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Research report

Short-term plasticity of the human auditory cortex

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Abstract

Magnetoencephalographic measurements (MEG) were used to examine the effect on the human auditory cortex of removing specific frequencies from the acoustic environment. Subjects listened for 3 h on three consecutive days to music ''notched'' by removal of a narrow frequency band centered on 1 kHz. Immediately after listening to the notched music, the neural representation for a 1-kHz test stimulus centered on the notch was found to be significantly diminished compared to the neural representation for a 0.5-kHz control stimulus centered one octave below the region of notching. The diminished neural representation for 1 kHz reversed to baseline between the successive listening sessions. These results suggest that rapid changes can occur in the tuning of neurons in the adult human auditory cortex following manipulation of the acoustic environment. A dynamic form of neural plasticity may underlie the phenomenon observed here.

Keywords: Cortical short-term plasticity; Functional deafferentation; Auditory system; Magnetoencephalography

1. Introduction

Several previous experiments have demonstrated that the functional organization of sensory maps is not statically fixed in adult cortex [9,12,13,15,18,27–29]. Early studies in animals utilized large and permanent changes of afferent sensory input, such as amputation of a forelimb [14,19,24] or mechanical destruction of part of the cochlea [12,25,26,32]. The findings showed that cortical regions that have lost their normal input take over and serve functions found in adjacent cortical areas [25,33]. Using magnetoencephalography (MEG) which allows non-invasive measurement in human subjects, changes in cortical maps similar to those observed in primate cortex have been demonstrated in patients with limb amputations and finger syndactyly [4,5,20,36].

Most studies of deafferentation-induced cortical reorganization including those just mentioned have investigated cortical reorganization on a time scale of days to weeks or more. However, other more recent studies have documented rapid changes in cortical dynamics following deafferentation. These studies have shown that neurons broaden and shift their receptive fields to sensory surfaces near or beyond the edge of the lesioned zone within a few minutes of deafferentation in the somatosensory [3] and visual [7] systems, and within hours in the auditory system [30]. Rapid retuning of sensory neurons has also been observed following reversible ''functional'' deafferentations in which sensory input from the environment is altered by procedures such as artificial scotomas [8] or digit ligation [31] rather than by permanent lesions of the receptor organs. Rapid expansion of receptive fields induced by lesioning or functional deafferentation appears to reflect an unmasking of existing excitatory connections when lateral inhibition is withdrawn following deafferentation [37]. However, because rapid changes in cortical dynamics continue to develop for an hour or more after deafferentation and are sensitive NMDA receptor blockade, plastic changes in synaptic efficacy have also been implicated. These observations suggest that cortical remodelling induced by deafferentation may be mediated by mechanisms similar to those activated by behavioral training which has been shown to alter the tuning of somatosensory [2] and auditory [34,35] cortical neurons within minutes to hours.

The objective of the present study was to determine whether plastic changes of frequency representation occur

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on a short time scale of a few hours when the adult human auditory cortex is deprived of sensory input. Subjects listened for 3 h to music notched at a narrow frequency band centered at 1 kHz. Immediately before and after listening to the notched music, auditory cortical representations were measured neuromagnetically for a ''test'' stimulus of 1 kHz centered on the notched region and a ''control'' stimulus of 0.5 kHz.

2. Materials and methods

2.1. Subjects

Three female and seven male subjects aged between 25 and 50 years (median 31 years) with no history of otological or neurological disorders participated in the study. A normal audiological status was assured with air and bone conduction thresholds of no more than 10 dB hearing level in the range from 250 to 8000 Hz. All subjects were right-handed according to the Edinburgh handedness questionnaire [21]. Informed consent was obtained from each subject after explaining to her/him the nature of the study. The experimental procedures were conducted in accordance with the Ethics Commission of the University of Münster and the Declaration of Helsinki. Subjects were paid for their participation.

2.2. Functional deafferentation

Subjects were asked to provide three favorite CDs from their CD collection. Music characterized by a narrow frequency spectrum was not accepted. The music was manipulated in such a way that a notch between 0.7 and 1.3 kHz, centered around 1 kHz, was produced using a band rejection filter (Bessel, 96 dB/oct) in the broad band spectrum of the music (see Fig. 1a). Although this manipulation initially produced a clearly perceptible effect, subjects reported that they adapted quickly to the modified sound and that their appreciation of the music during the listening time was unchanged. The subjects were asked to listen attentively to the music for continuous periods of 3 h. MEG measurements were taken before and after this period. Music was presented binaurally at a moderate loudness of about 60–70 dB SPL through earphones. During the time of listening, the subjects were allowed to read a book or surf the Internet. Owing to the presence of the notch, for this period of time the afferent input to cortical neurons tuned to frequencies around 1 kHz was abolished.

In order to measure the effect of notching on the neuronal representation of 1 kHz, MEG recordings to band-passed noise bursts centered at 1 kHz (test stimulus) were compared to band-passed noise bursts centered at 0.5 kHz (control stimulus). The 0.5 kHz band was chosen as

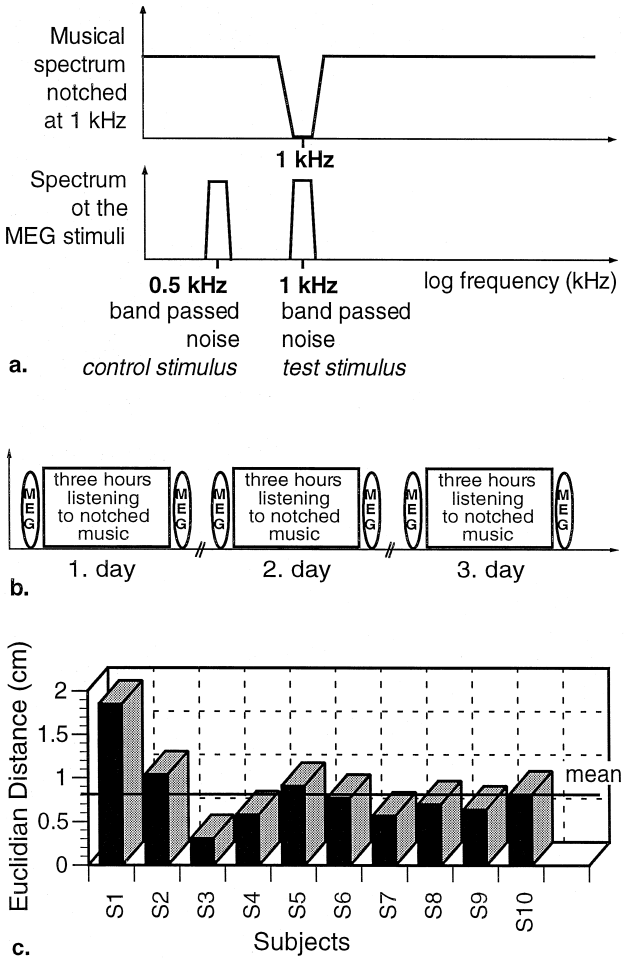


Fig. 1. Experimental design: (a) Music spectrum notched at 1 kHz (top) and spectral characteristics of the test and control stimuli for MEG recording (bottom). (b) MEG recordings were taken immediately before and after listening to notched music for 3 h on three consecutive days. (c) Difference in the mean Euclidian distance between the position of the subject's head and the MEG sensor array before and after listening to music for each subject.

control since its representation on the cochlea and in the auditory cortex was not too distant from that of 1 kHz, but being one octave apart, it was not likely to be affected by the notch in the spectrum of the music. The experiment was repeated three times in each subject, in most of the cases on consecutive days in order to address the time course and the reversibility of cortical remodelling induced by this procedure (Fig. 1b). These repetitions served to (i) enhance the number of observations available for statistical analysis, (ii) assess the suitability of MEG measurements for investigating short-term plasticity of the human cortex, and (iii) address the dynamics of cortical changes observed over 24 h and possible cumulative effects over 3 days of testing. Upon conclusion of the experiment, two subjects were available for further testing. These subjects were exposed to notched music for an additional 3 days. However, music was notched at 0.5 kHz (0.35–0.65 kHz) instead of 1 kHz. Therefore, 0.5 kHz became the test

stimulus and 1 kHz the control stimulus for this training period.

2.3. Stimulation and MEG-recording

Test and control stimuli were band-passed noise bursts of 500 ms duration (10 ms rise and fall time; cosine slope). This slope was sufficiently steep to elicit a prominent N1m component in the auditory evoked field (AEF), but gradual enough to retain a narrow frequency spectrum. The test stimulus was band-passed noise of 1 ± 0.2 kHz centered exactly in the notch of the music spectrum (cf. Fig. 1a). The control stimulus was band-passed noise of 0.5 ± 0.1 kHz. The spectral widths of the test and control stimuli (0.2 and 0.1 kHz, respectively) were comparable on a logarithmic scale. For each of the two stimuli, 128 stimulus presentations with interstimulus intervals varying randomly between 4.0 and 4.5 s constituted a stimulus train. Two test stimulus trains and one control stimulus train were applied in a randomized order before and immediately after listening to notched music. A delay of less than 5 min lapsed between the exposure to the music and the subsequent MEG measurement. The thresholds for the test and control stimuli were measured to within 2 dB for each subject. The intensity of each stimulus was set at 60 dB above each subject's measured threshold.

The auditory stimuli were delivered to the right ear by a special acoustic system with speakers (compressor driver type) situated outside the magnetically shielded room. Stimuli were conveyed echo-free to a silicon ear piece through a plastic tube 6.3 m in length and 16 mm in diameter [22]. To ensure a proper relationship between the notch in the music spectrum and the test and control stimuli, the acoustic signals were recorded at the silicon ear piece by means of an artificial ear (Brüel and Kjaer model 4152) equipped with a microphone (Brüel and Kjaer model 4153) coupled to a sound level meter (Brüel and Kjaer model 2203). The calculated power spectra confirmed the appropriateness of the applied stimuli.

Recordings were carried out from the left hemisphere in a magnetically shielded room using a 37-channel biomagnetometer (Biomagnetic Technologies). The sensor array was centered over a point about 1.5 cm superior to the position T3 of the 10–20 system for electrode placement and was positioned as near as possible to the subject's head. The spectral density of the intrinsic noise of each channel was about 5 $fT/\sqrt{Hz}$ in the frequency range above 1 Hz. The subjects rested in a right lateral position with their head, neck and body supported by a specially fabricated vacuum mattress. This mattress remained evacuated for each subject between daily MEG before/after measurements, to ensure that head and body position were repeated between the measurements. A photograph of the subject's head position with respect to the dewar was also taken. A sensor-position indicator system determined the spatial locations of the sensors relative to the head and indicated if head movements occurred during the recordings. No head movements sufficient to require discarding of data were observed in the study. During the MEG session, subjects watched cartoon videos intended to fixate their attention. The subjects were instructed to stay in a relaxed waking state and the compliance was verified by video-monitoring. Using a bandwidth from 0.1 to 100 Hz and a sampling frequency of 297.3 Hz, 128 epochs were recorded for each stimulus train and stored for further analysis.

2.4. MEG-source analysis

Magnetic fields evoked by the test and control stimuli were filtered within the band 0.1–20 Hz and averaged for each subject and daily session. Epochs contaminated by muscle or eye blink artifacts of more than 3 pT in any channel were automatically rejected from the averaging procedure. For each evoked magnetic field, a single equivalent current dipole (ECD) was fitted.

The principal parameters evaluated in this study were (in the time domain) the root mean square (RMS) value averaged over the sensor array (global source power), and (in source space) the dipole moment (Q) of the cortical source determined for each field pattern. Given a constant location and direction of the ECD, dipole moment indicates the total strength of the cortical activation, i.e., the number of neurons synchronously active. If this number increases, the dipole moment also increases, and vice versa. The mean dipole moment (Q) for each experimental condition was computed from about six time points surrounding the maximum dipole moment. These values were accepted for further evaluation only if the following additional requirements were satisfied: (1) a goodness of fit of the ECD model to the measured field $> 95\%$; (2) variation of the source coordinates for the same experimental condition before and after functional deafferentation of less than 10 mm in any plane; and (3) anatomical distance of the ECD to the midsagittal plane greater than 2 cm and inferior–superior plane greater than 3 cm (see [23]). Overall, 85.6% of the dipole moment estimates satisfied these requirements.

2.5. Statistical analysis

Analyses of variance evaluated main effects and interactions of the variables Days (1–3), Stimuli (test/control), Before/After (before and after functional deafferentation), and, for the test stimulus, the Repeated Measurements (first/second) that were taken before and after functional deafferentation. RMS field values and dipole moment were assessed by pre-planned *t*-tests contrasting test and control stimuli before and after listening to notched music. Unless otherwise stated, all significance levels reported herein are two-tailed.

3. Results

The comparison of the field amplitudes of selected MEG channels or of the RMS value for the sensor array before and after 3 h of listening to notched music is acceptable only if the position of the head with respect to the sensor array is more or less constant between the two measurement periods. Therefore, special efforts (retention of the evacuated vacuum cushion between measurements and photographs of head position) were made to achieve this relative constancy. The grand average of the Euclidian distance in head-sensor position measured between the before and after conditions is displayed for each subject in Fig. 1c. The mean over the 10 subjects was about 8 mm and thus comparison of RMS values was appropriate.

The AEF obtained for test and control stimuli before and after listening to notched music are shown for one representative subject in Fig. 2a. Channels 12 and 35, depicting the maximum and minimum of the AEF, respectively, are enlarged and shown for the test stimulus on the left, and for the control stimulus on the right. Whereas the AEF amplitudes measured before and after listening to notched music are almost the same for the control stimulus, the AEF amplitude for the test stimulus is about 10% smaller after listening to notched music than before. This result was also obtained when calculating RMS values over the sensor array for this subject, as shown in Fig. 2b.

The average goodness of fit obtained for single ECD was 97.85% (S.D. 0.27%) over all subjects and conditions, indicating that a single dipole model was appropriate for explaining the data. Fig. 3a and b show how Q and RMS values, respectively, changed after listening to notched music for 3 h. Before–after differences are shown separately for test and control stimuli averaged over all subjects and days. Inspection of Fig. 3 shows that Q and RMS values decreased for the test stimulus after listening to notched music, whereas these values did not change appreciably for the control stimulus. Paired t-tests contrasting measurements taken before and after notched music were not significant for the control stimulus when applied to Q [$t(9) = 0.894$, $p = 0.394$] or RMS [$t(9) = -0.447$, $p = 0.665$]. However, Q for the test stimulus diminished significantly after listening to notched music [$t(9) = -3.30$, $p = 0.009$]. An interaction of Before/After with Stimulus (test/control) was also found for Q [$F(1,9) = 6.71$, $p = 0.029$], indicating that Q for the test stimulus decreased more after listening to notched music than did Q for the control stimulus. Similar results were observed for RMS at

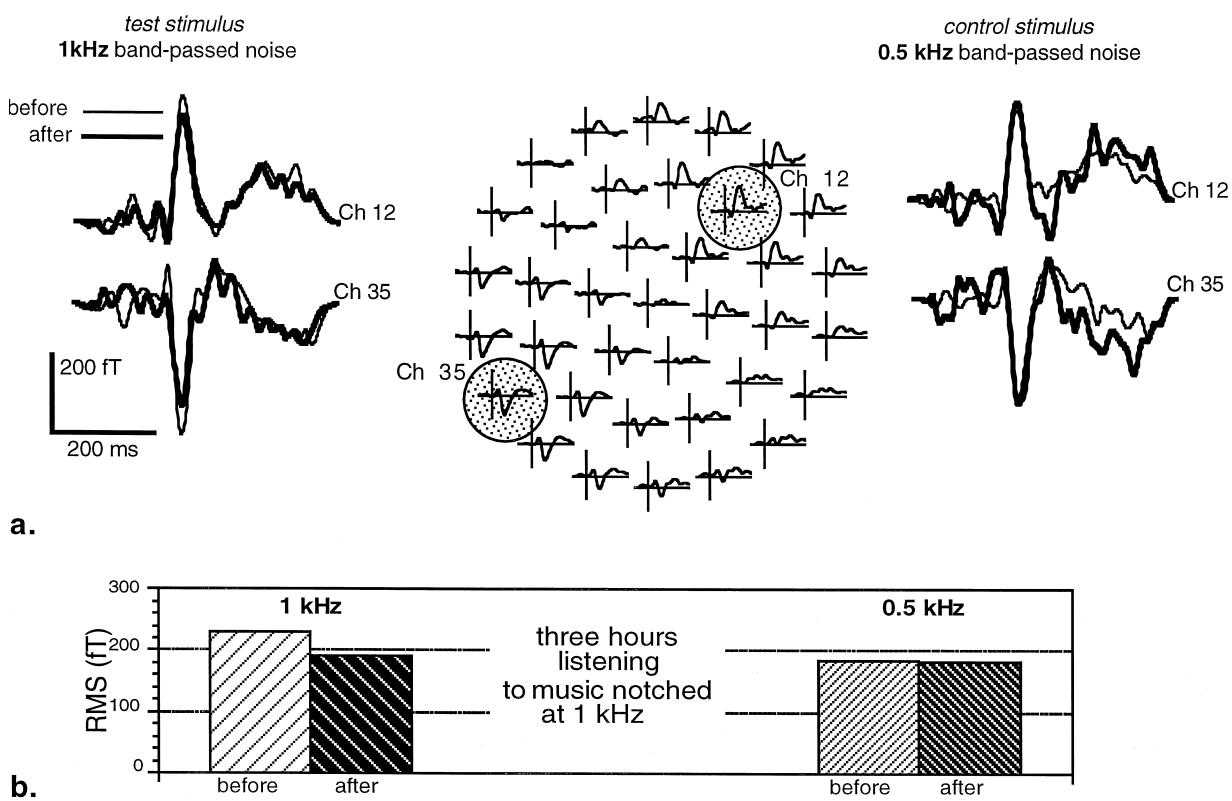
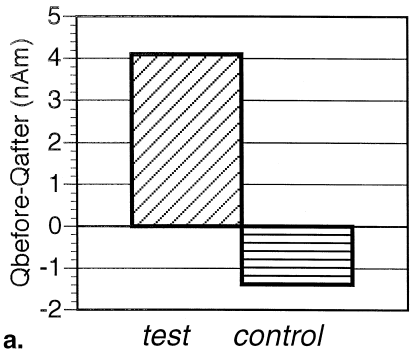


Fig. 2. (a) AEF of a single subject recorded for test stimulus (1 kHz, left panel) and control stimulus (0.5 kHz, right panel) before and after listening to notched music. The sensor array is given in the center. Channels 12 and 35 depicting the maximum and minimum of AEF, respectively, are enlarged and shown in the lateral panels. The thin line indicates the measurements before and the thick line the measurements after functional deafferentation. (b) RMS field values for the test (1 kHz) and control (0.5 kHz) stimuli averaged over the sensor array before and after listening to notched music for the subject reported above.



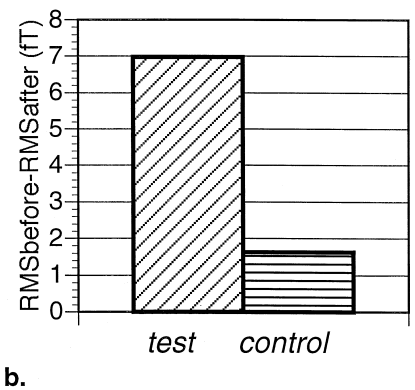


Fig. 3. Change in cortical representation produced by listening to notched music. (a) Change in the strength of the cortical source calculated as the moment (Q, nAm) of the equivalent current dipole fitted to the N1m component of the AEF for test and control stimuli averaged over subjects and days. (b) Change in the RMS (fT) of the N1m component of the AEF for test and control stimuli averaged over subjects and days.

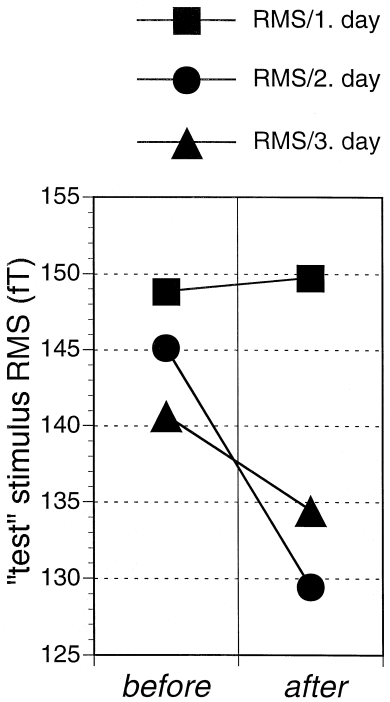


Fig. 4. Effects of exposure to notched music on RMS values for the test stimulus over days.

significance levels of $p < .10$. Comparison of Before/After measurements of RMS values for the test stimulus by a paired t-test yielded $t(9) = -1.43$ [$p = 0.093$], while analysis of variance yielded an interaction between Before/After and Stimulus (test/control) of $F(1,9) = 2.85$ [$p = 0.063$ (both one-tailed tests)]. These findings support the conclusion that the strength of the cortical source diminished for the test stimulus, but not for the control stimulus, after listening to notch music.

The effect of exposure to notched music over days was evaluated by analyses of variance applied to the test and control stimuli separately. These analyses were confined to RMS because for this measure data were available for every subject in all conditions. For the test stimulus, a significant interaction of Days with Before/After was obtained, $F(2,18) = 3.76$ [$p = 0.043$]. This interaction is depicted in Fig. 4 where it can be seen that the RMS response to the test stimulus decreased following exposure to notched music after the second and third session of listening, but not after the first listening session. No significant main effects or interactions attributable to Days or Before/After were obtained for the control stimulus. When control and test stimuli were included in the same analysis, an effect of Stimulus was found, $F(1,9) = 8.24$ [$p = 0.018$], indicating larger RMS responses to the test stimulus overall than to the control stimulus during the experiment.

Table 1 presents mean RMS and Q measurements taken before listening to notched music on each day, in order to provide information on the reversibility of notching effects within the time period of 24 h. Despite the small trend seen in the RMS values, no significant differences were observed between days in these measures.

Two measurements each consisting of 128 epochs were taken for the test stimulus both before and after listening to notched music. Comparison of the RMS responses between the two measurements showed that the second value (mean 131.6 fT) was 13.0% lower than the first one [(mean 151.2), $F(1,9) = 44.78$, $p = 0.000089$]. This finding indicates that partial habituation of the RMS response occurred between the two measurements. However, there was no interaction of First/Second with Before/After, $F(1,9) < 1$, indicating that the habituation effect did not differ between measurements taken before and after listen-

Table 1

	Test stimulus			Control stimulus		
	1 Day	2 Day	3 Day	1 Day	2 Day	3 Day
RMS	148.8	145.1	140.7	136.2	135.5	130.1
S.E.M.	12.1	12.4	11.4	17.3	15.9	14.5
Q	37.6	33.9	32.7	30.1	26.3	29.2
S.E.M.	3.4	3.3	3.2	3.2	4.2	4.8

ing to notched music. These analyses applied to Q yielded the same results.

Two of our subjects were available for continued testing beyond the first three sessions of the experiment. Three additional days were given to these subjects. However, in this case, music was notched at 0.5 kHz rather than 1 kHz on these days. Thus, for these subjects, 1 kHz served first as a test stimulus for the first 3 days of the experiment (1 kHz notch) and then as a control stimulus for the last 3 days (0.5 kHz notch), and vice versa for the 0.5 kHz stimulus. The effect of listening to notched music (Before/After difference) was not affected by the reversal of the stimulus conditions for the 0.5 kHz stimulus [$t(1) = 0.12$]. However, this effect was reversed for the 1-kHz stimulus, [$t(1) = 66.0$, $p = 0.0097$]. The RMS response to the 1-kHz stimulus decreased by 20 fT after listening to music notched at 1 kHz, whereas it increased by 2 fT after listening to music notched at 0.5 kHz.

4. Discussion

Animal studies have shown that removing spectral input by cochlear lesions is followed by a shift in the tuning of deafferented neurons in the auditory projection pathway to frequencies adjacent to the lesioned area [11,25,32]. The present MEG study examined the effect of ''functionally'' deafferenting the human auditory system. The effect of functional deafferentation was most evident in field patterns that were adequately modeled by a single ECD. Overall, the strength of the cortical source (Q) for the 1-kHz test stimulus decreased significantly by 12.3% after listening to music notched at 1 kHz for three consecutive days, whereas it increased non-significantly by 4.7% for the 0.5 kHz control stimulus over the same time. These results support the hypothesis that the frequency tuning of neurons in auditory cortex was modified by listening to notched music.

Subsequent analysis of the RMS values indicated that the decremental effect of the 1-kHz notch on the neural representation of the test stimulus was more pronounced on the second and third days of listening than on the first day, suggesting a cumulative effect. However, the RMS and Q measures taken before listening to the notched music on each day did not differ over days. This finding suggests that neurons that were functionally deafferented by the 1-kHz notch reverted to their initial frequency tuning within 24 h. Previous experiments have demonstrated that the cortical source of the N1m component of the AEF which was evaluated in this study remains stable across days in the absence of procedures intended to alter auditory cortical maps [17,22].

The possibility of habituation effects occurring within days was also examined for RMS and Q values. In order to increase measurement sensitivity for the test stimulus, two measurements were taken for this stimulus before and after each listening session. RMS and Q values decreased by 13% between these repeated measurements, indicating partial habituation of the cortical response during the measurement interval. However, this habituation effect occurred before as well as after listening to notched music and did not differ between these two conditions. Hence, it appears that it was the notch in the music and not habituation of the repeated measurements within days that was responsible for the effect observed at 1 kHz.

As an additional test of functional deafferentation, the spectral notch of the music was changed from 1 to 0.5 kHz for two subjects who were available for continued study. Restoration of the 1-kHz frequency band in the music reversed the decremental cortical response to the 1-kHz stimulus in these subjects. However, switching the notch to 0.5 kHz did not alter their cortical response to the 0.5 kHz stimulus. This may have happened because notching the music at 0.5 kHz did not appear to us to have altered the perceived quality of the music as much as notching at 1 kHz. The perceptual effects of notching and retuning of neurons may depend on spectral energy at frequencies adjacent to the notched region as well as upon the presence of a notch itself (i.e., a steep slope at the borders of the notched region, see Ref. [25]).

Taken together, our results suggest that reorganization of cortical representations can occur within time periods as short as a few hours following functional deafferentation of the adult human auditory cortex. The temporal properties of the notching effect are consistent with animal studies which have shown that cortical neurons deafferented by cochlear lesions display elevated response thresholds initially and then shift their tuning preferences away from the lesioned area to frequencies near the edge of the deafferented region over a period of a 1–3 h or more [30]. It should be noted that we placed our 0.5 kHz control stimulus some distance away from the site of the functional deafferentation (one octave), because the precise border of the lesioned area and the sensitivity of MEG measurements to dynamics occurring in this area were unknown. Whether augmentation of cortical representations at edge frequencies can be probed by test stimuli placed closer to the deafferented zone remains to be determined.

Several interrelated mechanisms appear to contribute to cortical remodelling induced by deafferentation, including (i) changes in the efficacy of existing excitatory synapses unmasked by lesioning [37], (ii) modification of synaptic efficacy by transcription of immediate early genes [16], and (iii) sprouting of new connections [1,6]. Of these mechanisms, the first and second appear most likely to account for our findings, and the third (synaptogenesis, which requires more time) the least likely. Evidence gathered in the visual [8] and motor [37] systems indicates that deafferentation leads to a rapid enhancement of the efficacy of existing lateral connections by an LTP-like process that is activated when intracortical inhibition is diminished

following the lesion. As a consequence, the receptive fields of the deafferented neurons shift toward the edges of the lesion. A similar mechanism could underlie loss of sensitivity in the deafferented zone in our study where lesions were imposed functionally rather than by physical destruction of the sensory receptor. Although the N1m component of the evoked auditory field that we measured is known to have a cortical source [10,22], effects expressed in the cortex could also reflect changes occurring at lower levels of the auditory projection pathway. Cochlear lesions have been found to induce reorganization in subcortical nuclei of neonatal [11] and adult mammals [26] although whether such changes occur following brief periods of functional deafferentation is speculative. Notching would not be expected to diminish the sensitivity of auditory receptors on the basilar membrane through habituation or fatigue-like processes because spectral energy in the region of the notch was removed by this procedure.

Acknowledgements

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