Behavioral/Systems/Cognitive

Learning-Induced Plasticity in Auditory Spatial Representations Revealed by Electrical Neuroimaging

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Auditory spatial representations are likely encoded at a population level within human auditory cortices. We investigated learning-induced plasticity of spatial discrimination in healthy subjects using auditory-evoked potentials (AEPs) and electrical neuroimaging analyses. Stimuli were 100 ms white-noise bursts lateralized with varying interaural time differences. In three experiments, plasticity was induced with 40 min of discrimination training. During training, accuracy significantly improved from near-chance levels to ~75%. Before and after training, AEPs were recorded to stimuli presented passively with a more medial sound lateralization outnumbering a more lateral one (7:1). In experiment 1, the same lateralizations were used for training and AEP sessions. Significant AEP modulations to the different lateralizations were evident only after training, indicative of a learning-induced mismatch negativity (MMN). More precisely, this MMN at 195–250 ms after stimulus onset followed from differences in the AEP topography to each stimulus position, indicative of changes in the underlying brain network. In experiment 2, mirror-symmetric locations were used for training and AEP sessions; no training-related AEP modulations or MMN were observed. In experiment 3, the discrimination of trained plus equidistant untrained separations was tested psychophysically before and 0, 6, 24, and 48 h after training. Learning-induced plasticity lasted <6 h, did not generalize to untrained lateralizations, and was not the simple result of strengthening the representation of the trained lateralizations. Thus, learning-induced plasticity of auditory spatial discrimination relies on spatial comparisons, rather than a spatial anchor or a general comparator. Furthermore, cortical auditory representations of space are dynamic and subject to rapid reorganization.

Key words: **electroencephalography (EEG); auditory-evoked potential (AEP); electrical brain imaging; spatial; interaural time difference (ITD); training; plasticity; sound localization; mismatch negativity (MMN)**

Introduction

Cerebral plasticity can occur within short delays after injury, sensory deprivation, or learning. Sensory representations can quickly reorganize after peripheral denervation of touch (Calford and Tweedale, 1988; Donoghue et al., 1990; Gerraghty and Kaas, 1991; Doetsch et al., 1996; Dinse et al., 1997; Faggin et al., 1997; Huntley, 1997; Barbay et al., 1999) or vision (Gilbert and Wiesel, 1992; Sur and Leamey, 2001; Calford et al., 2003). Striking effects on neural responses have also been observed in healthy animals after training with tools (Iriki et al., 1996; Iwamura, 2000) or specific auditory pitches (Edeline et al., 1993). Others have further demonstrated that modifications of receptive field properties were correlated with behavioral performance (Fritz et al., 2003, 2005; King, 2006).

Electrophysiological studies in humans have reported similar learning-induced plasticity. Näätänen et al. (1993) recorded auditory-evoked potentials (AEPs) during the time that and after subjects were trained to discriminate the pitches of two complex stimuli. AEP modulations, measured as a mismatch negativity (MMN), were only observed in subjects whose performance improved with training, whereas no changes were observed in subjects already performing well above chance levels before training. These results suggest that AEPs can be used as an index of training-induced neurophysiological changes and may furthermore be directly related to performance improvement. This hypothesis was further investigated by Gottselig et al. (2004), who recorded AEPs to tone sequences varying in the pitch of a single tone. Subjects actively discriminated tone sequences during a 6 min training session.

To date, studies investigating auditory plastic changes have focused on spectrally differing stimuli, including speech (Näätänen et al., 1993; Tremblay et al., 1997, 1998; Kraus et al., 1995; Menning et al., 2000; Atienza et al., 2002, 2005; Gottselig et al., 2004). Given the mounting evidence in humans for partially segregated brain networks mediating sound recognition and localization functions (Rauschecker, 1998; Hackett et al., 1999; Tian et al., 2001; Clarke and Thiran, 2004; De Santis et al., 2007), the present study addressed whether comparable plasticity occurs after learning to discriminate spatial features of otherwise identical acoustic stimuli. Psychophysical studies have shown that subjects can rapidly improve their ability to discriminate between

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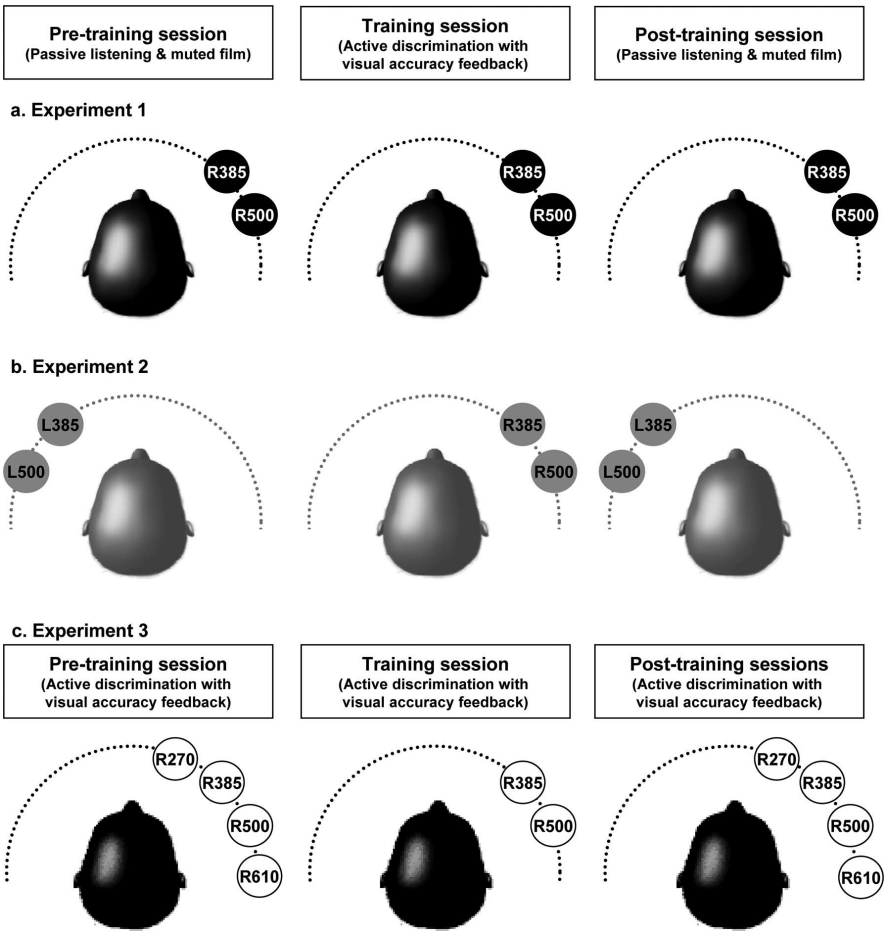

Figure 1. Experimental paradigm. Experiments 1 and 2 entailed three sessions, such that training, which involved active discrimination, was preceded and followed by passive listening sessions. ***a***, ***b***, The procedures for experiments 1 and 2 differed only in the loci of sound presentations during the pretraining (***a***) and post-training (***b***) sessions. For experiment 1, these sounds were presented to the right hemispace (i.e., the same loci as during the training session). For experiment 2, these sounds were presented to the left hemispace (i.e., the mirror-symmetric loci as during the training session). ***c***, Experiment 3 entailed the same training session as experiments 1 and 2, as well as one pretraining and four post-training sessions (immediately after the training, 6, 24, and 48 h later). Pretraining and post-training sessions required active discrimination between pairs involving nearby positions.

sounds differing by small interaural time differences (ITDs) or interaural intensity differences (IIDs); two binaural cues for sound localization (Wright and Fitzgerald, 2001). Electrophysiological studies, most using MMN as their dependent measure, have shown that spatial information, like other acoustic features, is processed preattentively (Paavilainen et al., 1989; Schröger and Wolff, 1996; Nager et al., 2003; Altman et al., 2004; Tardif et al., 2006). We combined psychophysical and electrophysiological methods to investigate mechanisms mediating training-induced plasticity in auditory spatial representations. Three experiments investigated (1) the relationship between performance improvements and post-training electrophysiological measures, (2) whether training-induced plasticity in auditory spatial representations extends to untrained locations, and (3) whether it is the spatial representations themselves or rather mechanisms for their comparison that are modified through training.

Materials and Methods

Subjects

Twenty-six healthy volunteers participated and were divided in three age-matched groups, each of which completed one of the three experiments. Experiment 1 included 10 subjects (three females, two left-handed using the Edinburgh questionnaire) (Oldfield, 1971) aged 21–28 years (mean age ± SD, 24.6 ± 2.7). Experiment 2 included 10 subjects (four females, one left-handed) aged 19–30 years (25.5 ± 3.3). Experiment 3 included six subjects (five females, one left-handed) aged 24–27 years (25.7 ± 0.5). Each subject provided written, informed consent to participate in the study. No subject had a history of neurological or psychiatric illness. All reported normal hearing. All procedures were approved by the Ethics Committee of the Faculty of Biology and Medicine of the University of Lausanne. Each subject completed three sessions that we refer to as pretraining, training, and post-training (Fig. 1), which are detailed below.

Stimuli

Auditory stimuli were 100 ms white-noise bursts (10 ms rise/fall envelope to minimize clicks; 44100 Hz digitization) generated using Adobe Audition 1.0 (Adobe Audition 1.0; Adobe Systems, San Jose, CA). Stimuli were lateralized by means of ITDs. Experiment 1 included two stimuli: with an ITD (right ear leading in time) of either 385 or 500 μs (hereafter termed R385 and R500, respectively). These sounds were lateralized to the right hemispace (see below). Experiment 2 included four stimuli. In addition to R385 and R500, which were used exclusively during the training session, mirror-symmetric lateralizations within the left hemispace were used exclusively during the pretraining and post-training sessions, corresponding to ITDs of −385 and −500 μs (hereafter termed L385 and L500). This was achieved by reversing the headphones. ITDs of 385 and 500 μs led to perceived lateralizations ~40° and 50° from the central midline, respectively [according to Blauert's complex formula (Blauert, 1997)]. Experiment 3 included four stimuli: R385, R500, and two additional positions with an ITD of either 270 or 615 μs (hereafter termed R270 and R615, respectively), which led to perceived lateralizations ~30° and 60° from the central midline, respectively. Each sound was presented via insert earphones (model ER-4P; Etymotic Research, Elk Grove Village, IL) at 86 ± 3 dB (measured using a CESVA SC-L sound pressure meter; CESVA Instruments, Barcelona, Spain).

Procedure and task

The rationale for the three experiments was the following. To determine whether spatial training in one hemispace generalized to the other hemispace, subjects of experiments 1 and 2 underwent the same training within the right hemispace, and effects of training on spatial discrimination were then assessed either at trained (experiment 1) or untrained (experiment 2) lateralizations. This design allowed us to ensure both groups showed behavioral improvement for the same spatial locations and also to control for the possibility of general repetition effects intertwined with effects of training-induced plasticity. Both behavioral and EEG data were collected throughout the length of experiments 1 and 2. Experiment 3 was conducted to better determine the basis of any training-related effects observed during experiments 1 and 2. Specific stimulus details are provided below. Briefly, we included additional pairs of adjacent lateralizations to disentangle whether subjects were learning spatial discrimination specific to the trained locations (R385 and R500) or more generally the discrimination of a relative spatial separation between sounds regardless of their specific lateralization. These pairings also allowed us to assess whether training-induced effects followed from subjects specifically learning and forming a spatial "template" or "anchor" of the R385

position; in which case, performance enhancement for all pairs involving the R385 position would be predicted. Second, we included sound pairs wherein the R500 lateralization was presented first (i.e., in contrast to the order used during the training session) to assess whether training-induced enhancement was sequence specific. Finally, participants in experiment 3 were also tested at multiple delays after training to assess the persistence of training-induced performance enhancements. Stimulus delivery and response recording were controlled by E-Prime (Psychology Software Tools, Pittsburgh, PA) while subjects sat in an electrically shielded and sound-attenuated room.

Pretraining and post-training sessions

In experiment 1, pretraining and post-training sessions consisted of pseudo-randomized presentations of R385 and R500 stimuli (Fig. 1*a*), which were respectively presented 87.5 and 12.5% of the time with the constraint that at least one R385 stimulus always preceded an R500 stimulus. Stimuli were blocked into series of 360 trials with an interstimulus interval of 1 s. Each participant completed five blocks before and five after the training session while watching a muted film with subtitles in their native language. They were given no instructions about the auditory stimuli, except to ignore them and to watch the film. Experiment 2 followed an identical procedure to that of experiment 1, except that L385 and L500 were presented instead of R385 and R500 (Fig. 1*b*).

Participants in experiment 3 underwent the same training session as used in experiments 1 and 2. Pretraining and post-training sessions were completed as follows: just before (H − 0), just after (H + 0), 6 h after (H + 6), 24 h after (H + 24), and 48 h after (H + 48) the training session. These sessions also consisted of a two-alternative forced-choice task. Stimuli duration, interstimulus and intertrial interval, response window, and visual feedback were the same as during the training session. Subjects discriminated whether the two items of the following stimulus pairs were the same or different: R270-R270, R270-R385, R385-R385, R385-R500, R500-R385, R500-R500, R500-R610, and R610-R610. Stimuli were blocked into series of 192 trials (24 × 8 pairs), subjects underwent two blocks per session. The procedure and calculation of sensitivity were the same as in the training session (see below).

Training session

In experiments 1, 2, and 3, the training session consisted of a two-alternative forced-choice task. Subjects discriminated whether the two items of stimulus pairs R385-R385 or R385-R500 were the same or different. Subjects pressed the left response-box button when they perceived the two stimuli of a pair at the same location and the right button if the stimuli were perceived at different locations. Stimuli of each pair were separated by 250 ms (from offset to onset) and were blocked into a series of 200 trials. Subjects were required to respond within 750 ms after trial offset. A fixed 1000 ms intertrial interval (ITI) followed response initiation (or 750 ms after trial offset in the case of an absent response). Visual feedback was given following responses, indicating whether the response was correct (green square), incorrect (red square), or too slow (yellow square). Participants completed five training blocks in a session that lasted ~40 min. Behavioral data for each block were analyzed according to signal detection theory (Green and Swets, 1966). Sensitivity (d') was calculated according to the following equation: $d' = z(\mathrm{H}) - z(\mathrm{FA})$, where z(H) and z(FA) represent the transformation of the hit and false-alarm rates into z scores (Macmillan and Creelman, 1991). In experiments 1 and 2, hits were the R385-R500 trials, reported as originating from different locations, and false alarms were R385-R385 trials, reported as originating from different locations.

EEG acquisition and preprocessing

Continuous EEG was acquired at 512 Hz through a 128 channel Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands) referenced to the CMS-DRL ground (which functions as a feedback loop driving the average potential across the montage as close as possible to the amplifier zero). Details of this circuitry, including a diagram can be found on the Biosemi website (http://www.biosemi.com/pics/zero_ref1_big.gif). All analyses were conducted using CarTool software (http://brainmapping.unige.ch/Cartool.htm). Epochs of EEG from 98 ms prestimulus to 486 ms poststimulus onset (i.e., 50 data points before and 250 data points after stimulus onset) were averaged for each of the stimulus position and from each subject. To maintain equivalent signal-to-noise ratios for AEPs in response to each condition, all trials in response to infrequent stimuli (i.e., in experiment 1, R500; in experiment 2, L500) and only trials from frequent stimuli (i.e., in experiment 1, R385; in experiment 2, L385) that immediately preceded infrequent trials were considered during epoching. In addition to the application of an automated artifact criterion of ±100 μV, epochs with blinks, eye movements, or other sources of transient noise were also rejected. Baseline correction was applied to the 98 ms prestimulus period. Before group averaging, data at artifact electrodes from each subject were interpolated (Perrin et al., 1987), and the data were recalculated against the average reference and bandpass filtered (0.68–40 Hz).

EEG analyses and source estimation

General analysis strategy. The main objective of this study was to examine the spatiotemporal mechanisms mediating plasticity in the spatial representation of sounds. Electrophysiological analyses, based on an electrical neuroimaging approach, using both local and global measures of the electric field at the scalp, were used. These allowed us to differentiate effects following from modulation in the strength of responses of statistically indistinguishable brain generators from alterations in the configuration of these generators (viz. the topography of the electric field at the scalp) as well as latency shifts in brain processes across experimental conditions. Because the electrophysiological methods have been extensively detailed previously (Michel et al., 2004; Murray et al., 2004; De Santis et al., 2007; for a recent publication of formulas, see Murray et al., 2006), we provide only the essential details here.

AEP waveform analyses. As a first level of analysis and to minimize the possibility of missed effects (type II errors), we analyzed waveform data from all electrodes as a function of time after stimulus onset in a series of pairwise comparisons (*t* tests). Correction was made for temporal autocorrelation at individual electrodes (Guthrie and Buchwald, 1991) through the application of an 11 contiguous data-point temporal criterion for the persistence of differential effects. The results of this analysis are presented as an intensity plot with the *x*-, *y*-, and *z*-axes, respectively, representing time (after stimulus onset), electrode location, and the *t* test result (indicated by a color value) at each data point. We would emphasize that although these analyses give a visual impression of specific effects within the dataset, our conclusions are principally based on global measures of the electric field at the scalp.

Topographic analyses. Topographic analyses were conducted in two ways. The first was a topographic pattern analysis on the collective dataset for each experiment (i.e., both as a function of time within each AEP and also a function of stimulus position and pretraining vs post-training sessions). This pattern analysis uses a hierarchical agglomerative clustering algorithm to identify the predominant topographies (i.e., maps) and their sequence within a given dataset (these methods are implemented in Cartool software) (see also Tibshirani et al., 2005). The optimal number of maps (i.e., the minimal number of maps that accounts for the greatest variance of the dataset) is determined using a modified Krzanowski-Lai criterion (Krzanowski and Lai, 1985).

Importantly, the topography of the electric field is independent of reference electrode (cf. Michel et al., 2004), and the pattern analysis is insensitive to pure amplitude modulations across conditions because normalized maps are compared. The pattern of maps observed in the group-averaged data were statistically tested by comparing each of these maps with the moment-by-moment scalp topography of individual subjects' AEPs from each condition. In other words, the methods described above generate a hypothesis concerning the sequence of maps observed in the AEPs and any differences between stimulus positions and/or sessions. To statistically assess this hypothesis, each time point of each AEP from each subject was labeled according to the map with which it best correlated spatially (Brandeis et al., 1995; Murray et al., 2006). We, hereafter, refer to this procedure as "fitting." This fitting method determines whether a given stimulus lateralization and/or experimental session is more often described by one map versus another, and therefore if different generator configurations better account for particular conditions/sessions. In addition to testing for modulations in the electric field to-

pography across conditions, this analysis also provides a more objective means of defining AEP components. That is, we here define an AEP component as a time period of stable scalp topography.

The second analysis of topography entailed calculation of the global dissimilarity between two maps (Lehmann and Skrandies, 1980). Global dissimilarity is an index of configuration differences between two electric fields that is independent of their strength (normalized data are compared). Values can range from 0 to 2, with 0 indicative of topographic homogeneity and 2 indicative of topographic inversion. It is calculated as the root mean square of the difference between two normalized maps and is statistically assessed using a Monte Carlo nonparametric bootstrapping procedure (Manly, 1991). This analysis is currently limited to pairwise contrasts. Thus, in the present study, dissimilarity was always measured between AEPs to the two lateralized stimuli from the pretraining and post-training sessions, separately. Because electric field changes are indicative of changes in the underlying generator configuration (Lehmann, 1987), this test provides a statistical means of determining if and when the brain network activated by 385 and 500 μs ITD cues differ.

Source estimations. We estimated the sources in the brain underlying the AEPs from each stimulus type and sessions using the local autoregressive averages (LAURA) distributed linear inverse solution (Grave de Peralta Menendez et al., 2001; 2004; for a comparison of inverse solution methods, see Michel et al., 2004). LAURA selects the source configuration that better mimics the biophysical behavior of electric vector fields (i.e., activity at one point depends on the activity at neighboring points according to electromagnetic laws). The solution space was calculated on a realistic head model that included 4024 nodes, selected from a $6 \times 6 \times 6$ mm grid equally distributed within the gray matter of the average brain of the Montreal Neurological Institute. The results of the above topographic pattern analysis defined time periods for which intracranial sources were estimated. We emphasize that these estimations, in the present study, provide visualization, rather than a statistical analysis, of the likely underlying sources.

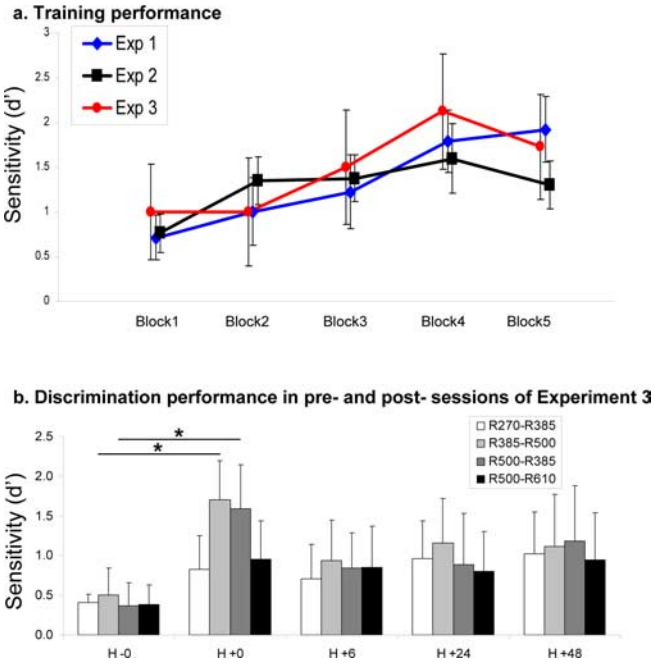

Figure 2. Behavioral results. ***a***, Group-averaged sensitivity ($d' \pm$ SEM) in discriminating sound lateralizations is plotted as a function of training block for experiment 1 (blue line), experiment 2 (black line), and experiment 3 (red line). Sensitivity significantly increased with training for both experiments, with no evidence of differences between participants in experiments 1, 2, and 3 (see Results for details). ***b***, Group-averaged sensitivity ($d' \pm$ SEM) in discriminating sound lateralizations is plotted as a function of pretraining and post-training sessions for experiment 3. The training improved discrimination performance only for pairs involving the two trained positions and did not persist over time. Exp, Experiment. *$p < 0.05$.

Results

Behavioral results

Training improved performance on auditory spatial discrimination during each of the three experiments (Fig. 2*a*). During experiment 1, all but one subject had a d' value <1.0 on the first training block, indicating that discriminating R385 and R500 lateralizations was difficult. Performance accuracy on the first block was 62.3 ± 3.9% correct (mean ± SEM) and on the fifth block was 79.3 ± 3.9% correct. Performance improved significantly across training blocks (d' submitted to a one-way repeated-measure ANOVA showed a main effect of block; $F_{(1,9)} = 13.12$; $p < 0.01$). Performance was significantly better on the fifth block than on either the first ($t_{(9)} = 4.681$; $p < 0.001$) or the second blocks ($t_{(9)} = 4.944$; $p < 0.001$). Performance was also better on the fourth than either the first ($t_{(9)} = 4.048$; $p < 0.003$) or the second blocks ($t_{(9)} = 3.862$; $p < 0.005$). During experiment 2, all but three subjects had d' values <1.0 on the first block. Performance accuracy on the first block was 63.6 ± 3.9% correct and on the fifth block was 72.2 ± 4.0% correct. As in experiment 1, submission of d' values to an ANOVA revealed that performance improved significantly across training blocks (main effect of block; $F_{(1,9)} = 14.60$; $p < 0.01$). Performance was significantly better on the fifth than the first block ($t_{(9)} = 2.843$; $p < 0.03$) and in the fourth than for the first block ($t_{(9)} = 2.876$; $p < 0.03$); this pattern of results mirrors that observed for experiment 1. During experiment 3, all but two subjects had d' values <1.0 on the first block. Performance accuracy on the first block was 65.2 ± 7.7% correct and on the fifth block was 75 ± 6.5% correct. As in experiments 1 and 2, submission of d' values to an ANOVA revealed that performance improved significantly across training blocks (main effect of block; $F_{(1,6)} = 20.95$; $p < 0.05$). Performance was significantly better on the fifth than the first block ($t_{(5)} = 6.60$; $p < 0.003$) and on the fourth than the first block ($t_{(5)} = 7.74$; $p < 0.01$). This pattern of results was identical to that of experiments 1 and 2. Sensitivity measures (d') from all three experiments were submitted to a repeated-measures ANOVA using the experiment as a between subjects factor and the block as the within subjects factor. The main effect of block was significant ($F_{(1,26)} = 3.319$; $p < 0.03$) and the main effect of group failed to meet the 0.05 significance criterion ($F_{(1,26)} = 1.962$; $p > 0.8$). These results indicate similar performance improvement with training across all three experiments (Fig. 2*a*).

Inspection of d' values from experiment 3 suggests that training improved discrimination performance only during the session immediately after training (i.e., H + 0 and not H + 6, H + 24, and H + 48) and only for pairs involving both of the trained positions. Training effects did not persist 6 h after training and did not generalize to adjacent untrained positions (Fig. 2*b*). Sensitivity (d') values from the pretraining and post-training sessions were submitted to an ANOVA. There was a significant interaction between the within-subjects factors of stimulus pair and session ($F_{(2,6)} = 2.364$; $p < 0.05$). We therefore conducted additional ANOVAs that were limited to each stimulus pair. Significant main effects of session were observed only for pairs involving both of the trained positions (R385-R500: $F_{(1,6)} = 8.42$, $p < 0.003$; R500-R385: $F_{(1,6)} = 4.47$; $p < 0.05$), for all other pairs, the effect of session failed to meet the 0.05 significance criterion. *Post hoc* analyses revealed that sensitivity improved significantly between H − 0 and H + 0 for the R385-R500 and R500-R385 pairs ($t_{(5)} = 6.73$, $p < 0.003$ and $t_{(5)} = 3.89$, $p < 0.03$, respectively). But this effect declined significantly within 6 h after the training [i.e., H + 0 vs H + 6 (R385-R500: $t_{(5)} = 4.90$, $p < 0.005$; R500-R385: $t_{(5)} = 3.17$, $p < 0.03$); H + 0 vs H + 24 (R385-R500: $t_{(5)} = 2.72$,

$p < 0.05$; R500-R385: $t_{(5)} = 4.86$, $p < 0.005$); H + 0 vs H + 48 (R385-R500: $t_{(5)} = 3.24$, $p < 0.03$; R500-R385: $t_{(5)} = 4.86$, $p = 0.055$)]. To test whether training-induced performance benefits already began to decline during the course of the H + 0 session itself, we split the data from this session in half chronologically and submitted them to a 2 × 4 ANOVA using session portion (first vs second half) and stimulus pair as within subjects factors. The main effect of session portion failed to meet the 0.05 significance criterion ($F_{(1,6)} = 0.926$; $p = 0.38$), suggesting that sensitivity did not decline over the course of the H + 0 session.

Despite the short duration of plasticity (<6 h), such a procedure may be useful in a clinical setting for training-based rehabilitation. Indeed, previous studies have shown that repetitive application of treatment with transient effects may lead to long-lasting changes (Schindler et al., 2002).

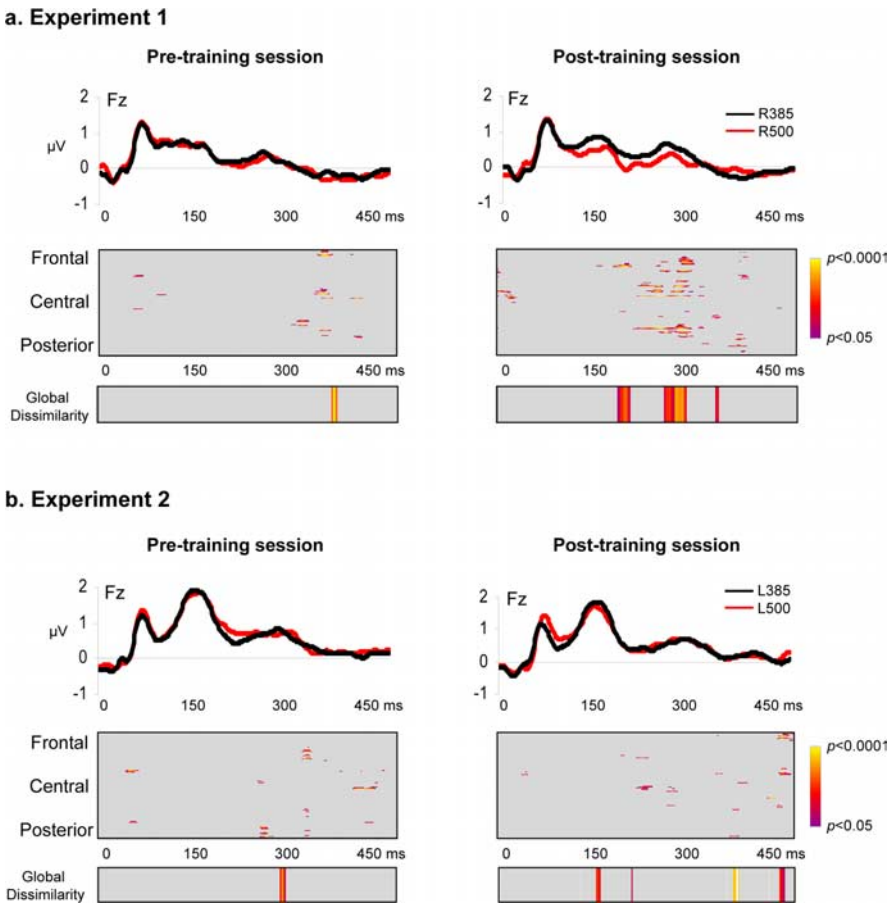

Figure 3. Electrophysiological results comparing responses to sound lateralizations. ***a***, Results from experiment 1 during the pretraining (left) and post-training (right) sessions. Group-averaged ($n = 10$) AEPs from an exemplar scalp site (frontal electrode) are plotted (voltage as a function of time). Below is an intensity plot, illustrating statistical tests across the entire electrode montage. The *x*-, *y*-, and *z*-axes, illustrate, respectively, time, electrode, and *p* value of a paired *t* test. The bottom-most plot within each panel displays the result of the test of global dissimilarity, which assessed topographic differences between conditions as a function of time. ***b***, Results from experiment 2 during the pretraining (left) and post-training (right) sessions; same conventions as in ***a***. Note that only the post-training session from experiment 1 exhibited robust response differences (see Results for details). Fz, Frontal electrode.

AEP waveform analyses

Figure 3 shows group-averaged AEPs in response to each session, stimulus condition, and experiment from an exemplar frontal electrode. This figure also illustrates the results of paired contrasts across the entire electrode montage separated between pretraining and post-training sessions for experiments 1 and 2. These contrasts reveal that AEP differences between the two stimulus positions were observed only for experiment 1 during the post-training session. Significant differences were widespread over the electrode montage during the ~200–300 ms poststimulus onset interval. No robust differences were observed in the pretraining session of either experiment. Nor were differences observed during the post-training session of experiment 2. Given this apparent selectivity of effects when the data from each electrode and session were separately analyzed, we focus our discussion on the analyses of the global electric field on the data from experiment 1, although all analyses were conducted on both experiments. As noted in Materials and Methods, analyses of the global electric field were prioritized because they are reference independent and also provide statistically based information on whether effects stem from topographic and/or strength modulations.

Topographic pattern analysis and global dissimilarity analysis

The output of the topographic pattern analysis of the collective data from experiment 1 is displayed in Figure 4*a*. Multiple maps were identified in the group-averaged data over the 0–39 ms interval, and these were differentially observed across sessions but not lateralizations. That is, there was a significant interaction between session and map over 0–39 ms after submitting these maps observed at the group-average level to the fitting procedure at the individual subject level ($F_{(1,9)} = 7.19$; $p = 0.025$). Additional ANOVAs were therefore conducted for each session, separately. Although both maps were equally often observed during the pretraining session (i.e., no main effects or interactions were observed), the map framed by a dotted line was significantly more often observed during the post-training session, as indicated by the main effect of the map ($F_{(1,9)} = 10.24$; $p = 0.011$). Single maps were identified in common across both lateralizations and both sessions over the 41–72, 74–135, 137–193, and 301–488 ms periods.

In contrast, over the 195–250 ms poststimulus period, different maps described AEPs in response to the R500 and R385 conditions during the post-training but not pretraining session. These maps are framed in black and dark green, respectively, in Figure 4*a*. The global dissimilarity between these maps is 0.374. As above, this pattern observed in the group-averaged data were tested in the data of individual subjects, using the above-mentioned fitting procedure (see Materials and Methods). The values of the fitting procedure (i.e., the amount of time over the 195–250 ms interval when each of the framed maps in Fig. 4*a* better correlated spatially with the data from each subject and condition, hereafter termed "map presence") were then submitted to a repeated-measures ANOVA using session, stimulus lateralization, and map as within-subject factors (Fig. 4*b*). There

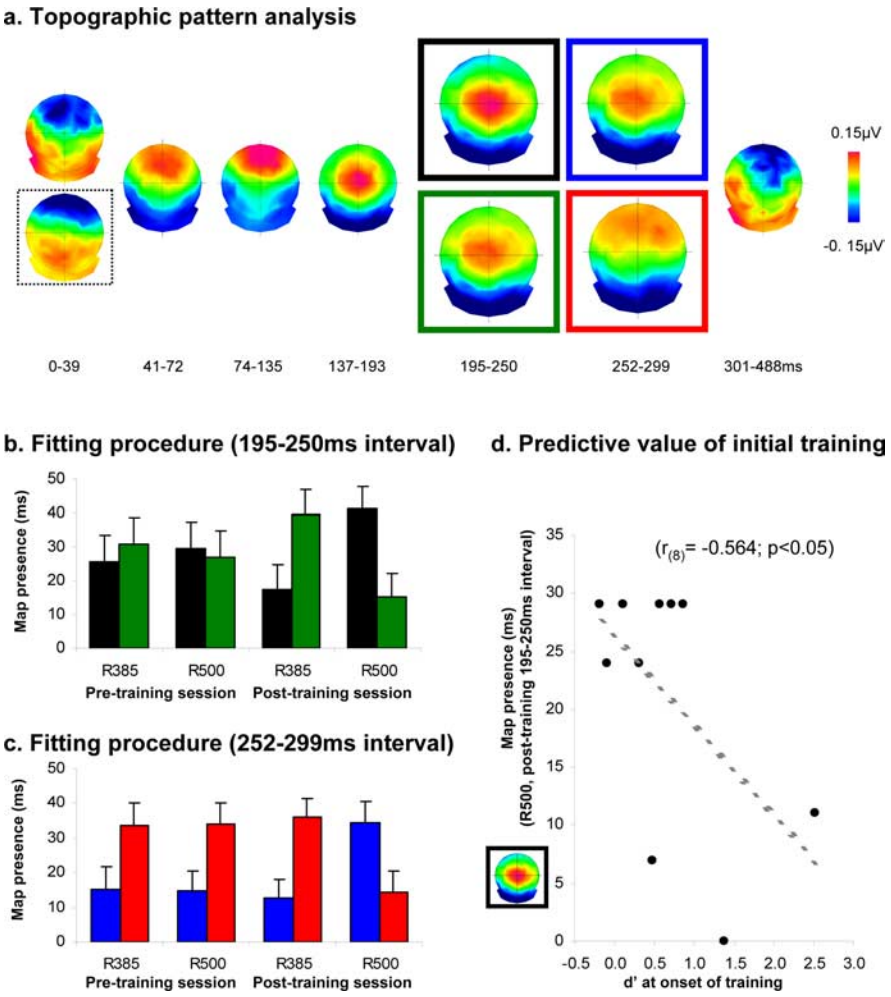

Figure 4. Electrical neuroimaging results. ***a***, The topographic pattern analyses identified seven time periods of stable topography across the collective 488 ms poststimulus period from the four conditions of experiment 1. All topographies are shown with the nasion upward and left scalp leftward. For some of these time periods, multiple topographies were identified in the group-average AEPs. These topographies are framed. The reliability of this observation at the group-average level was then assessed at the single-subject level using the fitting procedure (see Materials and Methods). ***b***, Over the 195–250 ms poststimulus period, different maps (framed in black and dark green) described AEPs in response to the R500 and R385 conditions during the post-training but not pretraining session. There was a significant three-way interaction between session, stimulus lateralization, and map. Additional analyses further revealed a significant two-way interaction between stimulus lateralization and map. Error bars indicate SEM. ***c***, Over the 252–299 ms poststimulus period, different maps again described AEPs in response to the R500 and R385 conditions during the post-training but not pretraining session (framed in gray and light green). As above, there was a significant three-way interaction between session, stimulus lateralization, and map. Additional analyses further revealed a significant two-way interaction between stimulus lateralization and map. Error bars indicate SEM. ***d***, The presence of maps in response to R500 after training significantly correlates with the initial discrimination performance (d'1) ($r_{(9)} = 0.567$; $p < 0.05$).

different configurations of intracranial generators (Lehmann, 1987), this pattern of results indicates that training lead to the activity of (partially) distinct brain networks in response to each of the two stimulus positions. We also tested for a linear correlation between map presence over the 195–250 ms interval and sensitivity at the onset of training to assess whether performance measures could be used to predict electrophysiological plasticity, which would be particularly important for planned extension of this research to clinical populations. We observed a significant negative correlation between sensitivity at the onset of training and the presence of the "black" map post-training ($r_{(8)} = -0.564$; $p < 0.05$), suggesting that the more a subject has room to improve his/her performance, the more the black map will account for his/her post-training AEPs in response to the R500 stimulus (Fig. 4*d*). We would note that this analysis does not account for how training directly impacted a subject's performance. Rather, this analysis would suggest that pretraining performance is predictive of post-training AEP topography, and by extension, configurations of intracranial generators.

Over the 252–299 ms poststimulus period, different maps described AEPs in response to the R500 and R385 conditions during the post-training but not pretraining session. These maps are framed in gray and light green, respectively, in Figure 4*a*. The global dissimilarity between these maps is 0.469. After the fitting procedure, analysis of map presence over this period revealed significant interactions between session and map ($F_{(1,9)} = 5.17$; $p = 0.049$) and between stimulus lateralization and map ($F_{(1,9)} = 8.15$; $p = 0.019$). Additional ANOVAs were therefore conducted for each session, separately. For the pretraining session, there was a main effect of map ($F_{(1,9)} = 5.33$; $p = 0.046$). Neither the main effect of stimulus lateralization nor the interaction between factors reached the 0.05 significance criterion. This pattern of results indicates that the map framed in light green predominated responses during the pretraining session (Fig. 4*c*, bar graphs). For the post-training, there was a significant interaction between stimulus lateralization and map ($F_{(1,9)} = 9.77$; $p = 0.012$), whereas neither main effect reached our 0.05 significance criterion. Similar to the effects over the 195–250 ms interval, this pattern indicates that during the post-training session, the map framed in gray predominated responses to the R500 lateralization, whereas the map framed in light green predominated responses to the R385 lateralization (Fig. 4*c*, bar graphs).

To complement the classification approach of the topographic pattern analysis and fitting procedure, we conducted a time-point by time-point statistical contrast of the global dissim-

was a significant interaction between session, stimulus lateralization, and map ($F_{(1,9)} = 6.98$; $p < 0.03$) over the 195–250 ms poststimulus period. There was also a significant interaction between stimulus lateralization and map ($F_{(1,9)} = 6.99$; $p < 0.03$). None of the other main effects (stimulus lateralization or map) or any other interaction reached our 0.05 significance criterion. We therefore conducted additional ANOVAs for each session, separately. For the pretraining session, neither main effect nor the interaction reached the 0.05 significance criterion. For the post-training session, there was a significant interaction between stimulus lateralization and map ($F_{(1,9)} = 8.39$; $p = 0.018$). That is, the map framed in black was more often observed in response to the R500 condition, whereas the map framed in dark green was more often observed in response to the R385 condition (Fig. 4*b*). Because different topographies at the scalp forcibly follow from

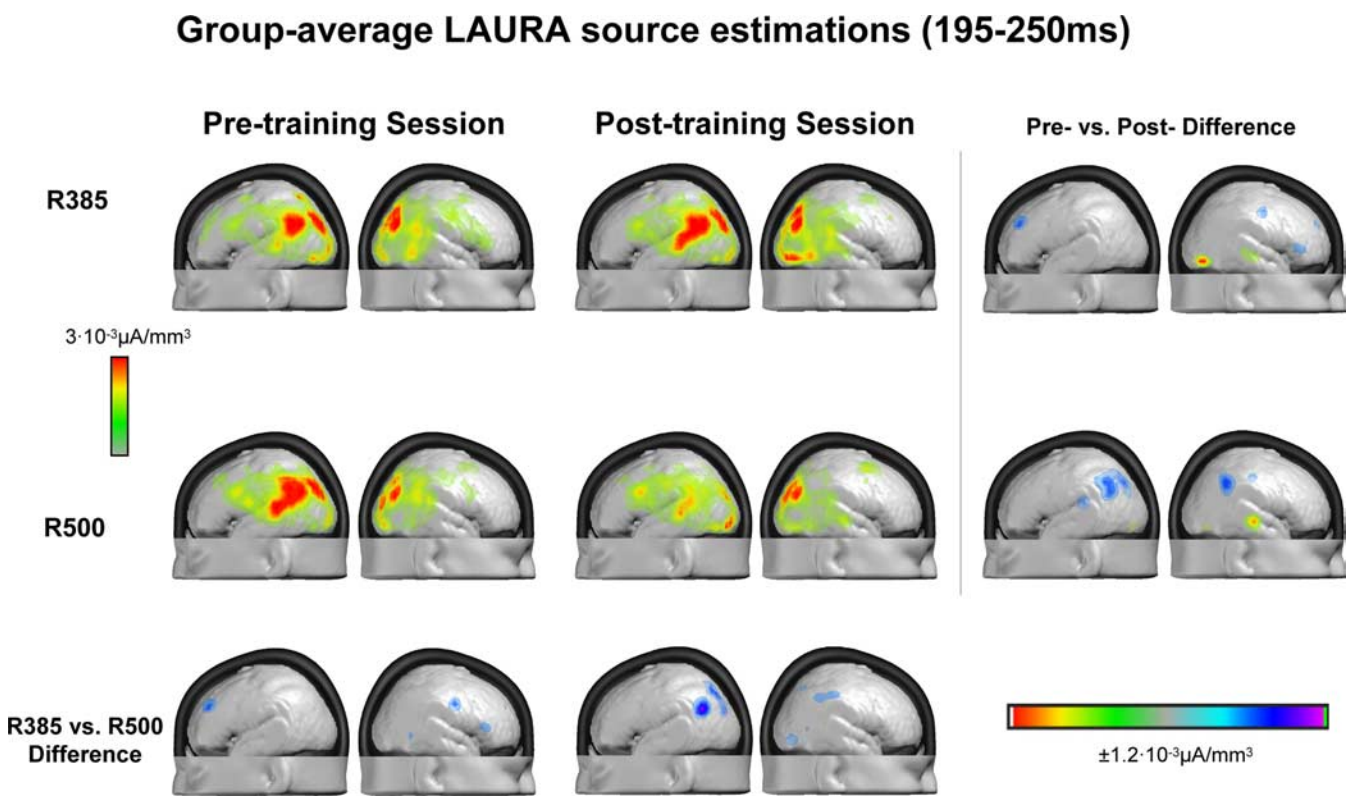

Figure 5. Source estimations. Group-averaged ($n = 10$) LAURA distributed linear source estimations were calculated over the 195–250 ms time period pretraining and post-training and are shown in response to the R385 and R500 conditions. The mean difference between these source estimations is also shown. Both the R385 and R500 lateralizations exhibited prominent sources within the parietal cortex bilaterally. Weaker sources were also observed in the prefrontal cortex. The difference revealed weaker activations to the R500 stimulus within the left inferior parietal cortex.

ilarity between responses to stimulus lateralizations of each session. The results of this analysis appear in Figure 3. This analysis confirmed that there was a significant topographic difference over the 195–215 ms and 271–307 ms intervals between responses to each lateralization during the post-training session. No significant differences were observed for the pretraining session of experiment 1.

To assess both the generalization of these effects to other lateralizations and also to rule out an explanation of these results in terms of general repetition, we conducted an identical topographic pattern analysis and analyses of global dissimilarity on the AEPs from experiment 2. No time period showed a significant interaction between session, condition, and map (all p values >0.25). Nor was there evidence of effects on global dissimilarity for either the pretraining or post-training session of experiment 2.

Source estimations

The likely intracranial generators of these effects were visualized using the LAURA distributed linear inverse solution. Source estimations were calculated using the data from experiment 1 over the 195–250 ms interval (i.e., when topographic modulations were observed). Data from each subject were averaged across the 195–250 ms interval to generate to a single data point per subject for each session and lateralization, separately. Source estimations were then calculated and group averaged (Fig. 5). Both the R385 and R500 lateralizations exhibited prominent sources within the parietal cortex bilaterally. Weaker sources were also observed in the prefrontal cortex. The group-averaged difference between source estimations for these conditions (scaled at one-third the current density of the original source estimations) was also calculated for the pretraining and post-training sessions, separately. This difference revealed weaker activations to the R500 stimulus within the left parietal cortex (maximal differences at −50, −62, 24 mm and −18, −78, 36 mm using the coordinate system of Talairach and Tournoux, 1988). These maxima correspond to Brodmann's areas 7 and 39, respectively.

Discussion

Auditory processing is thought to be mediated by partially segregated "what" and "where" pathways involved in sound recognition and localization, respectively (Rauschecker, 1998; Hackett et al., 1999; Clarke et al., 2000, 2002; Tian et al., 2001; Clarke and Thiran, 2004; De Santis et al., 2007). Previous studies have demonstrated plastic changes within the "what" stream as subjects learned to discriminate between frequency, duration, or intensity of sounds or between semantic features of complex environmental sounds or speech (Tremblay et al., 1998; Jäncke et al., 2001; Syka, 2002; Bergerbest et al., 2004; Gottselig et al., 2004). To our knowledge, ours is the first demonstration in humans that learning-induced plasticity is also observed for spatial "where" functions; the electrophysiological manifestations of which can be predicted by pretraining performance measures. In addition to providing insights on the neurophysiological mechanisms of auditory spatial representations, our results open possible training-based neurorehabilitation strategies (Bellmann et al., 2001; Spierer et al., 2007) involving repeated training sessions to induce long-lasting effects (Schindler et al., 2002).

Training for 40 min improved spatial discrimination performance and changed neurophysiological responses during subsequent passive listening. The time course of auditory perceptual learning is highly variable and depends on factors including the type of task and its difficulty as well as the complexity of the

trained auditory stimuli (Watson, 1980). In our experiments, most subjects performed poorly during the first training block and showed significant improvements after completing the training. Such rapid modification of auditory spatial processing has been previously shown using similar stimuli (Wright and Fitzgerald, 2001) and has also been demonstrated by Recanzone (1998), in which visually driven alteration of auditory spatial representations occurs after a 20–30 min training period. Wright and Fitzgerald (2001) had subjects indicate whether a target sound location was presented in the first or second position in a pair of sounds lateralized with different ITDs or IIDs. Extending the training over days led to further improvement in discriminating stimuli lateralized with IID but not with ITDs. Similarly, experiment 3 provides no evidence for long-lasting training effects with ITD-defined lateralizations. Effects of training on AEPs recorded subsequently during passive listening were also specific to the more lateral and less frequently presented location (R500), indicative of a learning-induced MMN. Such a pattern of results is not readily explained by a general learning or practice effect. Before training, subjects were unable to discriminate reliably between the two spatial positions (R385 and R500), and there was no evidence of neural response differences. Rather, responses to both positions engaged indistinguishable parietotemporal networks bilaterally. Effects on AEPs were in terms of the electric field topography and by extension the configuration of the underlying brain generators. Source estimations localized these changes to the left inferior parietal cortices.

In addition to the post-training AEP effects being limited to one of the trained positions, there was no evidence of generalization of training-induced effects to either the symmetrical positions in the opposite hemispace (experiment 2) or to equidistant spatial separations either medially or laterally within the same hemispace (experiment 3). The extent of generalization is typically interpreted as indicative of the level of processing that is affected by training (Fahle, 2005). In animal models, learning-induced changes in neuronal tuning at relatively early processing stages are believed to reflect specific effects of training (Irvine et al., 2000). Several psychophysical studies in humans have demonstrated improvements in perceptual discrimination that were specific to the trained stimuli (Karni and Sagi, 1991; Ahissar and Hochstein, 1997; Hawkey et al., 2004; Fitzgerald and Wright, 2005) or stimulus feature (Wright et al., 2001). However, other studies reported some generalization to untrained stimuli [tone sequences and synthetic phonemes, in Gottselig et al. (2004) and Tremblay et al. (1997), respectively]. Effects in our study were restricted to the trained positions but did not depend on the specific order in which stimuli at these positions were presented or depend on whether this order matched that used during training. This pattern is consistent with mechanisms involving the refinement of spatial representations and/or coding for the trained locations, rather than the establishment of spatial anchors, mnemonic templates, or general improvement in discriminating ITD cues. The specificity of our effects suggests that training affected relatively low-level process. This is further supported by the fact that training modified AEP responses passively recorded after training.

Differences between neural responses to the two positions during the post-training recordings occurred over the 195–250 ms poststimulus interval. Two lines of evidence suggest that this period entails the encoding of cortical representations of auditory space, rather than higher order process. First, it corresponds to the time period over which the MMN response has been observed to changes in the position of a sequence of sounds, particularly when behavioral discrimination is difficult and/or when there is minimal separation in terms of the physical features of the stimuli (Näätänen and Escera, 2000). We interpret the response change during the MMN temporal window as indicating that training-induced plasticity of the cortical representations of the two positions and/or the cortical mechanisms involved in position discrimination (Näätänen et al., 1978). It is worth noting that similarly early (and often earlier) effects have been observed on auditory processing (Woldorff and Hillyard, 1991), suggesting that the responses over the 195–250 ms period are not simply exogenous but rather also subject to endogenous processes. Second, the timing of the present effects are consistent with a multiphase model of auditory spatial processing proposed by our group (Ducommun et al., 2002; Tardif et al., 2006), wherein different spatial cues are integrated over the ~140–255 ms period and wherein spatial information is consolidated within different reference frames over the ~255–400 ms period.

The electrical neuroimaging analyses conducted in this study permit some speculation on the likely mechanism mediating training-induced plasticity of auditory spatial representations, beyond simply invoking the emergence of the MMN. Several types of neurophysiological modifications are conceivable, including alterations in the quantity of neurons recruited to respond to stimulation of a particular spatial location, in the synchrony of such neural responses, and in the spatial tuning of neural populations (for review, see Gilbert et al., 2001; Ohl and Scheich, 2005). Effects in our study were limited to topographic changes in the response to the more lateral and less frequently presented of the two simulated positions, with no evidence of modifications in response strength, indicative of generator changes that result in an MMN. Such results run counter to what would have been predicted had either neuronal recruitment or response synchrony been modified. For one, these mechanisms would likely not have specifically affected just one of the stimulated positions. Likewise, responses to both positions would be affected in the case of a general attention or arousal mechanism or a general learning-induced change in spatial coding. Second, these mechanisms would likely have resulted in a change in the strength of responses, rather than the configuration of underlying brain generators.

Our results are consistent with the refinement of neuronal spatial tuning at a population level. Previous studies have shown that pitch training was accompanied by an increase in neuronal selectivity and decrease of the corresponding cortical representation (Weinberger et al., 1990; Edeline et al., 1993; Recanzone et al., 1993). The present study revealed that training selectively changed the topography of the electric field yielded by the target stimulus by decreasing the activity of sources within left inferior parietal cortices (Fig. 5). A putative neural mechanism may involve inhibitory processes in generating plasticity via the exclusion of the activity of less specific neurons (Ghose, 2004; Ohl and Scheich, 2005) or noise-related responses (Rainer et al., 2004). Others have further extended this notion in terms of refining a perceptual template (Li et al., 2004), wherein those neurons that respond most strongly might not actually convey the greatest amount of information regarding a learned discrimination. Rather, greater differential responses to the spatial positions may instead occur in neurons exhibiting weaker response magnitude. In which case, it would be beneficial to inhibit such strongly responding neurons to produce a more informative response profile (Ghose, 2004). On the whole, our results lend additional support to the concept of auditory spatial representations based on population coding, which have been proposed in animal mod-

els (Recanzone et al., 1993; Rauschecker and Tian, 2000; King et al., 2001; Middlebrooks et al., 2002; Woods et al., 2006).

Source estimations localized the present effects to regions of the left inferior parietal cortex (Fig. 5). Parietal and posterior temporal cortices have been shown to be implicated in auditory spatial functions in man (Griffiths et al., 1998; Bushara et al., 1999; Maeder et al., 2001; Weeks et al., 2001; Ducommun et al., 2002; Deouell et al., 2006; Sonnadara et al., 2006; Tardif et al., 2006; De Santis et al., 2007) and nonhuman primate (Stricane et al., 1996; Schlack et al., 2005). Previous studies on ITD processing have shown that left hemisphere responds more specifically to stimuli lateralized in the right hemispace whereas right hemisphere respond to stimuli in the left or right hemispace (Kuwada and Yin, 1983; Caird and Klinke, 1987).

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