Plastic changes in the auditory cortex induced by intensive frequency discrimination training

Hans Menning, Larry E. Roberts[1] and Christo Pantev[CA]

Biomagnetism Center, Institute of Experimental Audiology, Kardinal-von-Galen-Ring 10, D-48129 Münster, Germany;
[1]Department of Psychology, McMaster University, Hamilton, Ontario, Canada L8S 4K1

[CA]Corresponding Author

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The slow auditory evoked (wave N1m) and mismatch field (MMF) elicited by sequences of pure tones of 1000 Hz and deviant tones of 1050, 1010 and 1005 Hz were measured before, during and 3 weeks after subjects were trained at frequency discrimination for 15 sessions (over 3 weeks) using an odd-ball procedure. The task of the subject was to detect deviants differing by progressively smaller frequency shifts from the standard stimulus. Frequency discrimination improved rapidly in the first week and was followed by small but constant improvements thereafter. N1m and MMF responses to the deviant stimuli increased in amplitude during training. This enhancement persisted until training was finished, but decreased 3 weeks later. The results suggest a plastic reorganization of the cortical representation for the trained frequencies. *NeuroReport* 11:817–822 © 2000 Lippincott Williams & Wilkins.

Key words: Auditory cortex; Discrimination training; Learning; MEG; Mismatch Field; Mismatch Negativity; Neuronal plasticity

INTRODUCTION

Everyday learning and training involves on the sensory, cognitive and behavioral levels a continuous improvement of our abilities. Animal research has shown that on the neurophysiological level it is possible to find a 'trace' of these processes in the sensory cortices of the brain. Recanzone *et al.* [1] trained owl monkeys for 60–80 daily sessions of 400–750 trials to make fine pitch discriminations in selected regions of the auditory frequency spectrum (these training frequencies differing from 2.5 kHz, 3 kHz, 5 kHz to 8 kHz between animals). Tonotopic mapping carried out invasively afterwards showed that the cortical area tuned to the trained frequencies was enlarged by a factor of 2–3 compared with untrained monkeys or animals that experienced the same acoustic stimuli passively while being trained on a somatosensory discrimination task. These results and other evidence for use-dependent plasticity in animals (summarized by Buonomano and Merzenich [2]) led us to investigate whether training to discriminate small differences in spectral pitch alters neuronal representations for the trained frequencies in the human auditory cortex.

The mismatch negativity (MMN) and its neuromagnetic counterpart, the mismatch field (MMF) reflect frequency-specific auditory discrimination processing in the human brain. A sequence of standard auditory input establishes a memory trace. Deviations from this memory trace generate a 'mismatch' response, which reflects a change detection process, occurring when the sensory input differs from a short-duration neuronal representation, which might form the 'echoic' memory [3]. Hence, the MMN offers a tool to evaluate automatic stimulus discrimination and the decay of the memory trace in the human auditory system [4]. An enhancement of the MMF amplitudes has been shown to correlate with improved pitch discrimination performance [5]. In the present study, an auditory stimulus of invariant spectral pitch (the standard stimulus) was repetitively presented in order to establish a memory representation. A deviant stimulus of different spectral frequency was then presented to generate the MMF. We measured the MMF while subjects were trained for 15 days to detect progressively smaller shifts in spectral frequency. The goal was to determine whether a MMF was observed as subjects detected progressively smaller deviants, and whether the amplitude of the MMF to the deviant stimuli was enhanced by training. These effects would imply a change in the neural assemblies representing the trained frequencies.

In addition, we examined changes in the magnitude of

the auditory N1m response (the magnetic peak waveform occurring about 100 ms after stimulus onset). In previous studies of experience-induced plasticity we have shown that the N1m evoked by piano tones is enhanced in musicians compared with non-musicians [6], and that the N1m evoked by a 1 kHz band-passed noise is diminished by listening for 3 h to music in which this frequency band was removed from spectrum by digital notching [7]. These findings suggest that the N1m may also be modified by training of pitch discrimination.

MATERIALS AND METHODS

Subjects: Ten healthy paid volunteers (seven males and three females) with normal audiological status and aged between 20 and 32 (mean 24.95) years participated. Informed consent was acquired from all subjects following procedures consistent with the Declaration of Helsinki and approved by the Ethical Committee of the University of Münster. All subjects were determined to be right-handed by the Edinburgh Handedness Inventory.

Discrimination training: The experimental procedure is outlined in Fig. 1a. After two baseline MEG measurements (see below), subjects received 15 daily sessions of discrimination training distributed over 3 weeks. Training sessions lasted about 1.5 h and were conducted at the same time of day for each subject. In each session 2500 stimuli of 100 ms duration were delivered with an interstimulus interval (ISI) of 1.2 s using an odd-ball procedure (see Fig. 1b). The standard stimulus (1000 Hz) occurred with a probability of 0.7 and the deviant stimuli (1020 Hz maximum) with a probability of 0.3. After each stimulus the subject responded 'standard' or 'deviant' by pressing either the left or right button, respectively, on a computer mouse with her/his right hand. A hit was registered when the deviant tone was correctly recognized, and a correct rejection when the standard was reported correctly (Fig. 1b). These outcomes were followed by presentation, on a computer monitor placed in front of the subject, of a green square (duration 300 ms), indicating that the response was correct. A miss was registered when a deviant stimulus was not detected, and a false alarm when a standard was misidentified as a deviant. These outcomes were followed by a red square indicating that an error had been made.

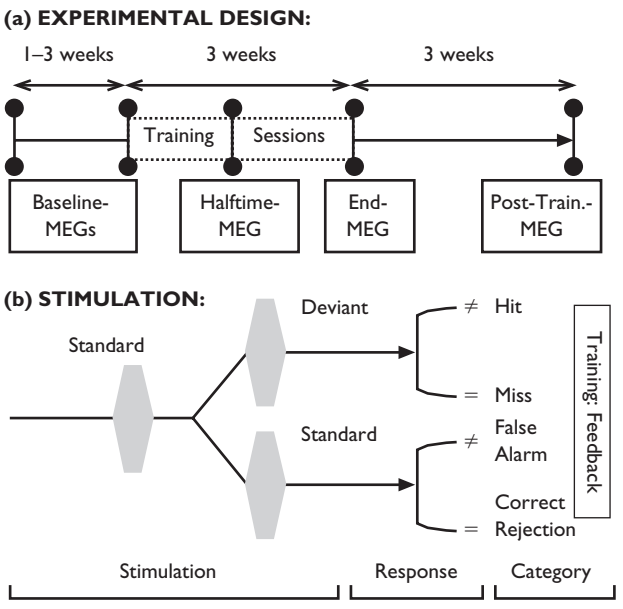

Fig. 1. (**a**) Before the training period of 3 weeks two baseline MEG recordings were performed. N1m and MMF were recorded before, after 1.5 weeks and 3 weeks of discrimination training as well as after another 3 weeks without training. (**b**) An oddball procedure was employed. In the training procedure a visual feedback was given, the discrimination tests and MEG recordings were performed without feedback.

A staircase procedure was used to adjust the deviant stimuli during the discrimination training. A minimum of five standard stimuli were presented in succession at the beginning of each session, before the first deviant (always 1020 Hz) appeared. The magnitude of the deviant stimulus (frequency difference between the deviant and the standard, or Δf) was reduced exponentially with each correct detection according to the formula:

$$\Delta f = S1\left[\left(1+\frac{\Delta f_0}{S1}\right)^{1-f}-1\right],$$

where Δf is the difference in frequency between the S2 (deviant) and S1 (standard), Δf_o is the preceding difference in frequency and f is a factor which determines the step width of the learning curve. In this training, f was adopted as 0.05. Thus the stairs were greater at the beginning of the training session (e.g. $\Delta f = 1.01$ Hz) and decreased as the subject neared threshold (e.g. $\Delta f = 0.3$ Hz). If the subject missed a deviant, the frequencies of the subsequent deviants were increased by the formula:

$$\Delta f = S1\left[\left(1+\frac{\Delta f_0}{S1}\right)^{1/1-f}-1\right].$$

The frequencies of deviant stimuli were also increased by a single step according to this formula when false alarms occurred.

Discrimination tests: Discrimination tests were administered before and after each discrimination training session to determine the pure discrimination performance (without feedback). Each discrimination test consisted of 126 standard tones of 1000 Hz and 124 deviant tones equally divided between 1003, 1005, 1010, and 1020 Hz. The standards and deviants were delivered in a semi-random order to give a total of 250 stimuli in each test (~50% standards and 50% deviants). As during training, the stimuli were 100 ms in duration and were separated by an ISI of 1.2 s. After each stimulus, subjects indicated whether the stimulus just heard was a standard or a deviant by pressing a mouse key. A minimum of five standard stimuli were presented at the beginning of each test session before the first deviant occurred. In contrast to discrimination training, the deviant stimuli were not adjusted according to the subject's performance during discrimination testing, and no feedback was given, whether their decisions were correct or false.

MEG measurements: MEG responses to the trained stimuli were measured twice over a 3-week period prior to the

first discrimination training session (baseline MEG). A third measurement was taken between sessions 7 and 8 of discrimination training (halftime MEG), a fourth measurement upon the conclusion of training (end MEG), and a fifth measurement 3 weeks later (post-training MEG; see Fig. 1a). MEG recordings were carried out in a magnetically shielded room using a 37-channel biomagnetometer (Magnes Biomagnetic Technologies). The gradiometer coils were arranged in a circular concave array (diameter 144 mm) with a spherical radius of 122 mm. A sensor positioning system was used to determine sensor location relative to the head and to indicate head movements during the measurement. The sensor array was placed over the left supratemporal cortex above the T3 position of the International 10-20-system for EEG electrode placement. Subjects rested supine on a vacuum cast to ensure a stable body and head position. Subjects watched an animated video to fixate their attention and were instructed to stay relaxed and awake. Compliance was verified by video monitoring.

Three deviant stimuli were used during the MEG measurement (1050, 1010 and 1005 Hz). Three blocks of stimuli were delivered, each block differing with respect to which of the three deviants was tested. The order of the blocks was counterbalanced between subjects. Each block consisted of 765 standard stimuli (probability of occurrence 0.85) and 135 deviant stimuli (probability of occurrence 0.15) for a total of 900 stimuli per block. Epochs of 700 ms (200 ms prestimulus interval) were recorded using a bandwidth of 0.1–100 Hz (sampling rate 297.3 Hz). This procedure was repeated twice in each MEG session resulting in a total of 5400 stimuli overall for the session (765 standards + 135 deviants × 3 deviants × 2 repetitions). The stimuli were tone bursts of 100 ms duration with 10 ms rise and decay times (cosine envelope). They were presented contralaterally through a non-magnetic and echo-free stimulus delivery system [8] at 60 dB SL (sensation level).

MEG data were averaged separately for each session and deviant stimulus type after removing eye blinks and movement artifacts. The averaged data were baseline corrected and band-pass filtered between 0.1 and 20 Hz. The test–retest runs within one measurement session were grand-averaged and the standard-stimulus response was subtracted from the deviant-stimulus response to yield the MMF (cf. [9]). A source analysis based on a single moving dipole model in a sphere was performed. The source parameters (location, orientation, magnitude, goodness of fit) of an equivalent current dipole (ECD) were calculated and submitted to statistical analysis. Repeated measures ANOVA were used to determine whether there were significant differences in the N1m and MMF brain responses before, during, at the end, and 3 weeks after discrimination training.

RESULTS

Psychophysics: Psychometric functions were determined for each subject and session of discrimination training by plotting the probability of a hit [p(H) number of hits/number of stimuli)] against the Δf associated with each deviant stimulus presented during the session. The first 200 stimuli of the 2500 stimuli delivered during the session were omitted in order to allow performance to stabilize. The threshold of detection was defined as the Δf corresponding to $p(H) = 0.5$. This measure is shown over the 15 training sessions for each subject in Fig. 2. Discrimination improved rapidly in the first week of training, with gains occurring between sessions 1 and 3 for every subject. In the second week (sessions 6–10), small gains continued to be recorded for several subjects, but by the third week (sessions 11–15) the limit of the threshold appeared to have stabilized near 2 Hz. This value is consistent with psychological studies which indicate the DL (discrimination limen, the smallest detectable change in frequency at normal stimulus intensity) to approach 2 Hz for a 1 kHz standard stimulus [10].

Mismatch field: The MMF was evaluated by using two methods. First, the MMF was calculated by averaging RMS values over all sensor channels for the time window 0–500 ms following standard stimuli and subtracting these values from the corresponding measurements following deviant stimuli. The results were separately averaged for each subject and deviant stimulus type during the MEG sessions administered before, during, at the end, and 3 weeks after discrimination training (10 subjects × 5 tests = 50 averages overall). A MMF was detectable in each subject and measurement session following the 1050 Hz deviant stimulus. Figure 3a shows the RMS amplitudes of the MMF difference waves of one subject. A clear increase from the baseline measurements to the middle and to the end of training is seen. These values decreased slightly 3 weeks after the end of training. The MMF latency, grand averaged across all subjects decreased from 169.7 ms during the baseline sessions to 155.5 ms by the end of the training period ($p = 0.0216$, Fisher's protected least significance difference test, PLSD) and were followed by an increase to 161.3 ms 3 weeks later (mean overall latency = 162.2 ms). The amplitude of the 1050 Hz MMF also changed, increasing from a mean of 90.48 fT during the baseline sessions to 100.12 and 100.50 fT at the end of training, respectively, followed by a slight decrease three weeks later (99.97 fT), although only the contrast of the

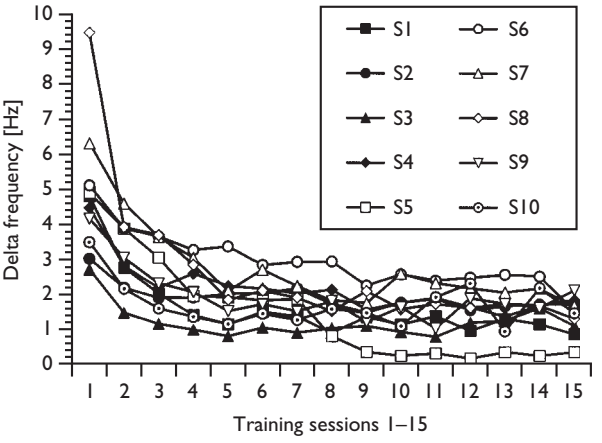

Fig. 2. The auditory frequency discrimination performance of all subjects (S1–S10) as revealed by the delta frequency at threshold over all training sessions.

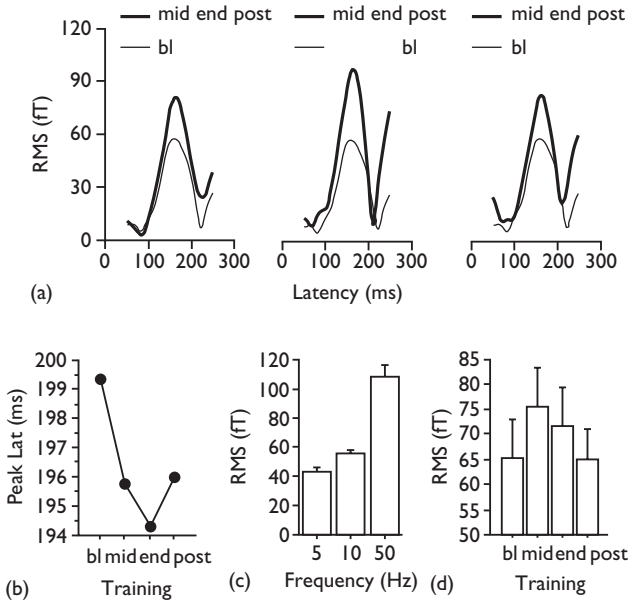

Fig. 3. (**a**) RMS values of MMF difference waves for 50 Hz deviant condition of a single subject. Thin line indicates the baseline condition, thick line the measurement in the middle (left) and at the end (center) of the training as well as 3 weeks after the training (right). (**b**) Latencies of the channel with maximal MMF amplitude before and over the training period as well as after the training. (**c**) Mean global field power (RMS) of the MMF for each deviant frequency, grand averaged over subjects. (**d**) Mean global field power (RMS) of the MMF grand averaged over subjects as recorded before discrimination training, after 1.5 and 3 weeks of discrimination training and 3 weeks after the discrimination training.

baseline tests to the middle test reached significance ($p = 0.0476$). At 1010 Hz a MMF was apparent in 36 (72%) of the 50 averages and peaked at 223.4 ms, which was significantly longer than for the 1050 Hz deviant ($p = 0.0018$, Scheffé's test). Across the MEG sessions latency and amplitude followed a course similar to that observed for the 1050 Hz deviant stimulus. At 1005 Hz an MMF was detectable in only 4% of the averages, which suggested that this frequency difference was too small to elicit a consistent MMF in an unattended paradigm.

In the second step of evaluation, the MMF amplitude and latency were defined as the largest peak occurring after the N1m in a time window from 130 to 300 ms, and with the same orientation as the N1m, on the deviant stimulus trials alone, in the channel showing the field maximum for each subject. The amplitude and latency of this peak were recorded for each subject and MEG session (baseline measurements collapsed) and assessed by analysis of variance for repeated measures with one factor training (consisting of the measurement times: baseline, half of training, end of training and 3 weeks post-training) and one factor deviant frequency. The MMF latency decreased from 199.5 ms during the baseline period to 194.0 ms at the end of training and recovered to 196 ms thereafter (Fig. 3b), but main effects and interactions involving these effects did not reach statistical significance.

A main effect of deviant frequency on the MMF was found ($F(2,24) = 18.826$, $p < 0.0001$; Fig. 3c). The MMF amplitude attenuated with increasing similarity of the deviant stimulus to the standard stimulus (1000 Hz), which is consistent with the results of previous studies of the MMF [3,11–14]. A main effect attributable to phase of training was also found ($F(3,9) = 3.91$, $p = 0.0116$; Fig. 3d). MMF amplitude increased between the baseline sessions and the middle of the training, at which time subjects had reached about 90% of their asymptotic discrimination performance, and diminished thereafter. *Post-hoc* tests (Bonferroni-Dunn) showed a significant difference between baseline and the middle of training ($p = 0.007$) and between middle of training and post-training measurements ($p = 0.005$). No other contrasts involving MMF amplitude reached significance. Analyses of MMF latency revealed a main effect of frequency of the deviant stimulus ($F(2,27) = 5.54$, $p = 0.0097$, with the 1050 Hz deviant showing a mean latency of 161 ms and the other two deviants latencies about 210 ms (both in good agreement with the first MMF analysis).

N1m responses: Both N1m responses evoked by the standard stimuli and those evoked by the deviant stimuli were identified from the field maximum and minimum within 130 ms following stimulus onset. Using averages computed separately for each subject and MEG session, the N1m amplitude was measured as the field maximum during this interval (maximum channel amplitude), and also as the RMS (root mean square, equivalent to the global field power) computed over all 37 sensors at the time point of the field maximum. In addition, a single moving dipole was fitted to the field distribution in a time window from 50 to 150 ms after stimulus onset, separately for each subject and MEG session. At seven successive time points surrounding the field maximum the median coordinates of the dipolar source were used to calculate the dipole moments with fixed coordinates. Only dipole fits accounting for more than 90% of the observed filed variance were accepted. The medium dipole moment (Q) of these fits was taken to estimate the strength of the cortical sources underlying the N1m for each subject and MEG session. The two baseline measurements were averaged and subsumed as the baseline condition.

These three measures of the N1m of the *standard* stimuli (dipole moment Q, RMS, and peak amplitude) are presented in Fig. 4, respectively, for each deviant stimulus and phase of training. For the maximum channel amplitude a main effect of phase of training was found ($F(3,24) = 6.778$, $p = 0.0004$). Bonferroni-Dunn *post-hoc* tests showed that N1m measurements differed significantly between baseline and the middle of training ($p = 0.025$), between baseline and the end of training ($p = 0.0018$), between the middle of the training and the post-training measurement ($p = 0.0014$), as well as between the end of training and the post-training measurement ($p = 0.0009$). Global field power changed similarly over the four phases of training ($F(3,27) = 9.569$, $p < 0.0001$), as did Q ($F(3,18) = 6.584$, $p = 0.007$), in each case with larger response amplitude during the middle and at the end of training than in the baseline and follow-up periods. Although N1m amplitude assessed by each of these measures was largest for the 1050 Hz deviant, main effects and interactions attributable to the frequency of the deviant stimulus were not significant. The

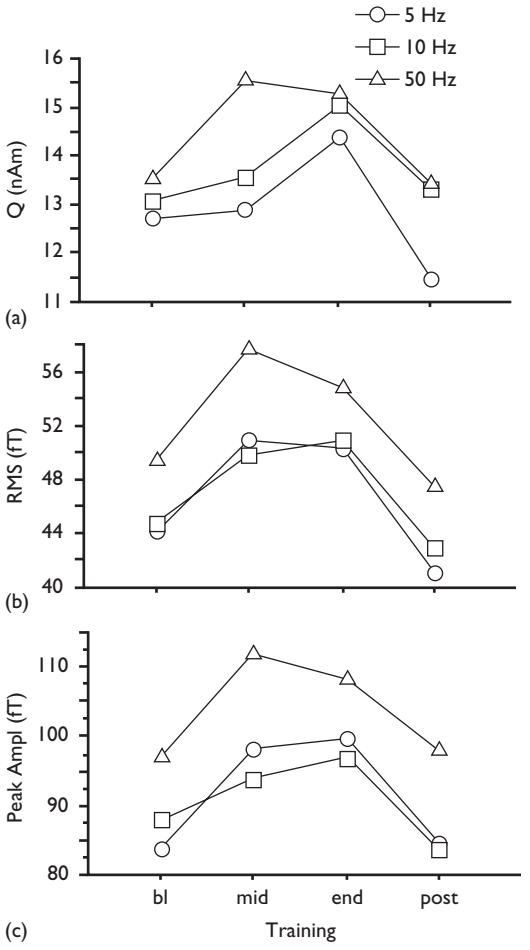

Fig. 4. Comparison of (**a**) strength of the cortical source (Q) of the N1m to the standards, (**b**) global field power (RMS) and (**c**) amplitudes of the channel with maximum amplitude, all grand averaged over all measurements and subjects.

peak channel amplitudes and RMS values of the N1m to the *deviant* stimuli showed a similar evolution over the training period as that to the standard stimuli, an increase from baseline to middle of training, a slight decrease to the end of training and also to 3 weeks after training, but with less significant effects. The RMS values showed in a repeated measures ANOVA a significant main effect for phase of training ($F(3,27) = 2.904$, $p = 0.0398$) with significant changes (Fisher's PLSD) between baseline and the middle of training ($p = 0.018$) and between the middle of the training and the post-training measurement ($p = 0.0138$), all other comparisons reaching no significance. As for the N1m of the standard stimuli, no significant effects have been found for the frequency of the deviant condition. The maximum channel amplitudes showed the same course, but with no significant main effect.

DISCUSSION

Modifications of synaptic strength among simultaneously active neurons due to practice and experience are widely suggested to provide the foundation for learning and memory consolidation [2,15–20]. In the present study subjects were trained using an odd-ball procedure to detect small differences in spectral frequency between a 1 kHz standard stimulus and deviant stimuli of slightly higher frequency. Over the course of 15 sessions of training the threshold for frequency detection diminished to about 30% of its initial value, reaching asymptote in about 10 sessions. Concurrently, the N1m source strength evoked by the 1 kHz standard stimulus increased over training blocks, indicating either that more neurons were activated or that the neurons representing this stimulus were firing more synchronously. The MMN evoked by the deviant stimuli also increased, indicating that the neural process responsible for preattentive comparison of the deviant and standard stimuli was similarly enhanced by discrimination training. The peak latency of the MMN mirrored this effect, diminishing by 5 ms during discrimination, although this effect did not reach significance. These findings are consistent with animal studies which have shown that auditory cortical representation can be remodeled by behavioral training over a wide range of time scales [1,2,21–22]. They also corroborate the findings of Kraus *et al.* [23], who observed augmentation of the MMN when human subjects were trained to discriminate phonemes. In addition, our findings provide information on how auditory cortical representations are modified by sensory experience. Magnetic source localization experiments have identified cortical generators for the N1m and MMN in the supratemporal plane, with sources of the MMF residing significantly more anterior, medial and inferior than the sources of N1m [9]. Although spatial overlap of N1m and MMN generators cannot be ruled out, the fact that the cortical sources of these responses are spatially resolvable, and that both were affected by discrimination training, suggests that dynamic remodeling of auditory representations is expressed at multiple levels of the cortical processing pathway. The N1m, which is sensitive to attention, may be augmented by plastic processes that take place either cortically or at subcortical sites that project to the auditory cortex. Possible subcortical sites include the magnocellular division of the medial geniculate nucleus which is known to recalibrate quickly during learning and to exert a modulatory effect on auditory cortical neurons, making them more sensitive to their preferred spectral inputs [24]. On the other hand, the MMN is known to be largely independent of attention and higher cognitive processing as well as of the signal value of a stimulus, and to be evoked by deviations in any of a large number of features of the acoustic input including intensity, duration and frequency [4]. These functional properties suggest that MMN ordinates from a preattentive, obligatory intracortical comparative process that operates independently of modulatory influences.

Similar to our findings, Kraus *et al.* [23] reported enhancement of the MMN in human subjects after six 1 h sessions of phoneme discrimination. Although improvement in discrimination was accompanied by augmentation of cortical representations in both of these studies, a different result was observed by Cansino and Williamson [25], who found in a single subject a decreased N1m amplitude over the course of 200 discrimination training sessions. This effect was interpreted as reflecting the use of fewer resources and a faster, effortless and automatic processing

after extensive practice. Our findings do not necessarily contradict those of Cansino and Williamson, because the extension of the training over a very long period is likely to exceed saturation level and to cause a dismiss of all unneeded neurons. In general, the time course of N1m and MMN amplitude enhancement remains to be investigated, as does the relation of enhancement to retention effects. In the present study N1m and MMN amplitudes were found to be diminished when evaluated 3 weeks after discrimination training had concluded.

CONCLUSION

Can learning produce plastic changes of cortical organization? Concomitant with clear improvements in discrimination performance during 3 weeks of training, changes in the neuromagentic responses N1m and MMN occurred, which may correspond to an increase of the representational areas of the trained frequencies as reported in animal studies [1,21–24]. Alternatively, an improvement of the synchronization of the activated neurons or a raising of the activation level in these neurons [24] may also have contributed to this effect. While the MMF seems to be a good measure of the automatic deviation detection, the N1m may reflect even more basic changes of the frequency representation in the auditory cortex or possible modulatory influences.

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