Cerebral Cortex January 2006;16:31-36
doi:10.1093/cercor/bhi081
Advance Access publication April 20, 2005

Dynamics of Auditory Plasticity after Cochlear Implantation: A Longitudinal Study

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Human representational cortex may fundamentally alter its organization and (re)gain the capacity for auditory processing even when it is deprived of its input for more than two decades. Stimulus-evoked brain activity was recorded in post-lingual deaf patients after implantation of a cochlear prosthesis, which partly restored their hearing. During a 2 year follow-up study this activity revealed almost normal component configuration and was localized in the auditory cortex, demonstrating adequacy of the cochlear implant stimulation. Evoked brain activity increased over several months after the cochlear implant was turned on. This is taken as a measure of the temporal dynamics of plasticity of the human auditory system after implantation of cochlear prosthesis.

Keywords: auditory cortex, auditory plasticity dynamics, cochlear implant, magnetoencephalography

Introduction

Hearing can be restored in deaf people through a cochlear implant (CI), an electronic device which transforms the acoustic signal into electric pulses stimulating the intact fibers of the auditory nerve (Clopton and Spelman, 2003; Francis and Niparko, 2003; Laszig *et al.*, 2004; Zeng, 2004). Auditory perception, however, would not be possible without substantial capabilities of self-organization and plasticity of the cerebral cortex. Intense research during the last two decades has revealed that functional organization even in the mature cortex is not statically fixed, but is adjusted in response to alteration of behaviorally relevant input (Elbert *et al.*, 1995; Buonomano and Merzenich, 1998; Pantev *et al.*, 1998; Weinberger and Bakin, 1998; Elbert and Flor, 1999; Rauschecker, 1999). After cochlear implantation, post-lingual deaf people, who lost hearing after language acquisition, may recover their hearing ability even to the extent that they can communicate over the telephone. In these subjects primary and non-primary regions of the auditory cortex, as well as association areas related to language processing, are recruited in an experience-dependent manner during the use of the CI. This provides an instructive model for understanding brain plasticity underlying the process of regaining auditory function after prolonged deprivation. On a macroscopic level, mechanisms of brain plasticity can be estimated by psycho-acoustic tests and more objectively by neuroimaging recordings. Although plasticity of the human auditory cortex has been demonstrated (Ponton *et al.*, 1996; Pantev *et al.*, 1998; Rauschecker, 1999; Giraud *et al.*, 2001), only few reports exist about its long-term dynamics (Vasama *et al.*, 1995; Bilecen *et al.*, 2000). Magnetoencephalography (MEG) is a neuroimaging method well suited for investigation of these dynamics because: (i) it is completely non-invasive; (ii) it does not generate any acoustical noise; (iii) its high reproducibility allows follow up measurement of brain activity over years; and (iv) the high temporal resolution allows distinction between the components of evoked activity.

MEG recording was not possible with most CI devices containing a strong permanent magnet, which fixes the transmitter coil. However, this problem appeared to be less difficult with a new generation of magnet-free prosthesis and a radio frequency (RF) shield, which prevents interference from RF signals transmitted by the external speech processor to the implanted device. A unique laboratory set-up was developed in our institute and was used to measure brain responses in two CI patients in a longitudinal study design over the period of 2 years. We investigated the temporal dynamics of plasticity in the human auditory system and compared electro-physiological data with results of corresponding behavioral tests.

Material and Methods

Subjects

Two cochlear implant patients, Patient 1 (43 years old) and Patient 2 (52 years old) were repeatedly investigated over the period of 2 years. Patient 1 had suffered from idiopathic progressive hearing loss for 27 years and complete hearing loss for 5 years prior to the cochlear implantation. This patient had no speech perception ability up to 120 dBHL, and light non-disturbing tinnitus of high-frequency pitch on both sides. Before cochlear implantation he communicated only via lip-reading. Patient 2 had repetitive acute hearing loss with unknown etiology for 15 years prior to cochlear implantation. He achieved 10% at 120 dBHL in the Freiburger Monosyllabic Word Test, used lip-reading partially supported by hearing aids and had high-frequency pitched tinnitus bilaterally. Patient 1 obtained a magnet-free 'Clarion 1.2' cochlear stimulator (Advanced Bionics Corp., Sylmar, CA), inserted into the left ear and Patient 2 a magnet-free 'Clarion CII' bionic ear (Advanced Bionics Corp.,) inserted into the right ear (Weber *et al.*, 1999).

A control group of 10 right-handed subjects (three female), aged 22–35 years (mean 25 years) participated the study. Control subjects had normal audiological status (air conduction thresholds no more than 10 dB hearing level at octave spaced test frequencies in the range of 250 Hz to 8 kHz). None of them had a history of otological or neurological disorders. The Ethics Commission of the Medical Faculty, University of Münster approved the study. Informed written consent was obtained from all subjects.

Stimulation

The stimulus used in this study was a continuously presented tone containing a sudden shift in carrier frequency from 950 to 1050 Hz and followed by reversed shift 500 ms later. Frequency shifts were repeated every 2 s. A schematic of the stimulus time trace is shown in Figure 1*C*. This frequency-shift stimulus was used for two reasons. The first reason was of a technical nature: a continuous sound contained no change in signal power over time and hence it produced much smaller artifacts. Particularly, the artifact in case of the frequency-shift stimulus was about 10 times smaller than the one caused by usual tone-burst stimulus.

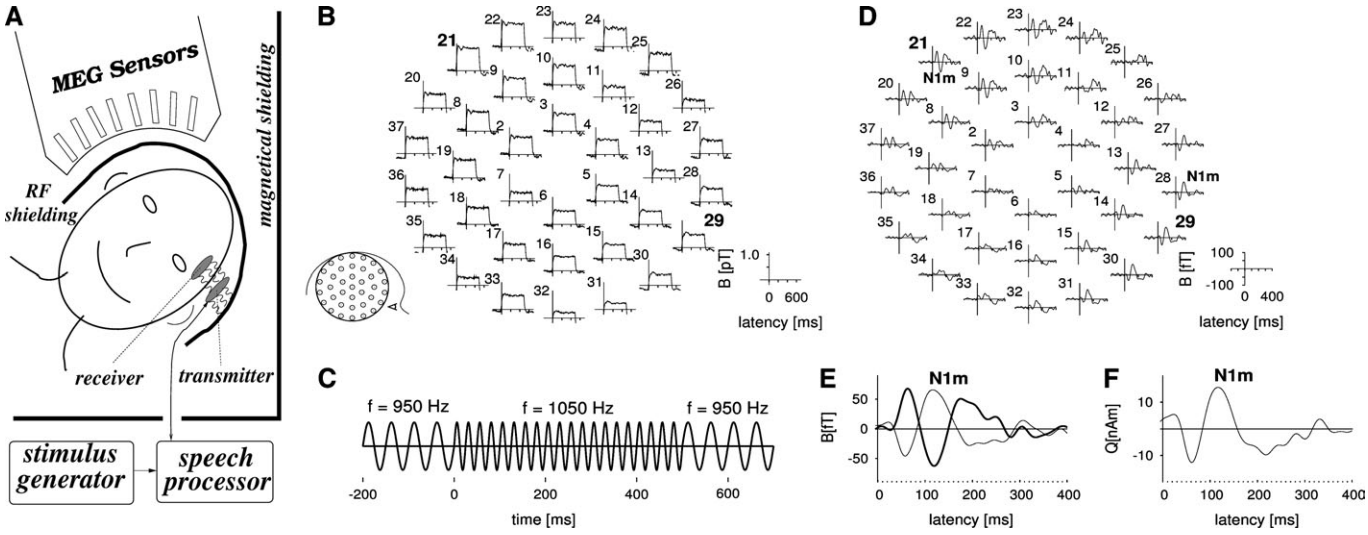

Figure 1. (*A*) Experimental setup: the stimulus generator and speech processor are located outside the magnetically shielded room. (*B*) Averaged waveforms of the recorded 37 channel magnetic field data. The evoked cortical activity is superimposed onto the residual interfering artifact, generated by the cochlear implant stimulus. (*C*) Schematic time course of the frequency-shift stimulus with duration of 500 ms, changing the frequency from 950 to 1050 Hz repeatedly every 2 s. (The schematically shown frequency of the stimulus is not in scale.) (*D*) Averaged waveforms of 37 channel magnetic field data after rejecting the stimulus artifact and low pass filtering at 24 Hz. (*E*) Averaged waveforms of two MEG channels of opposite polarity at the minimum and the maximum of the N1m component of the evoked field. (*F*) Cortical source strength of the evoked response after source space projection.

The second reason was of a physiological nature: the frequency shift is a very relevant stimulus since frequency transients are important elements in speech.

The stimulus was passed through an isolation transformer to the auxiliary input of the CI speech processor. The CI microphone was switched off to prevent artifacts caused by the environmental noise. To avoid further noise interference, all but three electrode channels that covered frequencies around the stimulus frequency were set to zero current levels. The stimulus level was adjusted for clear sensation below the level of discomfort. With respect to the dynamic compression of the speech processor, this setup corresponded to the sound level of ~60 dB above sensation threshold. This level was correspondingly used for measurements in the control group, in which the stimuli described above were presented acoustically through a magnetically silent delivery system. The system consists of speakers (one-inch compression driver, Renkus-Heinz Inc.) mounted outside the magnetically shielded room. They were connected to a silicon earpiece through 6.3 m of echo-less plastic tubing (16 mm inner diameter). The transfer characteristic of this system deviated less than ±10 dB in amplitude between 200 and 6000 Hz. Because the stimulus was defined in a narrow frequency band, the stimuli were not distorted by the frequency characteristic of the sound delivery system. A transmission delay of ~19 ms was compensated by an appropriate shift of the trigger signal. Before carrying out the experimental measurements, both the signal spectrum of the stimulus and its correct timing were checked by means of a 2 cm^3 ear simulator (Brüel & Kjær model 4157) that was equipped with a ½″ condenser microphone (Brüel & Kjær model 4134) and connected to the silicon earpiece at the end of the sound delivery system. The stimuli were presented monaurally to the subject's right ear at stimulus intensity of 60 dB SL (referred to the individual sensation threshold). For this purpose, the subject's hearing threshold was measured prior to each experimental session.

MEG Recording

Stable auditory evoked fields (AEF) were recorded from the CI patients in 10 consecutive MEG measurements over a period of 2 years. The first session took place 1 week after initial setup of the speech processor of the cochlear implant system. During the first 6 months five measurements at consistent intervals were carried out. Two sessions were performed in the following 6 months and three sessions during the second year.

MEG recordings were carried out in a magnetically shielded room (Fig. 1*A*) with a 37-channel array of first order gradiometers MEG (MAGNES, 4D-Neuroimage Inc., San Diego, CA), placed over the temporal aspect of the head contralateral to the implant (or the side of stimulation in the control group). This was done because auditory evoked responses are generally larger in the contralateral than in ipsilateral hemisphere and magnetic stimulus artifacts from the cochlear implant are smaller. The distance between sensor and patient's respectively subject's head was adjusted to be as small as possible. To determine the spatial positions of the sensor relative to the head, and to recognize movements occurring during the recordings a head position indicator system was used. In this study no data had to be discarded because of excessive head movements. We instructed the patients and subjects to stay alert and relaxed. Their compliance was verified using a video-monitoring system. During MEG recordings, patients and subjects watched a silent cartoon movie.

CI patients wore a textile cap encasing their head. The cap fabric was woven from silver-coated thread and contained a metallic non-magnetic net in front of the eyes and nose. This conductive cap was connected to the signal ground of the shielded room, and thus it created a local Faraday's cage around the patient's head. The cap shielded the MEG sensor from RF interferences in the range of several MHz that were generated by the CI-processor. Test measurements with current dipoles in a head phantom assured that the shielding cap introduced no damping at frequencies between DC and 100 Hz. Thus, the recorded signals in the frequency band containing the AEFs were not attenuated.

A typical field distribution of the residual interfering artifact is shown in Figure 1*B*. The residual noise in the pre-stimulus interval did not show a systematic bias. The magnetic field waveforms (Fig. 1*B*) demonstrate no baseline activity in the maximally responding channels. Figure 1 represents the average of 3 × 128 event-related epochs. The actual size of the artifact depended on the position of the implant relative to the MEG sensor and varied slightly between sessions. Because the artifact and the response signal have common spectral components, separating the artifact from the response signal using a filtering procedure was not an appropriate strategy. Even after applying the shielding cap, the artifact was about 10 times larger than the evoked response. However, the artifact waveform was consistent between channels. This fact allowed modeling in time domain. A modeled artifact waveform was calculated as largest component in a principal component analysis of the magnetic field distribution and was subtracted from the MEG signal as demonstrated in Figure 1*D*.

The dipolarity of the artifact-corrected signal is best represented by the overlaid channels with maximal evoked activity of opposite polarity

(Fig. 1*E*). Figure 1*F* shows the calculated equivalent cortical strength, which was used to perform further analysis of the data.

MEG Analysis

The MEG data were band-pass filtered from 0.1 to 100 Hz prior to sampling at the rate of 297.6 s^{-1} and digitization with 16-bit resolution. Two hundred and fifty-six stimulus-related epochs of 1 s duration, including a 300 ms pre-stimulus interval, were recorded in each experimental session. Subsequent data analysis included eye blink artifact elimination (exceeding 3 pT peak-to-peak on an individual channel) and 24 Hz low-pass filtering. Source analysis based on the model of a single moving equivalent current dipole (ECD) in a spherical volume conductor was applied to the measured field distribution. This resulted in estimates of the location and strength of auditory cortical activity. The dipole location and orientation were determined in a head based Cartesian coordinate system with the origin set to the midpoint of the medial–lateral axis (*y*-axis) between the entrances of the left and right ear canals. The posterior–anterior axis (*x*-axis) ran between the nasion and the origin, and the inferior–superior axis (*z*-axis) through the origin perpendicularly to the *x*–*y* plane. Source estimations were performed around the maximum of the magnetic field in the interval between 40 and 85 ms (P1m), as well as 70 and 140 ms (N1m) after stimulus onset. These estimates were accepted for further evaluation only if both the goodness of fit of the field of the estimated ECD to the measured magnetic field was >95%, and the distance of the ECD to the mid-sagittal plane was >3 cm. Based on the median of the source coordinates and orientations across the different measurements the method of source space projection (SSP) was applied (Ross et al., 2000). SSP combines the magnetic field waveforms obtained from each sensor weighted by the sensitivity of each sensor for a source at the specified location into a single waveform of magnetic dipole moment. The method is spatially sensitive because it maximizes the response from the region of interest. Contributions from other regions and uncorrelated system noise are reduced or respectively canceled out. The polarity of the dipole moment waveform was defined such that the N1m deflection around 100 ms, which is the magnetic counterpart of the slow cortical evoked N1 potential (Näätänen and Picton, 1987), had a negative polarity. P1m and N1m peak amplitudes were determined for each CI patient and control subject.

Results

Two years after initial switch-on of the cochlear implant both patients reached the ability for open communication. Patient 1 has good hearing skills, with better speech perception performance than the averaged cochlear implant users; he is even able to use telephone communication. Patient 2 achieved average hearing skills. In both patients, tinnitus was strongly reduced and partially disappeared after implantation.

Estimated N1m source coordinates from all MEG measurements in both patients are shown in Figure 2 in three orthogonal projections: Patient 1 on the left and Patient 2 on the right. The square symbols represent the mean source locations obtained from the individual sessions. The ellipses denote the 95% confidence limits of the mean across all repeated sessions shown by the star symbol. The small gray dots represent the patients' head shape, and the anatomical fiducial points, nasion and left and right ear canal, are shown as filled circles for comparison. The same illustration was performed for the P1m component in both patients and the corresponding results are shown in Figure 3. The comparison of Figures 2 and 3 reveals a trend for more medial location (by ~4 mm) for the P1m source as compared with the location of the N1m source.

By means of the source space projection method, the dipole moment, which is proportional to the number of synchronously activated cortical neurons (cortical source strength), was calculated for the control group and for the two CI patients. The source waveform averaged across the subjects in the control group is displayed in Figure 4 (bottom, thick line),

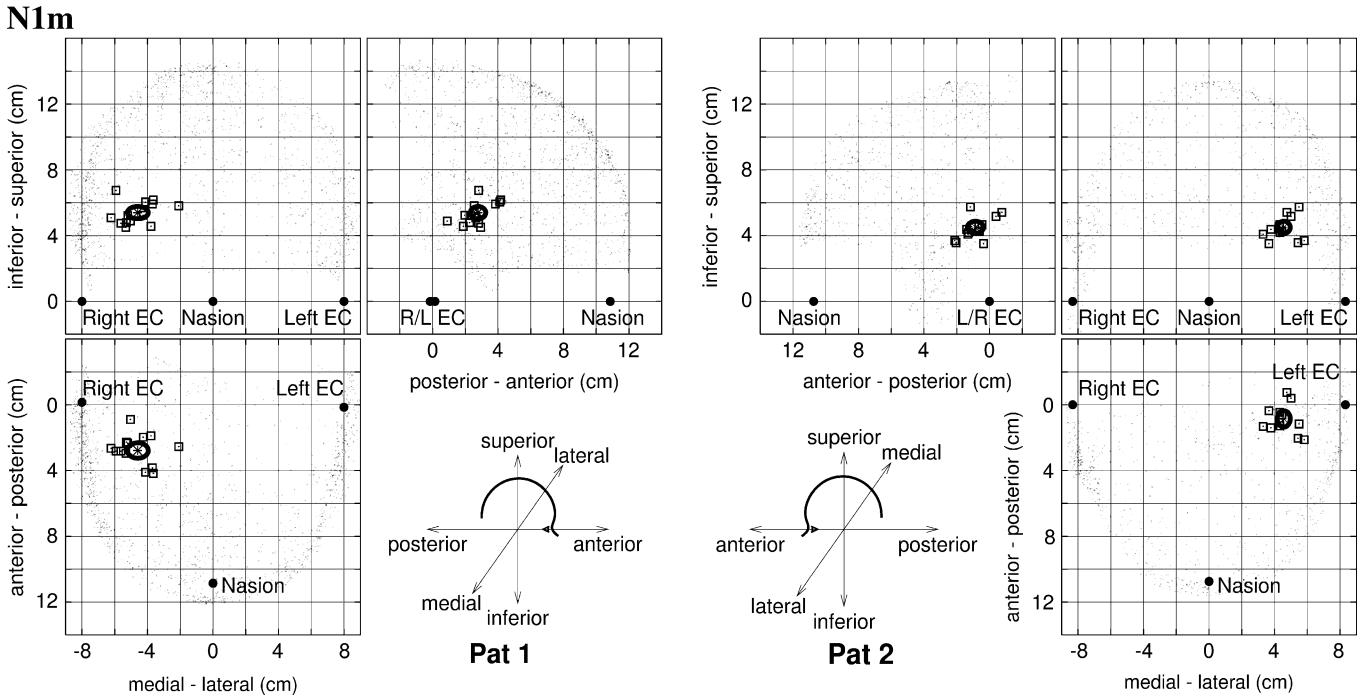

Figure 2. Estimated source coordinates of the N1m components for each single MEG measurement of Patient 1 (left) and Patient 2 (right) given in three orthogonal views. The squares represent the source locations obtained in subgroups of data in the individual sessions (test–retest). The ellipses denote the 95% confidence limits for the mean across all sessions (star giving the center of the ellipses). The nasion and the left and right ear canal are shown as filled circles as reference. The gray dots represent the patients' head shape scanned by the sensor position indicator.

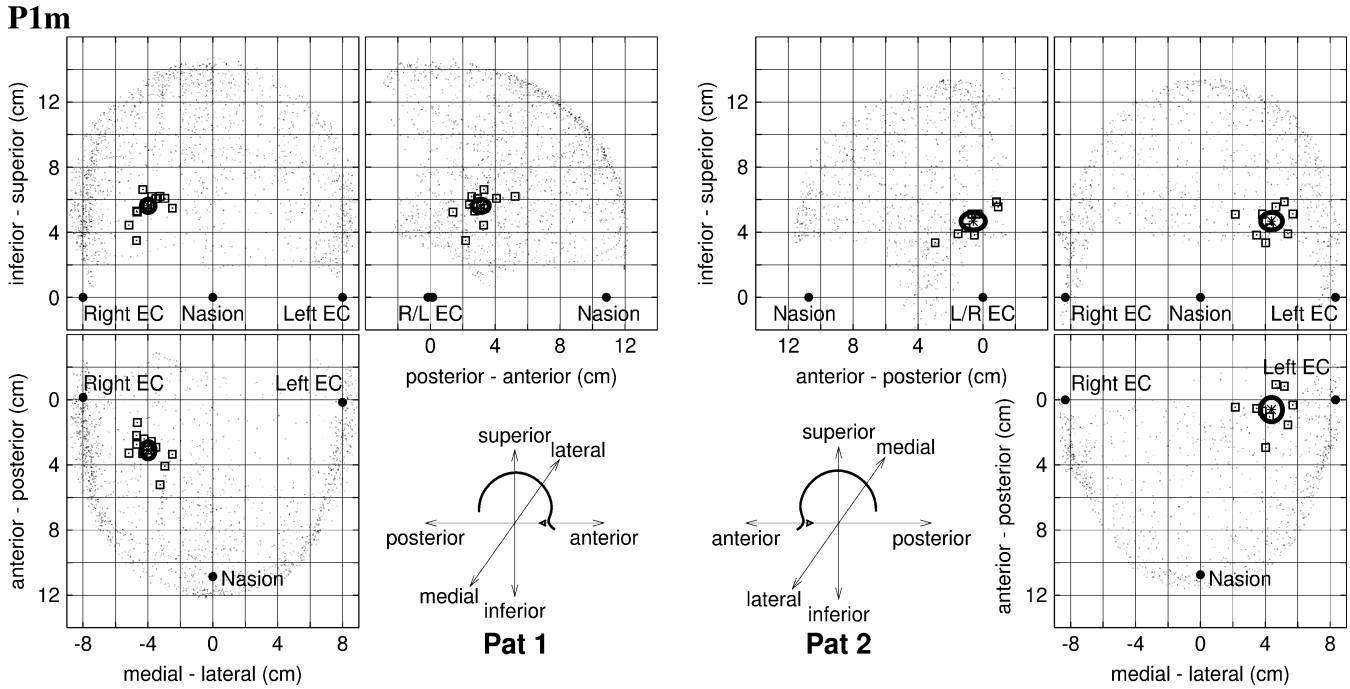

Figure 3. The same as Figure 2, but for P1m.

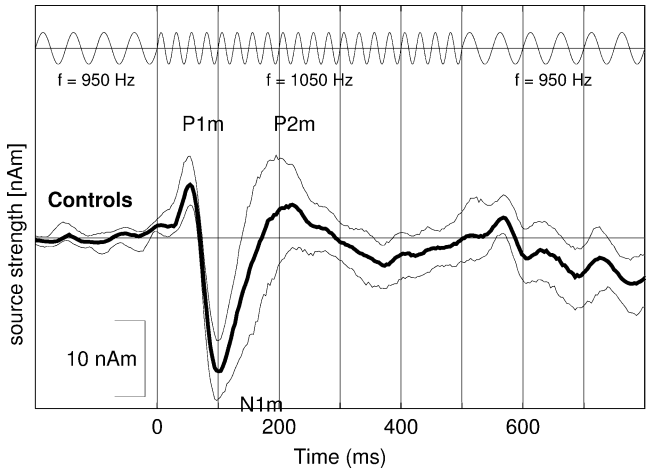

Figure 4. (Top) Time trace of the stimulus described in Figure 1. (Bottom) Time series of the source waveform averaged across the control group (thick line). The thin lines display the 95% confidence interval bounds for the mean value.

with thin lines displaying the 95% confidence interval bounds. Averaged source locations, orientations, amplitudes and latencies for the control subject group are summarized in Table 1. Corresponding source results from the last four measurements of the CI patients are also given in this table. Evoked response morphologies were similar between CI patients and control subjects, except for a small latency increase for both P1m and N1m components in the CI patients.

Speech intelligibility in the CI patients was measured by means of Freiburger Monosyllabic Word Test and the results are displayed in Figure 5*A*. The averaged fraction of correctly perceived words increased from ~10% to ~50% during the first 5–6 months after initial processor setup and stabilized at ~40% thereafter. The perception skills of the CI patients fluctuated slightly between the tests. In the last three measurements Patient 1 achieved 56.25, 40 and 47.5%, whereas Patient 2 achieved 37.5, 28.75 and 41.25%. However, the peaks displayed in Figure 5*A* are local extremes, which do not point out to a relevant change in perception skills.

The most important result of this study is displayed in Figure 5*B*. The P1m and N1m cortical source strength waveforms obtained from the CI patients are sketched accordingly to the repeated measures taken during the 2 years of study. The P1m peak amplitudes of the response waveforms are displayed as crosses. Filled circles denote the peak amplitudes of the N1m component. The solid (P1m) and dashed (N1m) lines are smoothed approximations to the time course of the peak amplitudes and characterize the dynamics of the dramatic increase of cortical source activity during the CI use. The responses of the auditory cortex were not pronounced during the first 2–3 months after initialization of the CI. They were not clearly identified and therefore they are not displayed in the figure. Subsequently the N1m component developed within a variable time of 6 weeks (Patient2) to 6 months (Patient1) achieving a normal size as compared to the control subject group. The P1m component showed a similar but somewhat longer period of development.

Discussion

In this MEG study on two CI patients who were progressively deprived of peripheral auditory input for 27 and 15 years before implantation, we demonstrated the temporal dynamics of plastic changes of auditory cortical structures that are probably triggered by plastic changes in subcortical structures. These methodologically challenging investigations were carried out over a 2 year period after CI implantation. The repeated post-implantation MEG measurements illustrated the development of

Table 1
Source locations, orientations, amplitudes and latencies

	Ant–post (cm)	Med–lat (cm)	Inf–sup (cm)	PHIx (deg)	PHIy (deg)	PHIz (deg)	Dipole moment (nAm)	Peak latency (ms)
N1m								
Patient 1	2.78 ± 0.47	−4.59 ± 0.64	5.4 ± 0.38	34.9 ± 3.71	80.3 ± 4.33	58.3 ± 4.48	8.5 ± 0.9[a]	131.0 ± 4.2[a]
Patient 2	0.86 ± 0.49	4.56 ± 0.4	4.5 ± 0.37	53.6 ± 3.7	85.3 ± 1.8	37.0 ± 3.9	23.6 ± 3.9[a]	116.0 ± 2.5[a]
Control	1.3 ± 0.44	3.83 ± 0.41	5.65 ± 0.51	52.8 ± 9.7	81.1 ± 2.0	39.0 ± 9.0	19.1 ± 4.7	107.5 ± 6.1
P1m								
Patient 1	3.1 ± 0.53	−3.98 ± 0.43	5.62 ± 0.41	46.0 ± 10.4	77.3 ± 5.2	49.0 ± 10.6	4.0 ± 1.8[a]	58.0 ± 6.3[a]
Patient 2	0.6 ± 0.75	4.38 ± 0.68	4.68 ± 0.53	58.2 ± 10.5	83.6 ± 3.4	34.1 ± 13.2	20.9 ± 4.9[a]	52.9 ± 0.8[a]
Control	1.39 ± 0.9	3.6 ± 0.35	5.62 ± 1.15	44.9 ± 11.7	75.2 ± 6.6	51.4 ± 1.3	7.8 ± 4.3	50.8 ± 3.4

Ant–post, anterior–posterior axis; Med–lat, medial–lateral axis; Inf–sup, inferior–superior axis.
[a]Last four sessions only.

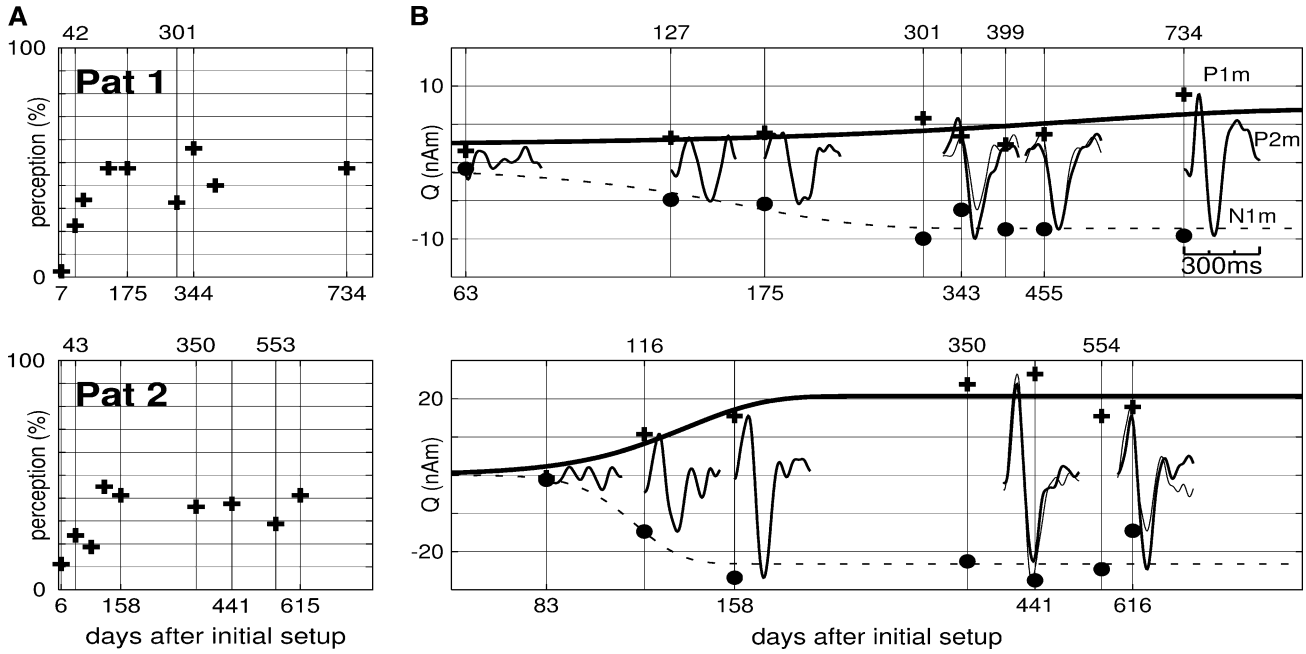

Figure 5. (*A*) Speech intelligibility measured by Freiburger Monosyllabic Word Test for both CI patients. (*B*) Cortical source strength waveforms obtained from the CI patients by means of source space projection for subsequent sessions according to the repeated measures during the two years of studying. The P1m and N1m peak amplitudes of the response waveforms are denoted as crosses and filled circles, respectively. The solid and dashed lines approximate the time course of these amplitudes.

cortical sources involved in the cortical auditory processing. During the follow-up study of 2 years this processing developed to normal as much as it can be assessed by almost normal component configuration of the auditory evoked fields with sources located in the auditory cortex. The increase of evoked brain activity over several months after implantation is the result of neural plasticity in the human auditory system. This observed plastic reorganization is expressed in the increase of cortical source strength, implying an increased number of activated cortical neurons and a correspondingly larger cortical area generating the evoked response or an increase in neural synchronization, or most probably a combination of both effects (Pantev *et al.*, 1998). The estimated source locations in the CI patients are consistent with activation of auditory cortical structures at the supra-temporal plane and do not differ significantly from source locations of the control subjects. The N1m source waveforms of the CI patients that are generated mainly in non-primary auditory cortical structures (Pantev *et al.*, 1995) resemble the ones of the normal hearing subjects. This suggests that CI stimulation is adequate for the development of the auditory perception.

The similar temporal dynamics of the behavioral (word test) and the electrophysiological (MEG) response indicates that the sound information is adequately processed in the auditory cortex and results in proper speech understanding. With respect to the relation between perception and the P1 and N1 amplitudes, it is commonly accepted that increased stimulus intensity (in a reasonable range) results in larger P1 and N1 amplitudes, which corresponds to a stronger percept. Furthermore, with respect to auditory plasticity, larger response amplitudes are an indicator for stronger cortical representation and might show that a larger neural population is involved in processing the auditory stimulus. The obtained results depicting cortical development in post-lingual cochlear implant patients suggest that use-dependent functional reorganization of the auditory system, as recorded by means of MEG, required about 6 months to reflect the pattern of sensory input provided by the speech processor. Our results suggest that within

6 months after implantation, CI patients may benefit most from post-implantation training, which should be as intensive as possible. Although speculative, some developmental trends seen in our late-onset post-lingual CI patients could be compared with those that occur in normal hearing children up to early adolescence (Ponton *et al.*, 1996). However, the time course of development and evoked response maturation was accelerated in our CI patients, perhaps because they were post-lingual cases and of an older age.

Notes

This work has been supported by the 'Deutsche Forschungsgemeinschaft' (Pa 392/6-3,4) and by Advanced Bionics Corp., Sylmar, CA, USA. We thank P. Matulat for patient support, K. Berning for technical assistance, and L. Roberts and A. Herdman for fruitful discussions.

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