good agreement with previous functional and architectonic studies. They bring additional support to the functional subdivision of the human auditory cortex into multiple cortical regions.

Notes

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