Neuroplasticity of auditory cortex after stape surgery for otosclerosis: a magnetoencephalographic study

Neuroplasticità della corteccia uditiva nei pazienti otosclerotici dopo stapedioplastica: studio magnetoencefalografico

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Key Words

Otosclerosis • Surgical therapy • Cerebral plasticity • Magnetoencefalographic responses

Parole chiave

Otosclerosi • Terapia chirurgica • Plasticità cerebrale • Risposte magnetoencefalografiche

Summary

Aim of the present study was to investigate the tonotopic reorganization of the primary auditory cortex in otosclerotic patients following functional stapedioplasty. Characteristics of auditory cortex activation have been evaluated in a series of 10 otosclerotic patients before and after surgery. In these patients, a magnetoencephalographic recording of evoked magnetic fields has been performed by means of tone-burst monoaural stimulation with frequency octaves between 250 and 2000 Hz. Brain topography of cortex response generators (wave N100m) in patients with otosclerosis has been compared with that observed in a control group of 10 healthy subjects: changes before and after surgery have also been correlated with the functional result as far as concerns improvement in hearing. A significant reduction has been observed in the cortical tonotopic extension in response to the acoustic stimulus in patients "pre-surgery" in comparison with controls: after surgery, tonotopic mapping showed an increase, dimensions becoming comparable to those in control subjects. This increase in size was found to be significantly correlated with duration of the post-operative period. Data emerging from the present study suggest that the cortical auditory areas in man are involved in a "plastic" functional reorganization following changes in the receptor or peripheral deprivation. Reduction in the cortical tonotopic mapping resulting from prolonged lowering of auditory "input" is modified by reorganization of the cortex after the recovery of auditory function: this process occurs over a period of a few weeks.

Riassunto

Scopo del presente lavoro è lo studio della riorganizzazione tonotopica della corteccia uditiva primaria nei pazienti otosclerotici dopo chirurgia funzionale di stapedioplastica. Le caratteristiche dell'attivazione della corteccia uditiva sono state valutate in un gruppo di 10 pazienti otosclerotici prima e dopo l'intervento chirurgico. In questi pazienti è stata effettuata una registrazione magnetoencefalografica dei campi uditivi evocati mediante stimolazione monoaurale con tone-burst alle ottave di frequenza tra 250 e 2000 Hz. La topografia cerebrale dei generatori della risposta corticale (onda N100m) nei pazienti otosclerotici è stata confrontata con quella di un gruppo di 10 soggetti sani di controllo: le modificazioni pre- e post-chirurgia sono state inoltre correlate al risultato funzionale in termini di recupero uditivo. È stata riscontrata una significativa diminuzione dell'estensione tonotopica corticale in risposta allo stimolo acustico nei pazienti "pre-operatori" rispetto al gruppo di controllo: dopo l'intervento chirurgico, la rappresentazione tonotopica ha mostrato un ingrandimento, avvicinandosi alle dimensioni dei soggetti di controllo. L'entità dell'ingrandimento ha mostrato una correlazione significativa con la durata del periodo post-operatorio. I nostri dati indicano che le aree uditive corticali nell'uomo vanno incontro a una riorganizzazione funzionale "plastica" in seguito ad alterazioni del recettore o a deprivazione periferica. La riduzione della rappresentazione tonotopica corticale causata da una prolungata diminuzione dell'"input" uditivo viene modificata dalla riorganizzazione corticale dopo il recupero della funzionalità uditiva: tale processo si sviluppa nel periodo di poche settimane.

Introduction

Study of auditory evoked magnetic fields by means of magnetoencephalography (MEG) has been employed by many Authors to characterise the cortical centres following acoustic stimulation [1-4] and, in the field of human diseases, in patients suffering from tinnitus and neurosensorial hypoacusia [3 4]. Over the years, much attention has been focused on this aspect to investigate the brain mechanisms of "neuroplasticity ", by way of which the damaged or destroyed neuronal function may be substituted by other groups of neurones which become able to react to afferent sensorial stimulus, deprived as a result of vascular, degenerative or traumatic, events [5 6].

The auditory apparatus has been investigated in exper-

imental studies employing a monolateral deafferentation (selective cochlear lesion) and conditioned stimulation: in these cases, neuronal "reorganization" has been observed, at different levels of the central acoustic pathway, reaching the auditory cortex [7 9].
Furthermore, human and animal studies demonstrated a cortical interference related to the intracortical [10 11] or transcranic [12] acoustic stimulation.
The models of neuronal "reorganization" differ from each other depending upon the duration of sensorial deprivation: in fact, the cortical tonotopic reorganization found in adult guinea pigs with an experimentally-induced monolateral deafness [13] has not been observed in cats after unilateral cochlear ablation in the neonatal period [14].
In human physiology, "plastic" reorganization of the auditory cortex has been evaluated in children with long-standing deafness [15] and in adults presenting different types of neurosensorial hearing loss [16] or, for example, in musicians, in whom an increase in the auditive representation has been demonstrated at the level of the cortical centres [17]. These studies have focused on neurosensorial hypoacusies, both cochlear (ototoxicity, acoustic trauma, presbiacusis) and retrocochlear (neuronal hypoacusia, auditive sensorial deficits of the cerebral trunk or of the cortex). No studies are available in the literature focusing on cortical acoustic deprivation due to a peripheral transmissive deficit, following an inflammatory-infectious disease or a middle ear dysfunction or stape-ovalar fixation due to otosclerosis.
Aim of the present study was to evaluate the possible plastic reorganization "phenomena" at the level of the primary auditory cortex in patients with transmissive hypoacusia due to otosclerosis, by means of a MEG evaluation before and after stapedioplasty with placement of a piston prosthesis.
In the first degrees [1 2] of otosclerosis, cochlear involvement with a concomitant neurosensorial deficit is not usually present, and, therefore, hypoacusia is mainly due to a deficit in acoustic wave transmission, the cochlear receptor and afferent acoustic pathway being completely intact.
Current otomicrosurgery techniques (platinectomy with interposition, platinotomy, platinotomy with stape tendon conservation) lead to functional improvement with a subtotal or total recovery of the auditive threshold in >95% of the cases submitted to surgery [18-20]. This allows a comparison between the pre- and post-operative conditions, once auditive function and afference have been recovered, in order to evaluate the 'plastic' cortical modifications as far as concerns reversibility and sensorial reorganization.
Effects of long-term transmissive hypoacusia, due to otosclerosis, and the "impact" of corrective functional surgery have been evaluated by evoked magnetic fields.
This newly developed electrophysiological technique can be used to detect activated areas in the primary auditory cortex [2 4] and allows their correlation with the anatomical centres of the brain [3].
MEG has been employed, in several studies, in man to demonstrate the tonotopic organization of the primary auditory cortex [3 21].
In the present study, the tonotopic organization of the auditory cortex has been investigated in patients with otosclerosis, by means of MEG evaluation before and after surgery, focusing on the ear presenting greater hypoacusia.

Patients and methods

The study population comprised 10 patients (5 male, 5 female, mean age 40 years, range 27-53) presenting otosclerosis, with transmissive hearing loss of variable severity: in 4, the more impaired threshold was in the right ear, while, in 6, the left ear was more damaged. Patients were enrolled after informed consent to the procedure was obtained, the study having been approved by the Ethics Committee of the Institute.
Patients had suffered from hypoacusia for a long time, range 1.5 to 5 years (mean ± SD: 2.8±1.3 years).
Data were compared with those obtained from a control group of 10 normoacusic volunteers (6 male, 4 female, mean age 37.5 years, range 29-46): all patients and controls were right-handed.
Patients with otosclerosis and normal controls were submitted to otoscopic examination, tonal audiometry and tympanometry (tympanogram and stapedius reflex threshold) prior to the MEG evaluation.
All subjects in the control group had a threshold ≥ 20 dB at all frequencies tested (125-8000 Hz), tympanograms of type A bilaterally and a threshold of stapedius controlateral reflex ≤ 90 dB.
Patients with otosclerosis showed an air-bone deficit >30 dB at all the frequencies examined, with greater changes in low-medium tones ("rigidity" curve), substantial integrity of the perception level with the exception of the initial deficit of the bone pathway at 2000 Hz ("notch of Cahrart") in 3 cases.
Type A tympanograms were found in all cases, without stapedius reflexes after ipsi- and contra-lateral stimulation and presence of an "on-off" effect.
After examination of the auditive function, all patients and control subjects have been evaluated by MEG, according to procedures described below.
Patients under study have been submitted, under local anaesthesia, to platinotomy, with resection of the stape with conservation of the stapedial muscle tendon and interposition of a piston prosthesis composed of mixed material, platino-teflon, and with a

diameter of 0.5 mm and length which varied according to the particular needs (4.5-5.75 mm).
This technique was preferred since it is more conservative, achieving comparable functional results, especially on account of less cochlear intra-operative trauma, greater comfort during the post-operative course and better post-operative bone threshold at high frequencies [18 20 22]. The pre- and post-operative audiometric threshold is shown in Table I; success of surgery and post-operative functional improvement have been defined from a post-surgery deficit air-bone <20 dB.

Procedures of MEG examination

Patients with otosclerosis have been submitted to MEG examination prior to surgery (mean 7±5 SD days before) and after total post-operative functional recovery (>45 days; mean, 4±2 months).
Auditive stimulation has been performed by pure tones at frequencies of 250, 500, 1000 and 2000 Hz in the ear with more severe hypoacusia, with contralateral masking, and in the right ear in the control group.
Duration of each tone was 300 ms, with 2 cycles of “rise time” and with an interval of 2641 ms between two subsequent stimulations, since no effect of habit was demonstrated with these intervals [23]; intensity of the tone has been settled at 50 dB above the subjective tonal threshold of the patient at each frequency.
Stimulation has been transmitted to the ear using a small rubber tube connected to the stimulator located at a distance of about 2 metres, and then the auditive thresholds have been measured.
In 4 cases (more severe hypoacusia), intensity of the stimulus has been limited to 20 dB above the threshold since the MEG instrument we used produces a maximum stimulation intensity of 105 dB. In the control group, the possible dependence of the tonotopic cortical organization upon the intensity of the stimulation has been evaluated in 5 control subjects by sending tone bursts at 20 dB and 50 dB above the threshold.
In one control subject, “test-retest” variability of the parameters evaluated has been controlled by repeating the examination procedure in two following times.
The MEG examination has been performed using an instrument with 28 channels [24], characterised by 16 first-order axial gradiometres (diameter: 1.8 cm, base: 8 cm) and 9 magnetometres (spool area: 81 mm^2) plus 3 balancing magnetometres to cancel the noise associated with dc-SQUIDs instruments, with an overall sensitivity of approximately 5-7 fT/Hz.
The 25 measurement sites have been uniformly distributed on a round surface about 180 cm^2 in size, with an interchannel distance of approximately 2.5 cm; all measurements have been performed in a magnetically protected room (Vacuumschmelze GmbH, Hanau, Germany).
The sensor used for recording the auditive evoked magnetic fields (AMEF) was placed always in the same position, centred upon the contra-lateral temporal lobe with respect to the stimulated ear, 1 cm above the positions T3-T4 of the 10-20 International EEG System.
The exact position of the sensor on the head of the subject examined has been defined by using 5 spools applied on the routine anatomical reference points (2 preauricular points, nasion, vertex and inion); the corresponding 3D positions have been digitalised at the beginning of the examination session (Polhemus Isotrack, Colchester, Vermont, USA). Mean duration of the recording procedure was 1 hour in each patient.

Analysis of data

Approximately 100 responses have been recorded (band width: 0.48-250 Hz; frequency of sample: 1 Khz) and MEDIATE for each stimulation frequency. The width of the AMEF has been calculated for each recording channel with a mean reference value of between 50 ms before and 20 ms after the beginning of the stimulation.
Characteristic deflection has been analysed at about 100 ms (N100m) of the AMEF after stimulation with pure tones: this component is usually stable and repeatable, and it is considered as the more reliable index of the arrival of the acustic stimulus to the primary auditory cortex [1 2]. The cortical generator of the

Table I. Auditive threshold* via air and bone (dB SPL) at the 4 frequencies used for MEG, before and after surgery. Before surgery, audiometric threshold corresponds to masked stimulation, i.e., transmitting a noise with low band to contra-lateral ear at 40 dB above SPL.

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

* Mean ± standard deviation; SPL: sound pressure level.

N100m component has been localised by using the Equivalent Dipolar Device (ECD) in a sphere with homogeneous conducibility [1 7 25].

Distribution of the magnetic field in the interval, with the start at 10 ms before, up until 10 ms after, the peak of N100m has been used to establish the position and the width of the dipole: results of localization have been considered reliable only in the presence of a variance >90%.

Equivalent dipole position (ECD) has been expressed by a cartesian coordinates system defined as follows: the axis of the abscissa passed through the two preauricular right and left points, with a right exit, the axis of the ordinates through the nasion, and z axis was perpendicular in the intersection point between the x and y axes.

In order to evaluate whether the characteristics of the activated cortical areas were significantly different between normal control subjects and the patients under investigation, two analyses of variance have been performed using ANOVA test for repeated measurements in the variable position (coordinate x): the frequency of stimulus has been considered as an intra-individual factor (4 levels: 250, 500, 1000 and 2000 Hz) and the investigated "group" as an inter-individual factor (patient group-control group).

Following surgery, the possibility of modifications in tonotopic cortical organization has also been evaluated: furthermore, the relationship between MEG findings and clinical history of the patient has been evaluated using the Spearman correlation coefficient (RS). For the analysis of these data, a value of $p<0.05$ was considered statistically significant.

Results

Control group

In normoacusic control subjects, morphology of the auditive magnetic fields was characterised by a prevalence in the response at 100 ms after the start of stimulation (N100m). Latency of N100m showed an increase of about 20 ms when the intensity of the acustic stimulus was reduced from 50 to 20 dB above the threshold; viceversa, the width of the above-mentioned wave was not significantly influenced by a modification in the intensity of the stimulus. Longer latencies have been found during stimulation at low frequencies than at high frequencies (250 Hz vs 2000 Hz) (Fig. 1).

Localization of N100m wave generators, as far as concerns the 4 frequencies under consideration, showed a well-known distribution [3 21]: indeed, a linear relationship has been demonstrated between the depth of the N100m dipole and logarithm of the stimulation frequency, only the linear component being statistically significant in terms of polynomial disgregation of the total variance.

Linear correlation has been shown to be comparable, in the 2 groups, stimulated at 20 and 50 dB above the threshold (Fig. 2); values obtained were certainly stable, in the same subjects, stimulated on two occasions.

Patients: pre-operative data

Morphology of AMEF in patients evaluated before surgery did not reveal any difference in comparison to the normal control group.

In the 4 cases stimulated at 20 dB above threshold, lower latency of AMEF ($p=0.15$, NS) and a greater width of ECD ($p=0.016$) were found than in healthy control subjects stimulated at 20 dB. Width of ECD was, in fact, comparable to that in controls at 50 dB above the threshold (Table I).

As far as concerns patients stimulated with an intensity of 50 dB above the threshold, latency and width of AMEF showed features similar to those in the normal control group stimulated with the same intensity (Table II).

With regard to localization of the N100m generators, preoperative data did not reveal any significant differences between the 2 tonotopic distribution, as far as concerns intensity of stimulation at 20 and 50 dB above the threshold.

Tonotopic distribution of the patients in the preoperative phase was significantly different vs the control group; indeed, this organisation was found to be much narrower, indicating lack of dependency of the position of the generator with respect to the function of the tone frequency (Fig. 3a, Table III).

Moreover, in these patients, the source activated by stimulation at 2000 Hz was more superficial than in controls, with the Wilcoxon test being statistically significant ($p=0.012$).

Patients: post-operative data

In all patients, control of the tonal audiometry showed excellent recovery of the auditive function with a via aerea-via ossea difference <20 dB at frequencies of 250-2000 Hz; 8 patients had a very good post-operative course, one patient complained of dizziness for ~60 days after surgery, 1 patient complained of permanent residual tinnitus.

Recording of AMEF was possible in the post-operative period, thanks to recovery of the auditive threshold, in all cases employing a stimulation at 50 dB above threshold.

Morphology, latency and width of the AMEF were comparable to findings in normoacusic control subjects.

As far as concerns localisation of activated sources, post-operative data showed that the cortical region corresponding to the 4 frequencies of stimulation

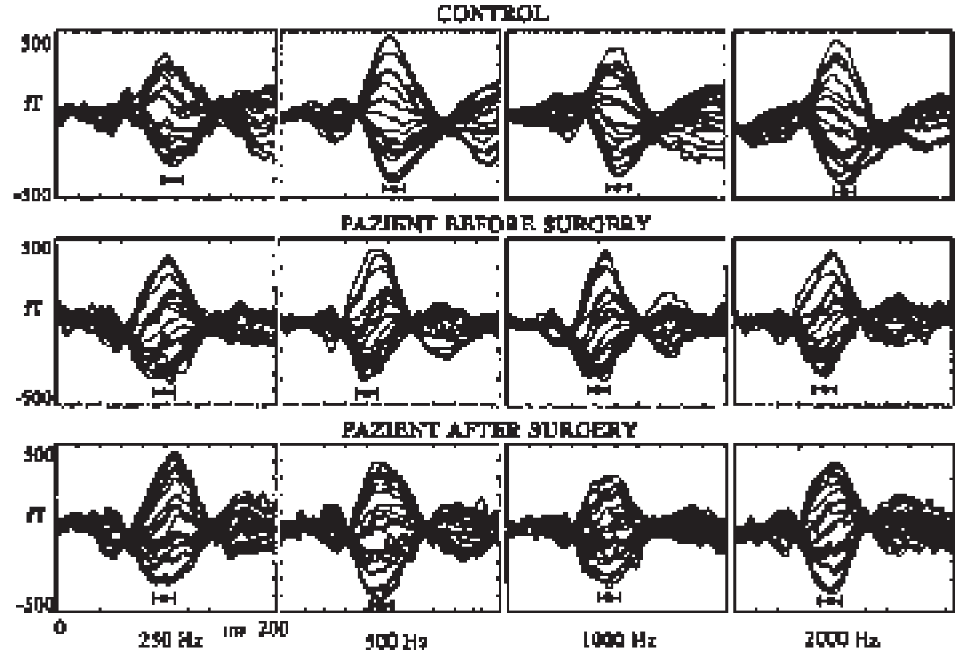

Fig. 1. Example of AMEFs in control subject (upper) and a patient before (middle) and after (lower) surgery: overlapping of recorded fields from each canal/channel in the 200 ms interval starting from onset of tone, in response to stimulation of the 4 frequencies (250, 500, 1000 and 2000 Hz) at 50 dB HL intensity.

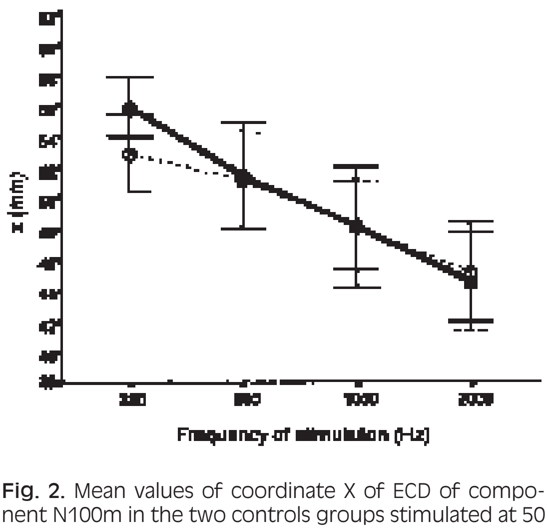

Fig. 2. Mean values of coordinate X of ECD of component N100m in the two controls groups stimulated at 50 [filled circle] and at 20 dB HL [empty circle].

was much wider than pre-operative data in 9 out of 10 patients.
In 2 of these 9 patients, the difference was quite considerable; one presented the greatest modification in threshold compared to pre-operative findings and the shorter period of auditive deprivation; this was the youngest patient in the group (27 years).

Comparing the tonotopic distribution of operated patients with that of the control group, no statistically significant difference was observed.

The reorganization and broadening of the cortical tonotopic representation (increase in length) was found to be inversely proportional to the duration of the period of pre-operative hypoacusia ($r_s=-0.752$, $p=0.03$).

Discussion

Data emerging from the present study indicate that the auditory cortex, in adult man, may undergo structural and functional modifications following peripheral alterations in the acustic sensorial input.

Indeed, a long-lasting reduction in peripheral input may lead to a reduction in the tonotopic representation of the contra-lateral cortex.

Decrease in activation of primary auditory cortex induced by otosclerosis may be interpreted in the light of a reduced stimulation which induces a spatial reduction in the activation of the neuronal "pool" within the auditory cortex.

In an earlier study, Vasama et al. [16] showed that in

Table II. Latencies and mean intensity of ECD of M100 (1 SD) related to the two stimulation intensities, mediated on all subjects and frequencies.

Intensity of stimulation			Characteristics of AMEF (M100)	
Absolute (dB SPL)	Above threshold (dB SPL)		Latency (ms)	Intensity (nA 2m)
61	50	Controls	99 1 8	28 1 9
31	20	Controls	121 1 10	17 1 7
98	50	Patients PRE	100 1 10	33 1 11
86	20	Patients PRE	109 1 16	30 1 13
73	50	Patients POST	100 1 9	35 1 17

AMEF: auditory evoked magnetic fields: SPL: sound pressure level.

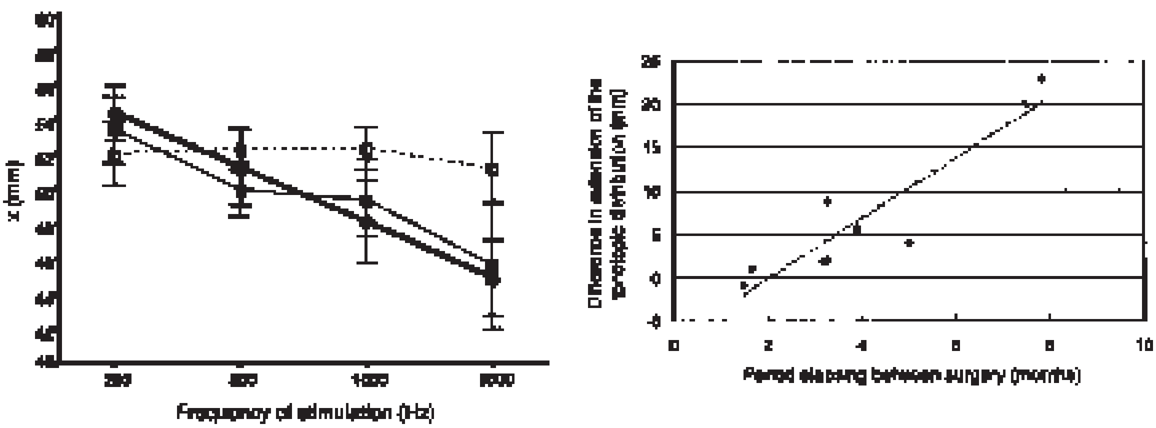

Fig. 3. a) As in Figure 2, comparison of coordinate X of ECD of component N100m in control subjects [full circle] and in patients before (empty square) and after surgery [filled square]. b) Difference in extension of the tonotopic distribution before and after surgery in relationship to duration of period elapsing between surgery and MEG examination.

congenital hypoacusias of the monolateral transmissive type, no reorganization of the cortex occurred following stimulation of the contra-lateral hearing.
However, it may be hypothesised that the hearing disorder occurring within a mature auditory system, in adult age, induces a different cortical reaction with respect to a congenital deficit: for example, no plastic reorganization was observed in the primary auditory cortex, in cat, following mono-lateral cochlear ablation in the neonatal period [14], whereas the phenomena of plasticity are present in adult guinea pig with mono-lateral hypoacusia [13].
It is interesting to observe that comparative statistical analyses show that the cortical sources activated by the highest frequencies are localized in more superficial areas in patients in the pre-operative phase compared to those in the control group.
These data should be interpreted in relationship to intrinsic characteristics of the otosclerotic disease, which causes a greater involvement of the threshold at the medium and low frequencies: thus, the cortical auditory region which represents low frequencies is less stimulated and the region corresponding to the high frequencies tends to invade the zones responsible for the recognition of the low tones.
The latency and width of AMEF following stimulation at 20 dB above the threshold in these patients, prior to surgery, presented similar characteristics to those found in controls at greater intensity.
In agreement with Pantev et al. [17], these data could be interpreted as if the responses of the patients, in the preoperative phase, were related to a more intense stimulation than that in effect used: for example, with the stimulation at 20 dB, the auditive/auditory field corresponded to an activation of 40 dB.
Recovery of auditive/auditory function following

Table III. Means and standard deviations in subjects of coordinate X of ECD of the N100m component for the 4 stimulation frequencies, at 50 and 20 dB HL.

int HL (dB)	Controls 250 Hz	Controls 500 Hz	Controls 1000 Hz	Controls 2000 Hz	Controls Extent	Patients PRE 250 Hz	Patients PRE 500 Hz	Patients PRE 1000 Hz	Patients PRE 2000 Hz	Patients PRE Extent	Duration of deficit (years)	Patients POST 250 Hz	Patients POST 500 Hz	Patients POST 1000 Hz	Patients POST 2000 Hz	Patients POST Extent
50	54±4	51±8	48±7	45±7	11±4	52±6	52±4	52±4	51±7	2±4	2±1	54±5	50±5	49±6	46±9	8±8
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						"grandaverage" 50				

All values, unless otherwise indicated are in mm. Tonotopic extensions are also shown (difference between values of coordinate X at 250 Hz and 2000 Hz, in mm.). "Grandaverage" is mean of position in all subjects and all frequencies. Last column of PRE-operative patients indicates duration of period of deficit before surgery (deficit duration).

stapedioplasty led, in our patients, to a "plastic" reorganisation of auditory cortex, displaying characteristics not unlike those in subjects with normal hearing. Age of the patient could play a determinant role as far as concerns the ability of a "plastic" reaction of the cortical areas, as would emerge from data obtained in the youngest patient in the group under examination, who showed an excellent cortical "reorganization" following surgery.

Further studies, on a larger series of patients, are needed to confirm this finding, however, these data are in agreement with those observed in children [15], in whom the auditory system maintains the "plasticity" characteristics even during a period of complete deafness, allowing maturation of the auditory cortex following stimulation induced by the effecting of cochlear implant.

In our group, we observed a significant relationship between duration of post-operative period and reorganization of auditory cortex (rs=0.92, p=0.01) (Fig. 3b): this finding demonstrates that the continuous exchanges between peripheral receptor and the central auditive areas contribute to the maintenance of the physiological tonotopic organization of the primary auditory cortex, and that the modifications of the sensorial afflux have a long-term effect upon the times, even weeks or months.

Conclusions

Studies on the AMEF in patients presenting monolateral hearing loss due to otosclerosis show that peripheral sensorial acustic deprivation induces significant modifications in the central areas responsible for the tonotopic representation of the input originating in the peripheral areas.

These areas, nevertheless, maintain their intrinsic ability of "plastic" transformation and regeneration, as shown by data obtained in our studies by means of AMEF recording after cofosurgery.

The functional recovery, in fact, led to a plastic reorganization of auditory cortex with morpho-functional and tonotopic characteristics identical to those in normal subjects.

AMEF studies, already used in patients affected by sensorineural hearing loss and tinnitus, as well as in children with congenital deafness, have been shown to be valid in ascertaining whether cerebral "plasticity" mechanisms are present related to the auditory cortex even in cases of acustic deprivation due not only to a neurosensorial deficit, but to a transmission deficit related to a disease of the stapedio-ovalar system.

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