DTD 5

ARTICLE IN PRESS

YNIMG-03640; No. of pages: 9; 4C:

ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage xx (2005) xxx – xxx

Improvement-related functional plasticity following pitch memory training

Nadine Gaab,[a] Christian Gaser,[b] and Gottfried Schlaug[a,*]

[a]*Department of Neurology, Neuroimaging Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA*
[b]*Department of Psychiatry, University of Jena, Philosophenweg 3, 07740 Jena, Germany*

Received 21 May 2005; revised 20 October 2005; accepted 18 November 2005

Functional activation patterns of an auditory working memory task were examined prior to and after 5 days of training (1 h/day). A control group with no training was scanned twice at the same intervals to assess test–retest effects. Based on behavioral improvement scores, the training group (*n* = 14) was divided into "Strong-Learners (SL)" and "Weak-Learners (WL)". No significant functional or structural brain differences were seen between the SL and WL groups prior to training. Imaging contrasts comparing post- with pre-training sessions showed a significant signal increase in the left Heschl's gyrus (HG) as well as in the left posterior superior temporal and supramarginal gyrus for the SL group, while the WL group showed significant signal increases in the left HG and anterior insular cortex as well as in a lingual–orbitofrontal–parahippocampal network. The test–retest analysis in the control group revealed only minimal signal increases in a right dorsolateral prefrontal region. A random effects analysis comparing the SL group with the WL group using the post- and pre-training contrast images showed increased activation only in the left supramarginal gyrus but not in HG. The importance of HG in pitch discrimination has been established in previous studies. The pitch memory component differentiated our task from a straight pitch discrimination task. It is most likely that the activation of the SMG reflects its importance in the short-term storage of auditory material, and it was this activation that best differentiated between subjects' levels of performance.

Introduction

The functional activation patterns of training-induced, short-term learning in the auditory domain have not been as well examined as those of training in other domains (e.g., motor skill learning). The few non-verbal, auditory training studies in humans that have been published to date (Cansino and Williamson, 1997; Menning et al., 2000; Jancke et al., 2001; Bosnyak et al., 2004) have not provided consistent results with regard to which brain regions are modulated by auditory training, whether training-induced performance improvement is associated with increases or decreases in regional signal, or how the improvement rate in the given task actually relates to the functional changes that were shown. In contrast, motor training studies (Jenkins et al., 1994; Schlaug et al., 1994; Karni et al., 1995; Hazeltine et al., 1997) have provided clear evidence for signal increases in primary and motor-related brain regions after an initial learning phase, while in later learning stages, more variation has been described both in the direction of signal change and the brain regions affected (Toni et al., 1998). Whether similar effects can be detected in the auditory domain and whether non-verbal auditory training leads to changes only in specialized neuronal circuits within the primary auditory cortex or also in higher order auditory association cortices has yet to be determined. Animal experiments have shown an increase in the cortical representation of trained frequencies as well as a correlation between the size of the cortical representation and training-induced performance improvement (Recanzone et al., 1993). Others have found no training-induced changes in frequency organization in the primary auditory cortex, but changes have been seen in the response characteristics of neurons with a frequency immediately above that of the trained frequency (Brown et al., 2004).

Studies in humans have shown a relationship between auditory training effects and electrophysiological changes in frequency discrimination designs (Cansino and Williamson, 1997; Menning et al., 2000). A recent auditory discrimination training study in non-musicians found evidence for an enhancement of auditory-evoked potentials that are typically localized to the secondary auditory cortex, but no enhancement was found in evoked potentials that are typically associated with primary auditory cortex (Bosnyak et al., 2004). An fMRI study revealed a relationship between signal decreases in both secondary and primary auditory cortices and performance gains in a group of strong improvers, while no significant regional changes were seen in either the group with weak improvement scores or the untrained control group (Jancke et al., 2001). The above-cited studies reported training-induced changes following frequency discrimi-

---

* Corresponding author. Fax: +1 617 632 892.
E-mail address: gschlaug@bidmc.harvard.edu (G. Schlaug).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.11.046

nation training and therefore can be classified as basic (perceptual) auditory learning studies (see Wright, 2001). The influence of training on more complex auditory tasks such as those involving non-verbal, auditory working memory requiring a higher cognitive load has not been examined. Some of the previous, perceptual auditory learning studies had various shortcomings such as (1) restricting the analysis to the superior temporal lobes only, (2) no examination of correlations between behavioral improvements and functional activation, and (3) lack of a control group to determine test–retest effects. The importance of correlating behavioral data with the functional anatomy was demonstrated by one of our recent studies in untrained subjects in which we found a correlation between good performance in a pitch memory task and increased activation of the supramarginal gyrus (Gaab et al., 2003). Considering the mixed findings of previous studies, the aim of our present study was to test (1) whether training on an auditory task that has components of both memory and pitch discrimination changes activity in primary and/or auditory association areas, and (2) whether auditory regions show MR signal increases or decreases as a result of the short-term training. In addition, our intent was to improve upon previous auditory training studies by acquiring whole brain data and, in particular, to examine training-induced changes outside of temporal lobe regions, control for test–retest by adding a control group that would be scanned twice, relate performance improvement with imaging changes, and use a sparse temporal fMRI technique that seems particularly well-suited for auditory studies (e.g., Gaab et al., 2003; Hall et al., 1999, 2000).

Materials and methods

Subjects

Twenty-four normal volunteers (age range: 19–34; 13 males, 11 females) participated in this study after giving written informed consent. Although some of the subjects had taken general, non-instrumental music education as part of their early education, none of the subjects had ever had any instrumental music training and, therefore, can be regarded as non-musicians. All subjects were strongly right handed (Annett, 1970) and had no history of neurological or hearing impairment. This study was approved by the institutional review board of the Beth Israel Deaconess Medical Center.

Experimental tasks

All subjects performed a pitch memory task, which was contrasted with a motor control task (see Fig. 1a). During the pitch memory task, subjects were instructed to listen to sequences of either 6 or 7 individual sine wave tones presented binaurally having a total duration of 4.6 s for each sequence. Subjects were asked to compare either the last or the second to last tone (specified by the visual prompt "*second last*" or "*very last*" which appeared immediately after the last tone was played) to the first tone and make a decision whether these tones were "*same*" or "*different*" (Fig. 1a). The total number of tones per sequence (6 or 7) and the comparison to be made ("*second last*" or "*very last*" tone with first tone) varied across sequences to reduce the possibility of inattention to the intervening tones. The interval between the end of each tone sequence and the start of the visual prompt was kept constant for both 6- and 7-tone sequences by introducing a short pause prior to the first tone for the 6-tone sequences. No analysis was planned to compare the 6-tone with the 7-tone conditions. Subjects were asked to keep their eyes open and fixate a cross in the middle of the screen that was interrupted only for the purpose of displaying the visual prompt. The motor control task was a rest condition with visual fixation, and subjects were asked to press a button in response to a visual prompt ("*right*" or "*left*"). The time lines for the pitch memory task and the motor control task were identical, and therefore, the timing of the given visual prompt did not differ between the two conditions. It always appeared 4.6 s after the beginning of the auditory stimulation and 4.6 s after the beginning of the silence period.

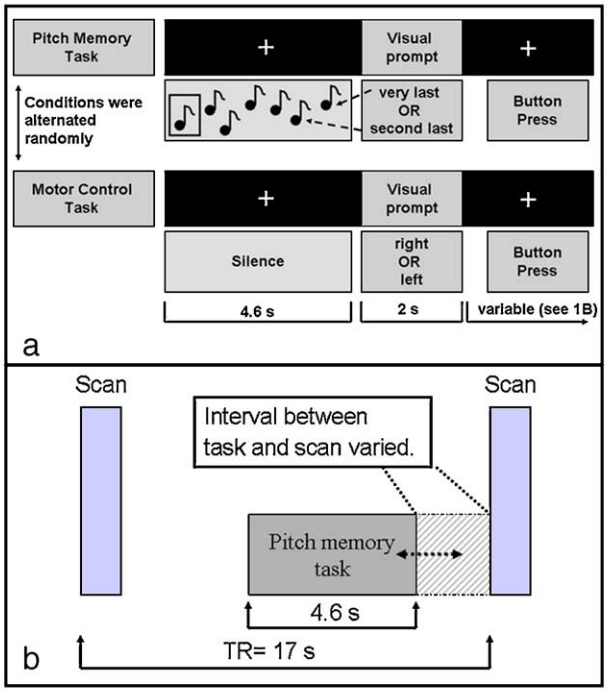

Fig. 1. Task design, timing (a), and MR image acquisition procedure (b) using a modified version of a sparse temporal sampling technique.

Each tone was 300 ms long with an attack and decay rate of 50 ms. All tones were generated using the software program Cool Edit Pro (Syntrillium Software). A pause of 300 ms separated each tone from the next. Target tones corresponded to the frequencies of semitones in the Western musical scale (based on A = 440 Hz) and ranged in frequency from 330 Hz (D #4) to 622 Hz (D #5). In those trials in which the first and last or second-to-last tone differed, the absolute difference in frequency varied between 41.2 Hz and 64.2 Hz (diff-1 = 41.2 Hz; diff-2 = 44.6 Hz; diff-3 = 51.7; diff-4 = 56.1 Hz and diff-5 = 64.2 Hz) among all trials. In each tone sequence, the frequency range from the lowest to the highest tone was not more than 108 Hz. The intervening microtones, whose purpose was solely to serve as distractors (modeled after Deutsch, 1974), deviated from the twelve semitones of the equal tempered system.

All 24 subjects were made familiar with the pitch memory task approximately 15 min prior to the first MR session. Investigators explained the tasks using simple drawings of various tone sequences and a fixed number of samples from the stimulation material. All subjects listened to the same number of trials. All subjects performed above chance in the pre-fMRI task familiarization phase. Behavioral performance during the actual fMRI session was calculated in terms of the number of correct responses

(%). The error rates (%) for each of the five frequency distances (diff-1 to diff-5) for the "different" conditions and the "*same*" condition were calculated separately.

Training

Fourteen of the 24 subjects were randomly assigned to the training group. The training took place on 5 consecutive days beginning the day after the pre-training fMRI session and ending the day before the post-training fMRI session (see Fig. 2). During each training session, subjects performed the previously described pitch memory task (see above) for 1 h with two short breaks in between. The auditory training was not adaptive. Training for the motor control task was not provided. The training duration (5 days) was chosen based on previous auditory training studies. Menning et al. (2000) trained subjects for 3 weeks, but their ability to discriminate improved rapidly only during the first week of training. Improvement gains were much smaller during the second week, and a nearly stable performance rate was recorded in the third week. Similarly, Jancke et al. (2001) showed significant performance gains and activity changes after a 1-week training in an auditory oddball procedure. Subjects in our training study did not receive any feedback for individual trials. However, they did receive feedback with regard to their overall performance (%correct trials) at the end of each of their training sessions. This experimental design was based on a study by Campbell and Small (1963) who found a considerably poorer performance rate in a frequency discrimination-training task when subjects were given feedback during the session compared to those who received no feedback on their performance.

Behavioral data analysis

The testing scores for the two fMRI sessions as well as the training scores (for each of the 5 training days) were obtained by dividing the number of trials answered correctly by the number of overall trials which resulted in a %correct value.

All statistical analyses were performed using the software program SPSS (SPSS Inc.). All subjects performed above chance in the pre-training fMRI session. An initial analysis of change scores (%change comparing the post-training to the pre-training session) across the entire training group indicated a high inter-individual variability. This suggested a large heterogeneity in the improvement scores and provided the possibility to divide the learning group into those that were "Strong-Learners" and those that were "Weak-Learners". A K-means cluster analysis as implemented in SPSS (SPSS Inc.) was performed to delineate the entire training group into two subgroups. Following this initial classification, between and within group differences for the behavioral improvement scores as well pre-training and post-training scores were analyzed using non-parametric tests since a normal distribution of the differences between the samples could not be assumed and the two subgroups had a small sample size.

We also performed Wilcoxon tests on the collective error rates of each group (pre-training vs. post-training) for each of the "*different*" conditions and the "*same*" condition in order to determine whether training effects showed any dependence on the frequency differences between the target and probe tones.

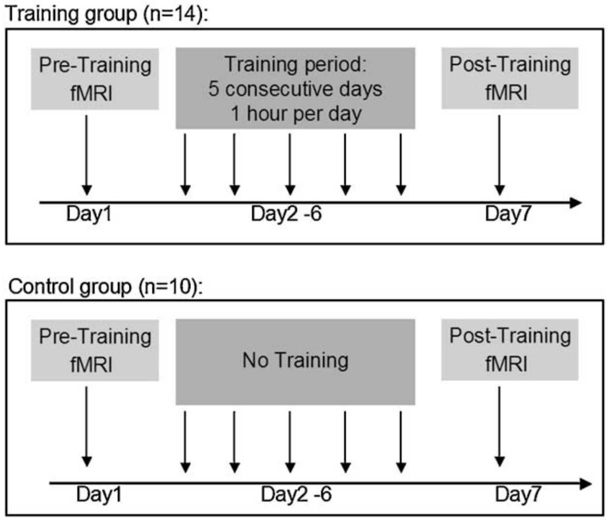

Fig. 2. Experimental design.

fMRI design and parameters

Functional magnetic resonance imaging (fMRI) was performed on a Siemens Vision (Siemens, Erlangen, Germany) 1.5 T whole-body MRI scanner, equipped with echo planar imaging (EPI) capabilities using the standard head coil for radio-frequency (RF) transmission and signal reception. A gradient-echo EPI sequence with an effective repetition time (TR) of 17 s, an echo time (TE) of 50 ms and a matrix of 64 × 64 was used. Using a mid-sagittal scout image, a total of 24 axial slices 4 × 4 × 6-mm voxel size) – parallel to the bi-commissural plane – were acquired over 2.75 s every 17 s. A TTL pulse from a PC triggered the initiation of the first set of 24 slices, and all subsequent MR acquisitions were synchronized with stimulus presentation. A high-resolution T1-weighted scan (1-mm^3 voxel size) was acquired for each subject for anatomical co-registration.

We used a variation of a sparse temporal sampling technique acquiring one set of 24 axial slices every 17 s to circumvent scanner noise interference. Although the TR was kept constant at 17 s, the MR acquisition actually varied in relation to the auditory stimulation. By moving the auditory stimulation frame within the 17 s time frame, the delay between the end of the stimulation and the onset of the next MR acquisition (see Fig. 1b) was varied with each trial. There was a minimum delay of 0 s and a maximum delay of 6 s between the end of the auditory stimulation and the onset of the MR acquisition (see Fig. 1b). We will refer to these imaging time points (ITP) as ITP0 through ITP6. Similarly, there was a minimum delay of 4 s and a maximum delay of 10 s between the end of the MR acquisition and the onset of the next auditory stimulation. We acquired 4 sets of axial images per time point during each run (in a randomized order), and each subject completed two runs. Thus, each acquisition time point was sampled 8 times.

fMRI data analysis

The SPM99 software package (Institute of Neurology, London, UK) was used to analyze our fMRI data. Each set of axial images acquired during individual subjects' pre- and post-training sessions was realigned to the first image. All images (pre- and post-training sessions combined) were then co-registered with the corresponding

T1-weighted data set, spatially normalized to the SPM99 template using a non-linear spatial transformation with 7 × 8 × 7 basis functions and smoothed with an isotropic Gaussian kernel (12-mm full-width-at-half-maximum). Conditions and subjects' effects were estimated using a general linear model (Friston et al., 1995). The effect of global differences in scan intensity was removed by scaling each scan in proportion to its global intensity. Low-frequency drifts were removed using a temporal high-pass filter with a cut-off of 200 s. The data were not convolved with the hemodynamic response function (HRF), and a low-pass filter was not applied. The pitch memory task was contrasted with the motor control task in order to obtain contrast images for each of the three groups. Second-level analyses with the SPM contrast images for the three groups were subsequently performed. We also determined signal changes in the right and left HG for each subgroup before and after training.

Voxel-based morphometry

An optimized method of voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Good et al., 2001) using the SPM99 package (Institute of Neurology, London, UK) was used to determine whether there were any pre-existing structural differences between our two subgroups.

Results

Behavioral results

A preliminary analysis of the entire training group indicated a high inter-individual variability in change scores ranging from −2% to +19%. Based on this preliminary analysis, we divided the training group into two subgroups, "Strong-Learners" (SL) and "Weak-Learners" (WL) using a K-mean cluster analysis as implemented in SPSS (SPSS Inc.). After two iterations, the analysis revealed two clusters with seven subjects in each cluster. The SL group showed a cluster center of 15.3% (improvement score), while the WL group revealed a cluster center of 4.8%. The two subgroups differed significantly from one another using a Mann–Whitney test ($Z = -3.035$, $P < 0.002$). A separation into three groups did not offer any useful results for further analysis, since one group contained 10 subjects (cluster center: 8.7%), while the other two groups consisted of considerably fewer subjects, one with three (cluster center: 18.7%) and one with only one subject (cluster center: −2%). The control group (whose members performed the experiment twice with no training in between) improved on average by 0.4%. A Kruskal–Wallis test with group as a factor revealed a significant difference in performance change scores ($\chi^2 = 13.45$; $df = 2$; $P < 0.001$) between the three groups (SL, WL, and control group). Post hoc Mann–Whitney tests showed a significant difference between the SL and WL groups ($Z = -3.148$; $P < 0.002$) and between the SL group and the control group ($Z = -3.035$; $P < 0.002$). However, there was no significant difference between the WL group and the control group ($Z = -1.561$; $P = 0.118$). The three groups did not differ in their performance scores prior to the training period ($\chi^2 = 0.617$; $df = 2$; $P = 0.735$). The SL and WL groups' behavioral performance data differed significantly during the post-training fMRI experiment and showed similar significant differences ($P < 0.05$) on each day of their training, although the differences on day 2 were only significant if tested one sided. Fig. 3a shows the learning curves for the two training groups over the 5-day training period.

Furthermore, we tested (Wilcoxon tests) whether the three groups showed a significant improvement by comparing the first and last testing session for the two training groups and the first and second testing session for the control group. The SL group ($Z = -2.36$, $P < 0.05$) and the WL group ($Z = -2.20$, $P < 0.05$) both showed a significant performance improvement comparing the post- with the pre-training tests. The control group showed no significant difference comparing the second to the first session ($Z = -0.17$, $P = 0.85$; Fig. 3b).

The Wilcoxon tests on the performance scores for the "*same*" condition and for each of the 5 frequency distances used in the "*different*" condition showed a significantly better performance within the SL group for the "*same*" condition ($Z = -2.375$; $P < 0.05$) and several of the "*different*" conditions ((diff-1) [(41.2 Hz) $Z = -2.226$; $P < 0.05$], diff-2 [(44.6 Hz) $Z = -1.841$; $P < 0.05$ one tailed] and the diff-5 [(64.2 Hz) $Z = -2.070$; $P < 0.05$]). The other two frequency distances (diff-3 and diff-4) showed a non-significant positive trend (diff-3: $Z = -1.342$; $P = 0.18$ and diff-4: $Z = -1.222$; $P = 0.222$). The WL group did not show any significant difference in their performance rates for any of the "*same*" or "*different*" conditions.

Imaging results

Baseline activation pattern

All three groups (Controls, WL, and SL) demonstrated a similar activation pattern in their baseline fMRI studies with no significant differences in all possible group comparisons ($P > 0.05$, corrected for multiple comparisons). Fig. 4 shows the combined activation pattern of all subjects that participated in the training study ($n = 14$) as an example of the activation pattern for each of the three groups. The group mean activation pattern for the contrast "pitch memory > motor control" revealed extended activation of the superior temporal

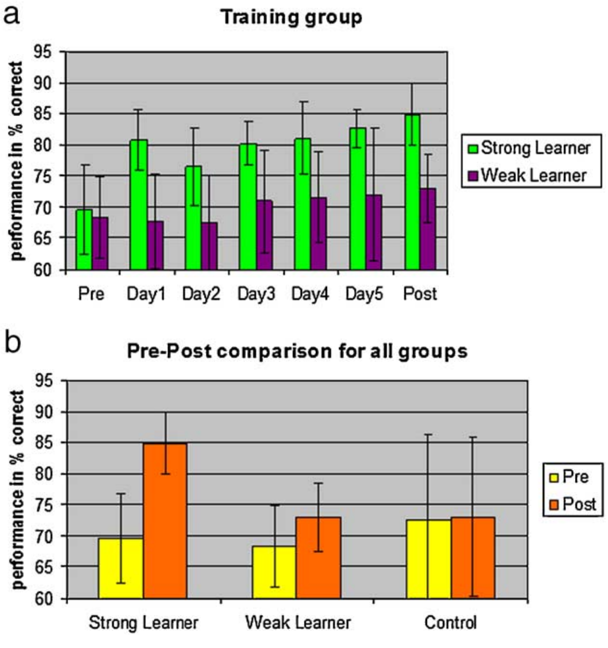

Fig. 3. Performance scores for the "Strong-Learners", "Weak-Learners", and Control Group.

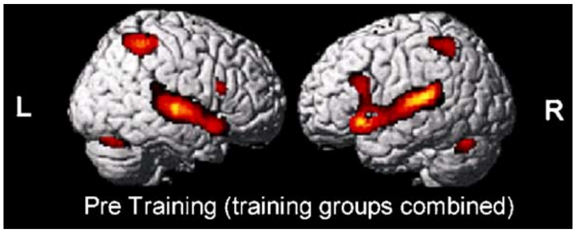

Fig. 4. Pre-training activation pattern for the entire training group shows prominent bilateral superior temporal gyrus, inferior frontal gyrus, intraparietal sulcus/superior parietal cortex, and cerebellar activation ($P < 0.05$, FWE, corrected) for the contrast pitch memory > motor control.

gyrus (STG) and the superior temporal sulcus (STS) bilaterally (Fig. 4). In addition, there was bilateral activation of the intraparietal sulcus/superior parietal region, the posterior inferior frontal gyrus (left more than right), the superior postero-lateral cerebellum (lobes V and VI) and the SMA.

Imaging effects in the "Strong-Learners" group

The post-training contrast of "pitch memory > motor control" showed a strong activation in the STG bilaterally (left: −47.2/−33.8/17.3; right: 51.3/−33.0/17.4; all coordinates are given in Talairach space) including primary and secondary auditory areas. In addition, there was strong activation in the anterior portion of the left supramarginal gyrus (−53.0/−30.5/19.0), the posterior portion of the left insular cortex (−35.3/−21.6/6.8), the posterior cingulate gyrus, and the posterior parahippocampal gyrus (−10/48/4) (Fig. 5a). Contrasting the post-training session directly with the pre-training session for the pitch memory contrast in a random effects model revealed significantly more activation of the left HG, the left SMG, and the left posterior cingulate (Fig. 5b). The reverse contrast (pre-training > post-training) showed significantly more activation in the superior parietal lobe (right: 40.5/−53.7/41.3; left: −42.3/50.1/42.3) bilaterally (right more than left) and a small activation in the right posterior premotor cortex (Fig. 5c).

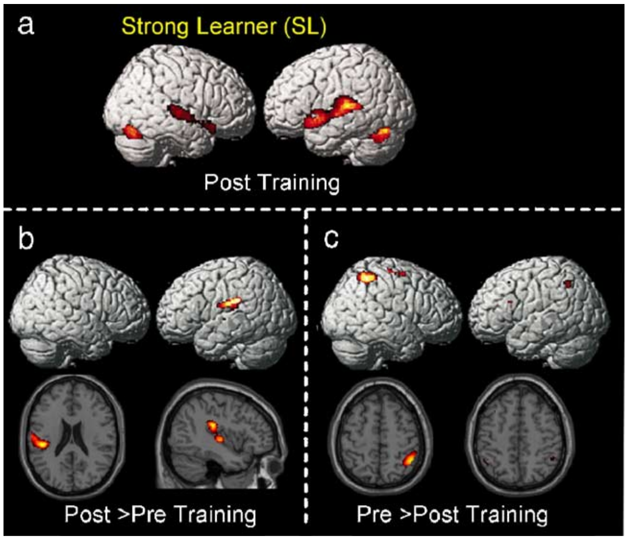

Fig. 5. "Strong-Learners Group": panel a shows surface projections of the brain activation pattern ($P < 0.05$, FWE, corrected) after 5 days of training for the contrast pitch memory > motor control. Panel b shows the activation pattern for the post- > pre-training contrast; panel c shows the activation pattern for the pre- > post-training contrast.

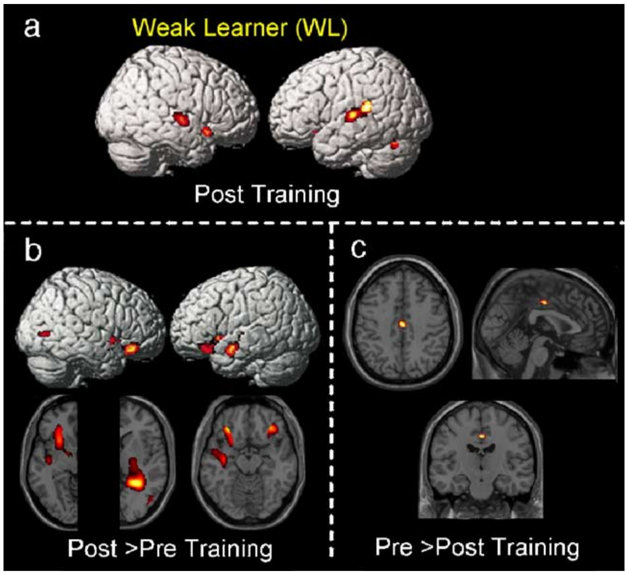

Fig. 6. "Weak-Learners Group": panel a shows surface projections of the brain activation pattern ($P < 0.05$, FWE, corrected) after 5 days of training for the contrast pitch memory > motor control. Panel b shows the activation pattern for the post- > pre-training contrast; panel c shows the activation pattern for the pre- > post-training contrast.

Imaging effects in the "Weak-Learners" group

The post-training contrast of "pitch memory > motor control" showed a strong activation in the STG bilaterally, much more centered around Heschl's gyrus (Fig. 6a) and not as much extending along the STG as can be seen in the SL group (see Fig. 5a for a comparison). Applying a random effects analysis model to a post-training > pre-training contrast, the WL group showed positive changes in the lingual gyrus bilaterally (right: 16.8/−49.8/2.3), the left anterior insula cortex (−26.3/12.2/−5.1), the orbitofrontal cortex bilaterally (29.1/29.7/−14.7 and −27.2/27.2/-11.3), and the

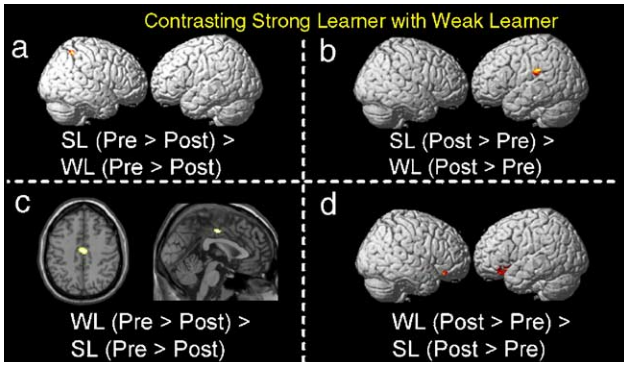

Fig. 7. A random effects analysis (t test) across both training subgroups using the post- > pre-training as well as pre- > post-training contrast images. There was significantly more activation of the left SMG and less activation of the intra-parietal sulcus/superior parietal cortex in the SL group compared to the WL group in the post- > pre-training contrast ($P < 0.05$, FWE, corrected). The WL group had significantly more activation of the orbito-frontal region and less activation of the posterior mid-cingulate region in the post- > pre-training contrast ($P < 0.05$, FWE, corrected). Panel c shows activation pattern for the WL group compared to the SL group in the pre- > post-training contrast, and panel d shows activation pattern for the SL group compared to the WL group in the pre- > post-contrast.

left parahippocampal gyrus (−32.4/−16.9/−13.6; Fig. 6b). A small activation was also seen in the mesial portion of the left HG (Fig. 6b). The reverse contrast (pre-training > post-training) revealed positive differences in the mid-cingulate gyrus (−0.8/−20.1/36; Fig. 6c).

Comparing the "Strong-Learners" with the "Weak-Learners":

When the training effects were compared between groups [SL group (post- > pre-contrast) > WL group (post- > pre-contrast)] significantly more activation was seen in the anterior part of the left supramarginal gyrus (−44.8/−32.4/−20.5; Fig. 7b). The reverse contrast [SL group (pre- > post-contrast) > WL group (pre- > post-contrast)] showed a positive effect in the right superior parietal cortex (36.1/−51.8/−54.0; Fig. 7a). A region within the cingulate cortex became significantly activated when the pre- > post-training contrast was compared between the WL and the SL group [WL group (pre- > post-contrast) > SL group (pre- > post-contrast); Fig. 7c]. The reverse contrast [WL group (post- > pre-contrast) > SL group (post- > pre)] showed a positive effect in the inferior orbitofrontal cortex bilaterally (Fig. 7d).

Although the SL as well as the WL subgroups showed higher post- vs. pre-training differences in mean-weighted parameter estimates in the left HG (3.0 (1.5) for the SL and 2.2 (1.7) for the WL group), the between-group differences in the left HG did not reach significance threshold. This might explain why only the SMG emerged as significantly different in the direct voxel-by-voxel comparison. The right HG did not show strong post- vs. pre-training differences in either group (1.0 (1.8) for the SL and 0.7 (1.4) for the WL).

Imaging changes in the control group

A random effects analysis (Fig. 8) comparing scan 2 with scan 1 in the control group revealed changes in the right dorsolateral pre-frontal cortex (27.4/12.7/22.4; Fig. 8). No significant changes were detected in the reverse contrast (scan1 > scan2). There was only a marginal change in the post- vs. pre-training differences in the weighted parameter estimates in the left HG (0.4 (0.7)) and the right HG (0.6(1.0)).

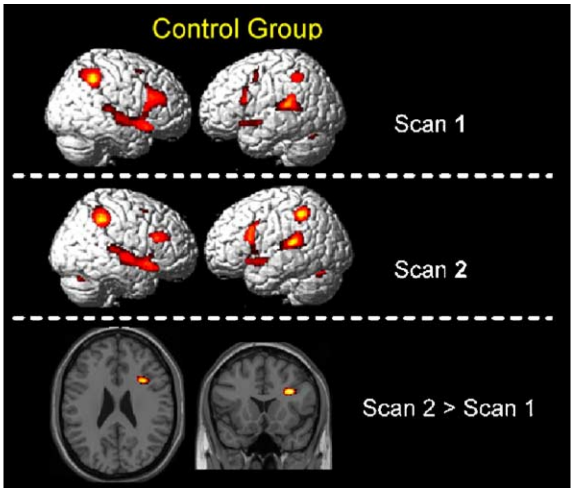

Fig. 8. Control group: brain activation pattern for the pitch memory > motor control contrast of the control group, scanned twice separated by one week ($P < 0.05$, FWE, corrected). Contrasting scan2 with scan1 revealed more activation in the right prefrontal cortex displayed on an axial and coronal slice.

Gray and white matter volumes in the "Strong-" and "Weak-Improvers"

In order to exclude the possibility that structural brain differences between the SL and WL groups contributed to the behavioral differences in training-induced changes, a voxel-based morphometric analysis was performed (Ashburner and Friston, 2000). This analysis did not reveal any significant structural differences ($P <$ 0.05, corrected) in white or gray matter volume between the two training groups.

Discussion

Our results showed MR signal increases in the mesial portion of Heschl's gyrus (HG), the posterior superior temporal and inferior anterior parietal brain region (supramarginal gyrus) on the left following training for a pitch memory (PM) task in subjects who showed a strong improvement in accuracy when comparing post- with pre-training assessments. The "Weak-Learners" showed changes in an orbitofrontal–parahippocampal–lingual network in addition to small changes in the anterior insular and mesial HG on the left when comparing post- with pre-training assessments. Comparison of the post- > pre-functional changes between these two subgroups (Strong-Learner vs. Weak-Learner) revealed significantly higher activation only in the left SMG. There was a positive trend in the left HG, but it did not reach significance. These changes in pattern reflect the two processes of our pitch memory task: (1) the ongoing and repetitive pitch discrimination process which is most likely related to the positive changes in Heschl's gyrus; the HG has been found to play a critical role in pitch discrimination tasks; and (2) the critical step of memorizing the initial pitch in the 6- to 7-tone sequences which may involve specialized regions for short-term auditory memory (e.g., the supramarginal gyrus). Our findings are also in agreement with previous auditory training studies finding covariations between functional activation patterns and performance improvements (e.g., Jancke et al., 2001; Golestani and Zatorre, 2004).

Training effects in the "Strong-Learners" group

On average, the SL group showed a 15.3% behavioral improvement over 5 days of training on the pitch memory task. Positive MR signal changes were found in left mesial HG, left posterior superior temporal and inferior parietal regions (Fig. 5b), and posterior cingulate and parahippocampal gyrus. A negative change was seen in the superior parietal lobule bilaterally. The strong effects in the mesial portion of Heschl's gyrus are most likely related to the ongoing pitch discrimination processes, which is in agreement with the published literature (Recanzone et al., 1993; Menning et al., 2000; Tramo et al., 2002; Brown et al., 2004), although Weinberger (2004) suggested a mnemonic function for primary auditory cortex. Nevertheless, it is most likely that the pitch memory component might require brain regions in addition to HG that are more specialized for the short-term storage of auditory information.

Several studies have shown the importance of auditory association areas in pitch perception and memory (Zatorre et al., 1994; Binder et al., 1996; Platel et al., 1997; Griffiths et al., 1999;

Ohnishi et al., 2001). Furthermore, there are recent electrophysiological data showing that enhancements after auditory discrimination training are seen predominantly in those auditory-evoked potentials that map to secondary auditory cortex (Bosnyak et al., 2004). Since previous studies have associated the SMG with short-term auditory storage (Caplan et al., 1995; Salmon et al., 1996; Vallar et al., 1997; Clarke et al., 2000), its strong positive change after training in this study may indicate a more general short-term auditory storage function for this region that includes verbal as well as non-verbal material. When the pre-training vs. post-training images were contrasted between the two training groups (SL and WL), the left SMG was the only region that was significantly more active in the SL group. This finding supports those of other studies that have identified the SMG as a short-term, auditory storage center (Caplan et al., 1995; Salmon et al., 1996; Vallar et al., 1997; Clarke et al., 2000; Paulesu et al., 1993; Sakurai et al., 1998). Celsis et al. (1999) already extended the verbal and phonological memory function of the SMG to the non-verbal domain by finding left SMG activation in a task requiring memory judgments between tones of different pitch height or spectral content. Our previous study showed a significant correlation between the degree of SMG activation and accurate performance in a pitch memory task in naïve subjects (Gaab et al., 2003). However, there is one alternative explanation for our findings. The visual cues in the pitch memory and control task were semantically different which could have lead to differences in the functional activation pattern due to irrelevant between-task differences in semantic processing time, reading speed, word frequency or memory load. Nevertheless, due to the timing of our sparse temporal design, an influence of these parameters seems unlikely and would, at the earliest, affect only the last two imaging time points of our seven imaging time points.

The parahippocampal as well as the posterior cingulate gyrus have been associated with memory functions (Maddock et al., 2001; Cabeza et al., 2002; Sakai et al., 2002; Glabus et al., 2003). Based on studies in both animals and humans, Engelien et al. (2000) suggested that the parahippocampal region might play an important role in selecting and filtering auditory information for entrance into the medial temporal lobe memory system for long-term storage. In addition, the posterior cingulate gyrus seems to be of importance in episodic memory functions (Shah et al., 2001). Tracing studies in monkeys have shown connections between posterior cingulate and auditory association cortices (Yukie, 1995; Vogt and Pandya, 1987). In addition to these regions showing positive signal changes after training, we also found bilateral signal decreases in the superior parietal lobules. This finding is consistent with those of previous studies in which decreased activation in the parietal association cortex has been shown following training. A more widely distributed set of active brain regions during the initial learning stage is shifted toward a more efficient network as a result of increased task familiarity and decreased attentional demands (Jenkins et al., 1994; Schlaug et al., 1994; Petersen et al., 1998; Kassubek et al., 2001; Petersson et al., 1999).

Training effects in the "Weak-Learners" group

Unlike the SL group, the WL group showed positive signal changes after training in the lingual and orbitofrontal gyrus bilaterally, the left parahippocampal gyrus, the right posterior temporal–occipital region, the left anterior insular and a small change in the left mesial HG. This activation pattern was associated with a mean performance improvement score of only 4.8%. Similar to the Strong-Learners group, a signal change was seen in HG on the left, however, this change seemed to be less than what was found in the SL group.

The strong activation of the lingual gyrus was unexpected. Previous studies have shown that activation of the lingual gyrus can be seen in working memory experiments (Honey et al., 2000; Ragland et al., 2002) and has also been seen associated with auditory tasks (Balsamo et al., 2002). In addition, there is an increasing amount of literature on connections between auditory cortex and orbitofrontal gyrus as well as on the involvement of the orbitofrontal gyrus in auditory information processing (Oscar-Berman, 1975; Hackett et al., 1999; Cavada et al., 2000). Frey et al. (2004) recently showed that the orbitofrontal cortex is involved in the encoding of non-verbal auditory information and observed a correlation between activity in the orbitofrontal cortex and the superior temporal gyrus. Rauschecker (2001) suggested that anterior superior temporal and orbitofrontal areas are responsible for the processing of complex auditory patterns possibly through top-down regulation of the orbitofrontal cortex on the superior temporal cortex. Several studies have revealed reciprocal connections between the orbitofrontal and parahippocampal regions (Deacon et al., 1983; Price et al., 1991), and this was further demonstrated by showing activation of parahippocampal regions in an auditory memory task (Engelien et al., 2000; Grasby et al., 1993). The post- > pre-contrast also showed positive changes in a right temporo-occipital region (Fig. 6b) which could indicate that the WL group used some form of visual encoding of the tonal information in order to solve the pitch memory task. It is most likely that the WL group used a network of regions consisting of lingual, orbitofrontal, and parahippocampal gyrus that was less efficient for non-verbal auditory learning. The WL group also showed signal decreases in the anterior portion of the posterior cingulate gyrus after training. This region has been implicated in memory tasks but also in the evaluation of sensory information (Shah et al., 2001; Vogt et al., 2003). There are extensive anatomical connections between the posterior cingulate cortex and the auditory cortex (Yukie, 1995; Vogt and Pandya, 1987). While there was only a very modest but significant improvement of 4.8% for this subgroup, there are several explanations for the prominent pattern of signal changes. First, it may be possible that skilled and unskilled performances of a particular task involve different brain regions, since these two stages in the learning process may actually be like performing two different tasks and, therefore, may involve different, but not necessarily exclusive brain regions [see Petersen et al. (1998) for more discussion on this]. The "Weak-Learners" group in our study may be at a different stage in the learning process than the "Strong-Learners" despite the fact that both groups started out at the same level and had the same amount of training. It is possible that continued training in the Weak-Learners might have lead to higher scores as well as changes in the activation pattern. Secondly, an alternative explanation for the differences in the activation pattern between the two training groups could be that the changes in the functional activation pattern reflect changes in non-performance related function. However, this is less likely, since one would expect to find a similar pattern across all three groups. Thirdly, the activation pattern in the WL group may indicate the use of a less efficient network for pitch memory and pitch discrimination, thus leading to only a modest gain in accuracy in the task. This, of course, could be a transition stage to a more efficient pattern of activated brain regions such as that seen in the SL group.

Test–retest effects in the "Control" group

In order to assess test–retest effects, a control group was scanned twice separated by a week with no training in between. Significant MR signal changes were found in the right dorsolateral prefrontal cortex (DLPFC), when scans at timepoint 2 were contrasted with timepoint 1. The DLPFC is a region commonly associated with working memory, particularly in relation to non-verbal material (Manoach et al., 1997; Barch et al., 1997; Kane and Engle, 2002; Funahashi and Takeda, 2002; Sakai, 2003), but recent publications also suggest that this region may be involved in basic aspects of attention, such as intrinsic and phasic alertness (Sturm and Willmes, 2001) and especially auditory intrinsic alertness (Sturm et al., 2004). Thus, there are two possible explanations for this test–retest effect. On one hand, the signal change might indicate a greater reliance on a classical working memory region, and on the other hand, intrinsic or phasic alertness might have differed within control group between the first and the second scan. This may have resulted in increased wakefulness and arousal or/and increased response readiness during the second scan without leading to any improved performance. Nevertheless, the test–retest effect did not explain the training-induced effects seen in the WL and SL group.

In conclusion, the results of our study support the "scaffolding-storage" framework proposed by Petersen et al. (1998). The authors hypothesized that strong and weak performances of a given task reflect two stages in a learning process and therefore should be treated as performing two different tasks. This may lead to the engagement of different, although not necessarily exclusive, brain regions. Strong improvement in a pitch memory task following a 1-week training was associated with increased signal in brain regions important for pitch discrimination (e.g., HG) and auditory short-term memory (e.g., SMG), while activity was decreased in brain regions associated with attention and multi-sensory integration (e.g., SPL). Interesting differences emerged between subjects that showed strong improvement and subjects that showed no significant improvement at all. Although both groups decreased attentional demands comparing post- and pre-training MR images, positive signal changes were seen in a posterior superior temporal and inferior parietal network in the SL group, while the WL group showed positive signal changes in an orbitofrontal–parahippocampal–lingual network. Both groups had positive signal changes in the left mesial HG, although the SL group showed a stronger trend. These signal differences in the post- vs. pre-training contrasts were not explained by test–retest effects. No baseline differences existed between the two subgroups, and the amount of training was the same for both groups. Besides highlighting the importance of the supramarginal gyrus for short-term verbal and non-verbal memory, our results also underscore the importance of obtaining and correlating behavioral changes with brain signal changes in order to better understand the functional correlates of learning.

References

Annett, M., 1970. A classification of hand preference by association analysis. Br. J. Psychol. 61, 303–321.

Ashburner, J., Friston, K.J., 2000. Voxel-based morphometry—The methods. NeuroImage 11, 805–821.

Balsamo, L.M., Xu, B., Grandin, C.B., Petrella, J.R., Braniecki, S.H., Elliott, T.K., Gaillard, W.D., 2002. A functional magnetic resonance imaging study of left hemispheric language dominance in children. Arch. Neurol. 59, 1168–1174.

Barch, D.M., Braver, T.S., Nystrom, L.E., Forman, S.D., Noll, D.C.7, Cohen, J.D., 1997. Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 35, 1373–1380.

Binder, J.R., Frost, J.A., Hammeke, T.A., Rao, S.M., Cox, R.W., 1996. Function of the left planum temporale in auditory and linguistic processing. Brain 119, 1239–1247.

Bosnyak, D.J., Eaton, R.A., Roberts, L.E., 2004. Distributed auditory cortical representations are modified when non-musicians are trained at pitch discrimination with 40 Hz amplitude modulated tones. Cereb. Cortex 14, 1088–1099.

Brown, M., Irvine, D.R., Park, V.N., 2004. Perceptual learning on an auditory frequency discrimination task by cats: association with changes in primary auditory cortex. Cereb. Cortex 14, 952–965.

Cabeza, R., Dolcos, F., Graham, R., Nyberg, L., 2002. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. NeuroImage 16, 317–330.

Campbell, R.A., Small, A.M., 1963. Effect of practice and feedback on frequency discrimination. J. Acoust. Soc. Am. 35, 511–1514.

Cansino, S., Williamson, S.J., 1997. Neuromagnetic fields reveal cortical plasticity when learning an auditory discrimination task. Brain Res. 764, 53–66.

Caplan, D., Gow, D., Makris, N., 1995. Analysis of lesions by MRI in stroke patients with acoustic–phonetic processing deficits. Neurology 45, 293–298.

Cavada, C., Company, T., Tejedor, J., Cruz-Rizzolo, R.J., Reinoso-Suarez, F., 2000. The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb. Cortex 10, 220–242.

Celsis, P., Boulanouar, K., Doyon, B., Ranjeva, J.P., Berry, I., Nespoulous, J.L., Chollet, F., 1999. Differential fMRI responses in the left posterior superior temporal gyrus and left supramarginal gyrus to habituation and change detection in syllables and tones. NeuroImage 9, 135–144.

Clarke, S., Bellmann, A., Meuli, R.A., Assal, G., Steck, A.J., 2000. Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. Neuropsychologia 38, 797–807.

Deacon, T.W., Eichenbaum, H., Rosenberg, P., Eckman, K.W., 1983. Afferent connections of the perirhinal cortex in the rat. J. Comp. Neurol. 220, 168–290.

Deutsch, D., 1974. Generality of interference by tonal stimuli in recognition memory for pitch. Q. J. Exp. Psychol. 26, 229–234.

Engelien, A., Stern, E., Isenberg, N., Engelien, W., Frith, C., Silbersweig, D., 2000. The parahippocampal region and auditory-mnemonic processing. Ann. N. Y. Acad. Sci. 911, 477–485.

Frey, S., Kostopoulos, P., 2004. Orbitofrontal contribution to auditory encoding. NeuroImage 22, 1384–1389.

Friston, K.J., Holmes, A., Worsley, K.J., Poline, J.B., Frith, C.D., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Funahashi, S., Takeda, K., 2002. Information processes in the primate prefrontal cortex in relation to working memory processes. Rev. Neurosci. 13, 313–345.

Gaab, N., Gaser, C., Zaehle, T., Jaencke, L., Schlaug, G., 2003. Functional anatomy of pitch memory—An fMRI study with sparse temporal sampling. NeuroImage 19, 1417–1426.

Glabus, M.F., Horwitz, B., Holt, J.L., Kohn, P.D., Gerton, B.K., Callicott, J.H., Meyer-Lindenberg, A., Berman, K.F., 2003. Interindividual differences in functional interactions among prefrontal, parietal and parahippocampal regions during working memory. Cereb. Cortex 13, 1352–1361.

Golestani, N., Zatorre, R.J., 2004. Learning new sounds of speech: reallocation of neural substrates. NeuroImage 21, 494–506.

Good, C.D., Johnsrude, I.S., Ashburner, J., Henson, R.N.A., Friston, K.J., Frackowiak, R.S.J., 2001. A voxel-based morphometric study of ageing in 465 normal adult human brains. NeuroImage 14, 21–36.

Grasby, P.M., Frith, C.D., Friston, K.J., Bench, C., Frackowiak, R.S., Dolan, R.J., 1993. Functional mapping of brain areas implicated in auditory–verbal memory function. Brain 116, 1–20.

Griffiths, T.D., Johnsrude, I., Dean, J.L., Green, G.G.R., 1999. A common neural substrate for the analysis of pitch and duration pattern in segmented sound? NeuroReport 10, 3825–3830.

Hackett, T.A., Stepniewska, I., Kaas, J.H., 1999. Prefrontal connections of the parabelt auditory cortex in macaque monkeys. Brain Res. 817, 45–58.

Hall, D.A., Haggard, M.P., Akeroyd, M.A., Palmer, A.R., Summerfield, A.Q., Elliott, M.P., Gurney, E.M., Bowtell, R.W., 1999. "Sparse" temporal sampling in auditory fMRI. Hum. Brain Mapp. 7, 213–223.

Hall, D.A., Summerfield, A.Q., Goncalves, M.S., Foster, J.R., Palmer, A.R., Bowtell, R.W., 2000. Time-course of the auditory BOLD response to scanner noise. Magn. Res. Med. 43, 601–606.

Hazeltine, E., Grafton, S.T., Ivry, R., 1997. Attention and stimulus characteristics determine the locus of motor-sequence encoding. A PET-study. Brain 120, 123–140.

Honey, G.D., Bullmore, E.T., Sharma, T., 2000. Prolonged reaction time to a verbal working memory task predicts power of posterior parietal cortical activation. NeuroImage 12, 495–503.

Jancke, L., Gaab, N., Wuestenberg, T., Scheich, H., Heinze, H.-J., 2001. Short-term functional plasticity in the human auditory cortex: an fMRI study. Brain Res. Cogn. Brain Res. 12, 485–497.

Jenkins, I.H., Brooks, D.J., Nixon, P.D., Frackowiak, R.S., Passingham, R.E., 1994. Motor sequence learning: a study with positron emission tomography. J. Neurosci. 14, 3775–3790.

Kane, M.J., Engle, R.W., 2002. The role of prefrontal cortex in working-memory, executive attention, and general fluid intelligence: an individual-differences perspective. Psychol. Bull. Rev. 9, 637–671.

Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., Ungerleider, L.G., 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature 377, 155–158.

Kassubek, J., Schmidtke, K., Kimming, H., Luecking, C.H., Greenlee, M.W., 2001. Changes in cortical activation during mirror reading before and after training: an fMRI study of procedural learning. Brain Res. Cogn. Brain Res. 10, 207–217.

Maddock, R.J., Garrett, A.S., Buonocore, M.H., 2001. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 104, 667–676.

Manoach, D.S., Schlaug, G., Siewert, B., Varby, D.G., Bly, B.M., Benfield, A., Edelman, R.R., Warach, S., 1997. Prefrontal cortex fMRI signal changes are correlated with working memory load. NeuroReport 8, 545–549.

Menning, H., Roberts, L.E., Pantev, C., 2000. Plastic changes in the auditory cortex induced by intensive frequency discrimination training. NeuroReport 11, 817–822.

Ohnishi, T., Matsuda, H., Asada, T., Aruga, M., Hirakata, M., Nishikawa, M., Katoh, A., Imabayashi, E., 2001. Functional anatomy of musical perception in musicians. Cereb. Cortex 11, 754–760.

Oscar-Berman, M., 1975. The effects of dorsolateral–frontal and ventrolateral–orbitofrontal lesions on spatial discrimination learning and delayed response in two modalities. Neuropsychologia 13, 237–246.

Paulesu, E., Frith, C.D., Frackowiak, R.S.J., 1993. The neural correlates of verbal component of working memory. Nature 362, 342–345.

Petersen, S.E., Van Mier, H., Fiez, J.A., Raichle, M.E., 1998. The effects of practice on the functional anatomy of task performance. Proc. Natl. Acad. Sci. U. S. A. 95, 853–860.

Petersson, K.M., Elfgren, C., Ingvar, M., 1999. Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. Neuropsychologia 37, 567–587.

Platel, H., Price, C., Baron, J.-C., Wise, R., Lambert, J., Frackowiak, R.S.J., Lechevalier, B., Eustache, F., 1997. The structural components of music perception a functional anatomical study. Brain 120, 229–243.

Price, J.L., Carmichael, T., Carnes, K.M., Clugnet, M., Kuroda, M., Ray, J.P., 1991. Olfactory input to the prefrontal cortex. In: Davis, J., Eichenbaum (Eds.), Olfaction as a Model for Computational Neuroscience. MIT, Cambridge, MA, pp. 101–120.

Ragland, J.D., Turetsky, B.I., Gur, R.C., Gunning-Dixon, F., Turner, T., Schroeder, L., Chan, R., Gur, R.E., 2002. Working memory for complex figures: an fMRI comparison of letter and fractal n-back tasks. Neuropsychology 16, 370–379.

Rauschecker, J.P., 2001. Cortical plasticity and music. Ann. N. Y. Acad. Sci. 930, 330–336.

Recanzone, G.H., Schreiner, C.E., Merzenich, M.M., 1993. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci. 13, 87–103.

Sakai, K., 2003. Reactivation of memory: role of medial temporal lobe and prefrontal cortex. Rev. Neurosci. 14, 241–252.

Sakai, K., Rowe, J.B., Passingham, R.E., 2002. Parahippocampal reactivation signal and retrieval after interruption of rehearsal. J. Neurosci. 22, 6315–6320.

Sakurai, Y., Takeuchi, S., Kojima, E., Yazawa, I., Murayama, S., Kaga, K., Momose, T., Nakase, H., Sakuta, M., Kanazawa, I., 1998. Mechanism of short-term memory and repetition in conduction aphasia and related cognitive disorders. A neuropsychological, audiological and neuroimaging study. J. Neurol. Sci. 154, 182–193.

Salmon, E., Van der Linden, M., Colette, F., Delfiore, G., Maquet, P., Degueldre, C., Luxen, A., Franck, G., 1996. Regional brain activity during working memory tasks. Brain 119, 1617–1625.

Schlaug, G., Knorr, U., Seitz, R., 1994. Inter-subject variability of cerebral activations in acquiring a motor skill: a study with positron emission tomography. Exp. Brain Res. 98, 523–534.

Shah, N.J., Marshall, J.C., Zafiris, O., Schwab, A., Zilles, K., Markowitsch, H.J, Fink, G.R., 2001. The neural correlates of person familiarity. A functional magnetic resonance imaging study with clinical implications. Brain 124, 804–815.

Sturm, W., Willmes, K., 2001. On the functional neuroanatomy of intrinsic and phasic alterness. NeuroImage 14, S76–S84.

Sturm, W., Longoni, F., Fimm, B., Dietrich, T., Weis, S., Kemna, S., Herzog, H., Willmes, K., 2004. Network for auditory intrinsic alertness: a PET study. Neuropsychologia 42, 563–568.

Toni, I., Krams, M., Turner, R., Passingham, R.E., 1998. The time course of changes during motor sequence learning: a whole-brain fMRI study. NeuroImage 8, 50–61.

Tramo, M.J., Shah, G.D., Braida, L.D., 2002. Functional role of auditory cortex in frequency processing and pitch perception. J. Neurophysiol. 87, 122–139.

Vallar, G., DiBetta, A.M., Silveri, M.C., 1997. The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. Neuropsychologia 35, 795–812.

Vogt, B.A., Pandya, D.N., 1987. Cingulate cortex of the rhesus monkey: II. Cortical afferents. J. Comp. Neurol. 262, 271–289.

Vogt, B.A., Berger, G.R., Derbyshire, S.W.G., 2003. Structural and functional dichotomy of human midcingulate cortex. Eur. J. Neurosci. 18, 3134–3144.

Weinberger, N.M., 2004. Specific long-term memory traces in primary auditory cortex. Nat. Rev., Neurosci. 5, 279–290.

Wright, B.A., 2001. Why and how we study human learning on basic auditory tasks. Audiol. Neuro-otol. 6, 207–210.

Yukie, M., 1995. Neural connections of auditory association cortex with the posterior cingulate cortex in the monkey. Neurosci. Res. 22, 179–187.

Zatorre, R.J., Evans, A.C., Meyer, E., 1994. Neural mechanism underlying melodic perception and memory for pitch. J. Neurosci. 14, 1908–1919.