Tonotopic Cortical Changes Following Stapes Substitution in Otosclerotic Patients: A Magnetoencephalographic Study

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Abstract: The aim of the study was to investigate and follow up the tonotopic organization of the primary auditory cortex in otosclerotic patients before and after corrective surgery. The characteristics of primary auditory cortex activation were studied in ten otosclerotic patients (i.e., subjects suffering from a conductive hearing loss, prior to and following stapes substitution). Magnetoencephalographic recordings of auditory evoked fields by tone-burst stimulation at octave frequencies between 250 and 2000 Hz were performed during monaural stimulation. The brain topography of the main cortical response (N100m) generators at different tones was studied in patients and compared with ten healthy controls; pre-post-surgical changes were also correlated to their clinical outcome following corrective surgery. A significant decrease of the tonotopic extension in the cortical region responsive to the four explored frequencies was found in patients before surgery with respect to the control population. At the time of postsurgical follow-up, the tonotopic representation had enlarged and was approaching the dimensions seen in normal subjects, although with higher variability. The extent of the enlargement of the postoperative tonotopically organized area was directly correlated with the postsurgery period duration. Our findings indicate that auditory cortical areas of human adults undergo functional reorganization following peripheral alteration of the sensory input entering the CNS. The restriction of the cortical tonotopic region caused by the long-term reduction of acoustic input is followed by a reorganization within the usual boundaries following the recovery of auditory function; this process is taking place in a time scale of a few weeks. *Hum. Brain Mapping* 10:28–38, 2000. © 2000 Wiley-Liss, Inc.

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INTRODUCTION

Progressively more research has been devoted to the investigation of brain mechanisms underlying "plastic" rearrangements, in which previously functionally silent or differently operating neuronal pools vicariate a lost function, or react to the lack of a physiological amount of sensory flow. Neuronal reor-

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ganization mechanisms have been investigated in animals at different relays of the auditory sensory pathway, induced both by cochlear selective lesions [Harrison et al., 1998; Popelar et al., 1994; Robertson and Irvine, 1989] and conditioning stimulations [Bakin and Weinberger, 1990; Cruikshank and Weinberg, 1996]. Cortical interference via intracortical microstimulation [Ahissar et al., 1992; Maldonado and Gerstein, 1996; Sil'kis and Rapoport, 1995] and by transcranial magnetic stimulation [Wang et al., 1996] has also been reported. Different cortical types of reorganization have been found to be age-dependent, relative to the onset of the deficit: for instance, the tonotopic map reorganization found in adult guinea pigs following partial unilateral deafness [Robertson and Irvine, 1989] was not found in cats following unilateral cochlear ablation in the neonatal period [Reale et al., 1987]. This "age" segregation is less evident in humans, plastic reorganizations having been described in children [Ponton et al., 1996] and adults [Vasama et al., 1994] suffering from sensorineural damage of acoustic pathways, or as a result of intense musical training [Pantev et al., 1998].

In the present study, the possibility of plastic reorganization of neural substrates occurring in the supratemporal auditory cortex of otosclerotic patients before and after corrective surgery has been investigated. In these subjects, a progressive hearing deficit is caused by the anomalous growth of the bone around the annular ligament locking the stapes footplate to the oval window.

The effects of this long-term conductive hearing loss and the impact of corrective surgery have been studied by magnetoencephalography (MEG). This technique reliably identifies activated sources within the supratemporal auditory cortex [Hari et al., 1980; Pantev et al., 1990; Papanicolau and Banmann, 1990]. Moreover, MEG has been used to noninvasively confirm in humans the tonotopic organization of the primary auditory cortex [Pantev et al., 1991; Romani et al., 1982; Verkindt et al., 1995]. In our otosclerotic patients, the tonotopic organization of the primary auditory cortex has been MEG-characterized, focusing on the representation of the most affected ear. In order to discriminate if the observed effects have a cortical origin or accrue solely or partly at cochlear level, auditory brain stem responses (ABR) to stimuli with different frequency contents have been collected using brief tone bursts at the same frequencies of the MEG study. In this regard, others [Chisin et al., 1983a] previously showed that high-intensity click evoked-ABR latencies and threshold could be used to characterize the effects of stapedioplasty in otosclerotic patients.

However, no analysis has been performed in relation to different tone frequencies. McGee and Clemis [1982] compared an ABR latency-intensity function with the audiometric air-bone gap to evaluate the ABR ability in characterizing the degree of conductive loss: an indication of tone pips ABR differentiation, as a function of stimulating tone frequencies, was found.

No damage to sensorineural pathways is present in pure otosclerosis. Different degrees of hearing loss may be related to disease duration. Nowadays, surgical procedures have been introduced which are able to repair this kind of hearing impairment by platinotomy and stapes substitution [de Campora et al., 1996; Glasscock et al., 1995; Shea, 1988]; it is therefore possible to examine patients prior to and following the total or partial recovery of hearing function, and to assess the impact on cortical centers organization to a new (quantitative and qualitative) flow of acoustic input.

SUBJECTS AND METHODS

Ten patients suffering from otosclerosis (five males, five females, age range 27–53 years) and ten normal hearing subjects (six males, four females, age range 29–46 years) were enrolled for this study, after having obtained their informed consent and the approval of the local Ethics Committee. Patients were diagnosed with a hearing deficit for a period ranging from 1.5 to 5 years (mean 2.8 ± 1.3). This deficit was bilaterally present even if with a unilateral predominance: in six subjects the left ear was the most affected and in four subjects the right ear. All patients and control volunteers were right-handed.

A careful audiometrical examination was carried out before the MEG recording session, to measure pure-tone air and bone hearing thresholds at octave frequencies between 250–8000 Hz. Data between 250–2000 Hz (the ones employed for MEG recordings) are reported throughout the text. All the healthy controls had air and bone thresholds lower than 20 dB Sound Pressure Level (SPL). In patients, the otosclerotic hearing loss was determined when a gap between air and bone hearing thresholds was 20 dB or more. Impedance tests (tympanometry and stapedial reflex threshold) were also performed; the acoustic reflex was absent in all otosclerotic cases. None of the patients had vestibular disease.

Patients underwent surgical correction consisting of platinotomy and stapes substitution by a Shea platinum-teflon piston [Shea, 1988]. Pre- and postsurgery audiological features are shown in Table I. Successful recovery on follow-up, performed after 40 ± 15 days

TABLE I. Mean $\pm$ standard deviations of auditory air and bone thresholds (dB SPL) at the four frequencies used for the MEG study, before and after surgery*

	PRE				POST			
	250 Hz	500 Hz	1000 Hz	2000 Hz	250 Hz	500 Hz	1000 Hz	2000 Hz
Air	52 $\pm$ 10	51 $\pm$ 12	51 $\pm$ 14	42 $\pm$ 9	22 $\pm$ 4	21 $\pm$ 7	25 $\pm$ 9	23 $\pm$ 8
Bone	14 $\pm$ 6	16 $\pm$ 6	19 $\pm$ 5	26 $\pm$ 12	9 $\pm$ 2	11 $\pm$ 3	12 $\pm$ 5	16 $\pm$ 6

* Before surgery the audiometric thresholds correspond to masked stimulation [i.e., narrow band noise was simultaneously delivered to the contralateral ear at intensity of 40 dB above individual hearing threshold (HL)].

from surgery, was defined when postoperative air-bone gap dropped to less than 20 dB.

Control measurements to assess the place of resonance of the stimuli on the basilar membrane were performed in two controls and two otosclerotic patients, by recording auditory brainstem responses (ABRs) to brief tones at 500 and 2000 Hz. In fact, these two-tone frequencies characterize the two extremes of the spatial segregation on the basilar membrane; therefore, the increase in the wave V latency to lower vs. higher-frequency tones reflects the longer cochlear travel time to reach the apical region of the cochlea [Stapells and Oates, 1997; Stapells et al., 1985]. Tone bursts of 500 and 2000 Hz were delivered to the most affected ear (the right ear in normal hearing volunteers), one cycle of plateau (resulting in stimulus duration of 2 ms and 0.5 ms, respectively, for 500 and 2000 Hz, [Barry and Barry, 1996]), and 9.9 Hz of repetition rate [Beattie and Torre, 1997]. Sound intensities of 35 dB HL were utilized, following the hearing threshold characterization for each subject and each frequency, in relation to the stimulus used for ABR recording. In the case of stimulus intensities of more than 90 dB SPL, in addition to contralateral ear masking white noise, ipsilateral (stimulated) ear noise was also gathered at 30 dB less than the brief tone intensity [Stapells and Oates, 1997]. The recorded electrical activity was band-pass filtered (100–2000 Hz), sampled (5000 Hz) and averaged (around 1500 artifact-free trials). At least two replications of each recording were made. Latencies of the evoked responses were measured in accordance with international standards [Stapells and Oates, 1997] by focusing on the complex IV-V and the main wave V, presumably generated by the inferior colliculus.

Procedures

Patients were studied prior to surgery (mean 7 ± 5 days) and following (more than 45 days, mean 4 ± 2 months) postsurgical stabilization of audiological tests. Auditory stimulation was performed by pure tone bursts with carrier frequencies of 250, 500, 1000,

2000 Hz presented to the most affected ear (the right ear for normal hearing subjects). To not overburden the examined patients, we could not investigate the reorganization of the response pattern to the stimulation of the less clinically affected ear. To avoid non-stimulated ear activation because of bone transmission, the noise masking of the other ear at an intensity of 50 dB less than the stimulated ear was undertaken. Each tone burst lasted 300 ms, with a 2641 ms of interstimulus interval. The tone-burst amplitude was set at 50 dB above the subject's hearing threshold (HL) for each frequency. In four cases (patients P5, P6, P7, P10), the tone-burst intensity was limited to 20 dB HL, because the stimulating apparatus could only provide sound intensities of up to 105 dB. In healthy controls, the influence exerted on the tonotopic organization by the stimulus intensity had been checked by stimulating five subjects at 20 and 50 dB HL, using average absolute sounds intensities of 61 and 30 dB. In one control subject, the test-retest variability of measured parameters was checked by repeating the entire procedure at two successive times.

MEG recordings were performed by a 28-channel system [Foglietti et al., 1991]. This apparatus features 16 first-order axial gradiometers (1.8 cm coil diameter and 8 cm baseline) and nine magnetometers (pick-up area 81 mm²), as well as three balancing magnetometers for noise cancellation coupled to low-noise dc-SQUIDS, with an overall sensitivity of about 5–7 fT/(Hz)^{1/2}. The 25 measuring sites were regularly distributed on a spherical surface covering an area of about 180 cm², with an interchannel distance of about 2.5 cm. All the measurements were performed inside a magnetically shielded room (Vacuumschmelze GMBH). A single sensor position was used to record the auditory evoked fields (AEFs), centered over the mid-temporal lobe contralateral to the stimulated ear, 1 cm above the T3/T4 positions of the 10–20 International EEG System. Exact dewar position with respect to the subject's head was detected by using five coils [Ernè et al., 1987] attached on standard head landmarks (nasion, the two preauricular points, vertex and

TABLE II. ABR wave V latencies (ms) in three normal hearing subjects and in three patients before and after corrective surgery for the two tested stimulation frequencies*

	Control		Patient			
			Pre		Post	
	500 Hz	2000 Hz	500 Hz	2000 Hz	500 Hz	2000 Hz
S1	7.30	6.96	7.90	7.50	6.80	6.60
S2	7.22	6.92	7.95	7.48	6.86	6.68
S3	7.36	7.12	8.10	7.64	7.30	6.80
Mean	7.29	7.00	7.98	7.54	6.99	6.69
	0.29		0.44		0.29	

* The latency delay between 2000 and 500 Hz is on average (last row) 0.3–0.4 ms in all conditions.

inion), whose 3D-positions were digitized at the beginning of the recording session. The entire recording procedure lasted about 1 hr.

Data analysis

One hundred artifact-free trials were acquired (0.48–250 Hz bandwidth, 1 kHz of sampling rate) and averaged for each stimulation frequency. The amplitude of AEFs in the 200 ms poststimulus epoch was calculated for each channel, with respect to a baseline level chosen as the mean value between 50 ms before and 20 ms following the stimulus onset.

The characteristics of the poststimulus brain response peaking around 100 ms (N100m) were studied; in fact, even if earlier components of AEF reflect the initial input to auditory cortex, the N100m response is stable, reproducible, and large enough to be widely accepted by the neuromagnetic community as the marker of the stimulus processing in the primary auditory cortex [Elberling et al., 1980; Hari et al., 1980; Reite et al., 1978].

The cortical generator subtending the N100m component was localized using a standard procedure as the single Equivalent Current Dipole (ECD) model inside an homogeneously conducting sphere [Elberling et al., 1982; Gallen et al., 1992; Pantev et al., 1998]. The field distribution at 1 ms step starting 10 ms before and up to 10 ms following the peak of the N100m was used to calculate the ECD position and strength using a fixed dipole model [Mosher et al., 1992]. Localization results were accepted only if the explained variance was above 90%. The ECD position was expressed in the individual cartesian coordinate system, defined as follows: x-axis passing through left and right preauricular points, outgoing rightward, the positive y-axis through the nasion, and the z-axis perpendicular to the point of bisection between x- and

y-axes. It should be noted that in this reference system the x-coordinate is simply related to the source depth. When averaging data across different subjects, the x-coordinate was normalized to a standard head (width 144 mm). The extension of the tonotopic representation was calculated as the x-coordinate difference between 250 and 2000 Hz.

To demonstrate whether the cortical source characteristics were significantly different in normal hearing subjects and in patients prior to and following surgery, two analyses of variance for repeated measures were performed with “stimulation frequency” as a within-subjects factor. In addition, a similar ANOVA test was applied within the patient group to assess any changes of tonotopic organization because of surgery, when appropriate Greenhouse-Geisser correction of degrees of freedom was applied. The association between MEG findings and clinical history was evaluated by means of Spearman’s rank correlation coefficient (r_s). Throughout the statistical analysis, the significance value was set at 0.05.

RESULTS

Tonal ABR assessment of stimuli segregation on basilar membrane

ABR wave V latencies at 500 and 2000 Hz brief tones showed both in controls and otosclerotic patients a similar variation of about 0.3–0.4 ms (Table II). Such an interval was stable preceeding surgery and during postsurgical follow-up, paired with the known increase of absolute latencies of ABR waves induced by otosclerosis as index of the conductive impairment; latencies as in normal hearing subjects are found following surgery. Stable latency variation between 500 and 2000 Hz supports the idea that topography of tones along the cochlear receptors is neither affected

Figure 1.

Example of AEFs in one control subject (top) and in one patient prior to (middle) and following surgery (bottom); superimposition of all the recording channels in the 200 ms interval from the burst onset, in response to the four stimulation frequencies (250–2000 Hz) with 50 dB HL of stimulus intensity.

by otosclerotic process, nor by surgical, corrective procedures.

Control group

AEF morphology. In healthy subjects, AEF morphology was invariably characterized by the dominant response occurring at approximately 100 ms following stimulus onset (N100m, Fig. 1, top).

Latency and strength. As previously found [Reite et al., 1982], latencies of N100m ECDs showed a delay of about 20 ms when decreasing acoustic stimulus intensities from 50 to 20 dB HL (nonparametric Mann-Whitney $p = 0.008$). On the other hand, the N100m ECD strengths were not significantly modified by sound intensities (Mann-Whitney $p = 0.056$, Table III). Slightly longer latencies were found with stimuli at low frequency tones (i.e., 250 Hz).

Localization. Localization of the N100m ECDs relative to the four carrier frequencies confirmed a tonotopic distribution with low-frequency tones being more shallow, as repeatedly reported by previous studies [Fig. 2a; Lockwood et al., 1999; Pantev et al.,

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TABLE III. N100m ECD mean latencies and strengths and their standard deviations in relation to the two stimulation intensities, averaged across subjects and frequencies

Stimulation intensity			AEF characteristics (N100m)	
Absolute (dB SPL)	Above threshold (dB SPL)		Latency (ms)	Strength (nA · m)
61	50	Controls	99 ± 8	28 ± 9
31	20	Controls	121 ± 10	17 ± 7
98	50	Patients pre	100 ± 10	33 ± 11
86	20	Patients pre	109 ± 16	30 ± 13
73	50	Patients post	100 ± 9	35 ± 17

TABLE IV. Averages and standard deviations across subjects of the X-coordinates of the N100m ECD for the 4 stimulation frequencies, at 50 and 20 dB HL*

Int HL (dB)	Controls					Patients					Deficit duration (years)	Pre
	250 Hz	500 Hz	1000 Hz	2000 Hz	Length	250 Hz	500 Hz	1000 Hz	2000 Hz	Length		
50	54 ± 4	51 ± 8	48 ± 7	45 ± 7	11 ± 4	52 ± 6	52 ± 4	52 ± 4	51 ± 7	2 ± 4	2 ± 1	
20	53 ± 6	51 ± 7	48 ± 9	45 ± 7	8 ± 4	52 ± 4	52 ± 4	52 ± 4	50 ± 6	2 ± 1	3 ± 2	
	grandaverage = 50					grandaverage = 52						
						250 Hz	500 Hz	1000 Hz	2000 Hz	Length	Δ thr (dB)	Post
						54 ± 5	50 ± 5	49 ± 6	46 ± 9	8 ± 8	32	
						grandaverage = 50						

* All numbers, if not differently indicated, express millimeters. Average tonotopic extensions (length) are indicated. Grandaverages are across subjects and frequencies. The last column of the pre-operative patients indicates the duration of deficit periods before surgery (deficit duration); the last column of follow-up results indicates the postsurgery variations of average (across stimulus frequencies) hearing thresholds (Δ thr).

1990; Romani et al., 1982]. Our results did not show any significant dependence on frequency of y and z coordinates (y : $F = 2.4$; $d = 2.3$, 20; $p = 0.111$; z : $F = 1.5$; $d = 3.27$; $p = 0.234$), in agreement with others [Pantev et al., 1995]. For this reason, the localization dependence on the stimulation frequency has been described only through the x coordinate. Tonotopic extension was on average 9 mm (Table IV), ranging from 16 to 5 mm. ANOVA analysis of variance showed that the location was highly dependent on stimulation frequency ($F = 26.1$; $df = 3,27$; $p < 0.001$; Table IV), whereas no dependence was found with respect to stimulation intensity ($F = 1.0$; $df = 3,27$; $p = 0.382$). In particular, the linear relationship between the N100m ECD depth and the logarithm of the stimulation frequency was confirmed, with only the linear component in the polynomial decomposition significantly ($F = 60.7$; $df = 1,8$; $p < 0.001$) accounting for the total variance. Even if the tonotopic extension was smaller for less intense stimuli, no statistically valid difference was found for this parameter between the two groups stimulated at 20 and 50 dB HL (Fig. 2b). All the measured parameters were fairly stable in the subject studied twice (in particular only 1 mm of tonotopic extension difference).

Patients

As above described ABR assessment confirmed that also in otosclerotic patients a distinct place of resonance of employed stimuli due to cochlear segregation of pure tones was present as in healthy volunteers and it was not influenced by corrective surgery (Table II).

Pre-surgery

AEF morphology. Morphological properties of AEFs in the patients before surgery did not show any significant difference with respect to the normal hearing population (Fig. 1, middle).

Latency and strength. In the four subjects stimulated at 20 dB HL, sound intensities of more than 90 dB in average were utilized. In these cases, AEFs were shorter in latency (not significant $p = 0.15$) and ECDs slightly stronger ($p = 0.016$), compared with normal subjects stimulated at 20 dB HL. The ECD strength was comparable to that recorded in controls during 50 dB stimuli (Table III). As far as the patients stimulated at 50 dB HL were concerned, the AEFs had latency and strength characteristics similar to those of normal subjects stimulated at the same intensity (Table III). ECD strengths did not show significant variation with respect to stimulation frequency.

Localization. As in normal subjects, the findings for pre-operative patients did not show significant differences between the two slopes of tonotopic distributions related to the stimulus intensities at 20 and 50 dB HL ($F = 0.4$; $df = 3,24$; $p = 0.74$). For this reason, data comparing patients and normal hearing subjects have been presented averaging ECDs activated by both intensities (Fig. 3a). On the other hand, pre-operative tonotopic distributions in patients resulted in significantly different slopes with respect to control subjects ($F = 8.4$; $df = 3,54$; $p < 0.001$; Fig. 3a). In fact, tonotopy in patients was almost absent, the mean value of the ECD depth being little affected by the stimulus frequency content (tonotopic extension in Table IV, Fig.

Figure 2.

(a) N100m ECD positions in one control subject, in response to 250 (a), 500 (b), 1000 (c), and 2000 (d) Hz tone bursts, showing the relation between ECD depth and the x-coordinate. Superimposition with MRI confirms dipoles positioning within the depth of the supratemporal Sylvian fissure. (b) Mean values of the N100m ECD x-coordinate in the two groups of normal hearing subjects stimulated at 50 (closed circle) and 20 dB HL (open circle).

3a). When comparative analysis of AEF characteristics to individual frequencies between patients and controls was carried out, significant differences were only observed at 2000 Hz, whose ECD localizations were significantly more superficial in patients ($p = 0.048$).

Postsurgery

Clinical results. In all patients, pure-tone audiogram showed good recovery of auditory function with air-bone gap decreasing to less than 20 dB (Table I); all patients reported good recovery of auditory function in everyday life.

Eight patients recovered from surgery without complaints, one suffered from dizziness for over 60 days following the operation, and the last had a residual permanent tinnitus. MEG recordings were in all cases performed once the postsurgery recovery process had reached a clinically stabilized condition.

AEF morphology, latency, and strength. MEG recordings were in all cases carried out with a stimulus intensity of 50 dB HL. The AEF morphology, latency, and strength characteristics were in all cases comparable to normal subjects (Fig. 1, bottom).

Localization. At postsurgery, the extension of the cortical region responding to the four stimulating tone frequencies was enlarged with respect to the pre-operative measurements in all but two of the patients. Indeed, tonotopic extension was on average 8 mm (Table IV), ranging from 24 to 2 mm. In particular, in two patients the tonotopic extension exceeded that recorded for the control group; one of these was the youngest of the patient group (i.e., a 27-year old). Cortical sources had a tonotopic distribution similar to normal subjects; in fact, the linear dependence of the source depth on the logarithm of the stimulation frequency was statistically significant ($F = 6.2$; $df = 1,7$; $p = 0.04$). The tonotopic extensions were statistically different with respect to those recorded prior surgery (paired t -test = 2.6, $df = 7$, $p = 0.03$). Because of such changes, tonotopic distributions in operated patients were no more significantly different from controls ($F = 1.6$; $df = 3,51$; $p = 0.20$ n.s.; Fig. 3a).

Cortical tonotopic region enlargement (tonotopic length increase) resulted significantly and were directly correlated with the duration of the period separating surgery from MEG recordings ($r_s = 0.92$; $p = 0.01$; Fig. 3b), although the patients' conditions appeared stabilized on clinical examination.

DISCUSSION

In our sample of otosclerotic patients, the normal tonotopic organization was practically lost; in fact, the cortical auditory sources activated by different tone frequencies presented spatial overlap without an evident segregation. Meanwhile, the strength of the frequency-dependent sources did not show any significant variation, neither with respect to the con-

Figure 3.

(a) As in Figure 2b comparing NI00m ECD x-coordinates in normal hearing subjects (closed circle) and patients before (open square) and following surgery (closed square). (b) Tonotopic extension difference between post- and pre-surgery times in relation to the period duration following the operation. (c) An explanatory scheme describing a hypothesis about the cortical area's reorganization in patients prior to surgery with respect to control subjects: the ECD activated by different tones seemed to

be spatially overlapping (black dots, representing the ECD positions, i.e., the baricentres of the activated neuronal pools, show average distance from 9 mm in controls to 2 mm in patients). Rectangles represent neuronal regions activated by different tones and their areas the number of synchronously firing neurons (measured by the ECD strength): areas remain the same for all frequencies in control and patients, provided the same intensity of stimulation above subjective threshold is used.

trol population nor compared with each other. In the ECD source modeling, the ECD strength is related to the number of synchronously firing neurons; in fact, it is possible, by considering the neuron shape and the dendritic diameter and conductance, to evaluate the magnetic field generated by a single neuron as an ECD of about 30 fAm (femto ($= 10^{-15}$) ampere $\times$ meter) strength. Because the magnetic field is proportional to the source strength, once the source position is fixed, it is possible from the intensity of the recorded field to evaluate the order of magnitude of the number of synchronously firing neurons. In our case, the independence of the source strengths on the different frequencies in patients and controls might be explained by a substantial redistribution of the activated areas within the primary auditory cortex in patients affected by otosclerosis and not by a different number of recruited neurons (Fig. 3c). When the cortical specialization—as reflected by the tonotopic

organization—is lost, the auditory cortex is probably becoming a neuronal amalgam which fires to the acoustic input regardless of its frequency content; such a response activates a number of neurons similar to the one elicited in controls when the same stimulation intensity over individual threshold is used.

The reduced tonotopic extension in the supratemporal auditory cortex could be interpreted in the light of similar phenomena observed in the somatosensory system, where the cortical representation of a district that sends a decreased sensory inflow either starts to be invaded by those of the neighboring still active ones, which become overrepresented, or remains deprived with functionally silent synapses [for auditory system; Harrison et al., 1998; Willott et al., 1993]. In this respect, our finding of the high frequency (2000 Hz) generator sources being significantly more shallow than in controls could be ascribed to auditory deprivation, which in otoscle-

rosis starts with hearing loss in the low frequency range. This, with time, might allow higher frequencies to invade the cortical representation of the lower ones, this cortical area being deprived of its physiological inflow. This effect is not so strong as to induce a detectable increase in the ECD strength activated by 2000 Hz stimulation, at least at the intensities used in the present paradigm. On the other hand, no decrease of the ECD intensities for the other frequencies is present.

Possible pitfall in data interpretation might derive from any "peripheral" change of tonotopic organization. One of the most important would be represented by a lack of spatial segregation of different frequency tones along the cochlear basilar membrane. This, in fact, would be directly reflected in a loss of tonotopic representation along the whole auditory system, including the cortical level. However, previous studies and our own recordings showed that cochlear segregation of frequency tones is not affected in otosclerosis [Chisin et al., 1983b; McGee and Clemis, 1982] as reflected by a latency shift of wave V peak between 500 and 2000 Hz evoked ABR [Stapells and Picton, 1981; Stapells et al., 1985]. Moreover, such a tonotopic cochlear organization does not seem to be influenced by corrective surgery procedures.

Latencies and strengths of AEFs following stimulations at 20 dB HL at the pre-surgery stage behave as if the patients had heard sounds stronger than the ones actually delivered; in fact, these characteristics appeared similar to those in normal subjects stimulated at stronger intensities (HL). This might reflect in otosclerotic patients an amplified excitability of the auditory system in response to high absolute intensity stimulations, although these were quite low above the individual threshold. Moreover, it might also be ascribed to increased "amplification" properties at the receiving cortex, a well-known phenomenon through which CNS counterbalances the poverty of environmental input because of "peripheral" deficits [i.e., increased amplification of somatosensory system in peripheral chronic neuropathies; see Noel et al., 1996; Rossini and Cracco, 1987].

The recovery of auditory function following surgical correction of the otosclerotic defect provokes a reorganization of the auditory cortex; the resumption of tonotopic topography extends within the normal boundaries as measured in healthy subjects. Patient age might play an important role with regard to tonotopic reorganization, as suggested by the optimal surgical outcome observed in our youngest patient showing a postsurgery tonotopic extension exceeding the

normative value. This is in line with findings in children [Ponton et al., 1996], where the auditory system maintains its ability to reorganize despite a prolonged period of complete deafness; in fact, following a successful cochlear implant the normal maturational sequence is resumed. The effect of age on plastic reorganization of the auditory system is somewhat controversial, at least in the animal model. It is possible that an alteration occurring in the mature auditory system induces a different cortical reaction with respect to a congenitally acquired deficit; for example, no plastic reorganization appeared in the auditory cortex of cats following unilateral cochlear ablation in the neonatal period [Reale, 1987], whereas plastic phenomena were present in adult guinea pigs with partial unilateral deafness [Robertson and Irvine, 1989]. Our patient population, however, is too small to draw any conclusions on the age-related influence.

The direct correlation between the duration of the postsurgery period and the cortical tonotopic enlargement indicates that natural auditory stimulation can modify the primary cortical organization [Vasama et al., 1998], and that this process takes place in a time scale of several weeks, as has been demonstrated in monkeys [Recanzone et al., 1993].

CONCLUSIONS

The main finding of the present investigation is that the primary auditory cortex of human adults may undergo functional reorganization following stabilized changes of the acoustic input entering the CNS, both when a conductive hearing loss induces a reduced inflow from the periphery and when surgical correction of the middle ear abnormality induces recovery of the sensory afference.

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