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Review

Plasticity of the human auditory cortex related to musical training

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ABSTRACT

During the last decades music neuroscience has become a rapidly growing field within the area of neuroscience. Music is particularly well suited for studying neuronal plasticity in the human brain because musical training is more complex and multimodal than most other daily life activities, and because prospective and professional musicians usually pursue the training with high and long-lasting commitment. Therefore, music has increasingly been used as a tool for the investigation of human cognition and its underlying brain mechanisms. Music relates to many brain functions like perception, action, cognition, emotion, learning and memory and therefore music is an ideal tool to investigate how the human brain is working and how different brain functions interact. Novel findings have been obtained in the field of induced cortical plasticity by musical training. The positive effects, which music in its various forms has in the healthy human brain are not only important in the framework of basic neuroscience, but they also will strongly affect the practices in neuro-rehabilitation.

Contents

1. Introduction

The structural and functional organization of the human brain becomes increasingly differentiated during child development. In higher mammals, including humans, neurons are formed prenatally as are some of their interconnections formed into neural networks. For many years the prevailing opinion was that network connections between neurons are built primarily during cerebral maturation processes in the childhood and it was thought that this network pattern, almost like a connection diagram, would not change later. However, humans respond with considerable flexibility to new challenges throughout their entire life. Since the early eighties, increasing experimental evidence demonstrated that the connectivity of the adult brain is in fact only partially determined by genetics and early development, and may be substantially modified through sensory experiences. Neuroscience research over the last

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three decades has revealed that even in the adult brain the functional organization in the mammalian cortex adjusts in response to alteration of behaviorally relevant input and processing. The knowledge that cortical representations are dynamic and continuously modified by experience is based on a series of classical animal studies. Several previous experiments have demonstrated that the functional organization of sensory maps is not statically fixed in adult cortex (Gilbert and Wiesel, 1992; Irvine and Rajan, 1995; Jenkins et al., 1990; Kaas et al., 1990; Merzenich et al., 1983a,b; Rauschecker et al., 1995, 1997; Recanzone et al., 1993). Early studies in animals utilized large and permanent changes of afferent sensory input, such as amputation of a forelimb (Irvine and Rajan, 1995; Kaas, 1991; Merzenich et al., 1984; Pons et al., 1991; Rajan et al., 1993; Rajan and Irvine, 1998; Schwaber et al., 1993) or in the auditory system, injuries such as deafferentation through damage of a section of hair cells in the cochlea (Irvine and Rajan, 1995; Rajan et al., 1993; Rajan and Irvine, 1998; Schwaber et al., 1993). These experiments have shown that cortical regions that have lost their normal input take over and serve functions found in adjacent cortical areas (Rajan and Irvine, 1998; Stanton and Harrison, 1996).

The development of new, non-invasive scientific methods for recording neuronal activity has made it possible to prove the hypothesis of plasticity in functional neuronal networks in humans. The electrical activity of single neurons can only be recorded invasively in animals or in special cases in patients undergoing brain surgery (at least local field potentials, e.g. in patients with deep brain electrodes). However, derived potentials that reflect the activity of a group of neurons can be recorded non-invasively on the scalp surface by means of electroencephalography (EEG). The magnetic counterpart of the EEG is the magnetoencephalography (MEG), which has become an established method for noninvasive study of the activity of the human cortex (Hari, 1990). The main sources of cortical evoked magnetic fields are the pyramidal cells, which produce currents flowing tangentially to the surface of the head. Though MEG measurements provide only a macroscopic view of the function of the brain, the spatial resolution achieved with this technique is sufficient to give indications of functional organization and reorganizational plasticity of the human cortex by localizing the sources of evoked magnetic fields, which are elicited by defined peripheral excitation. Thus, using MEG, which allows non-invasive measurement in human subjects, changes in cortical maps similar to those observed in primate cortex have been demonstrated in patients with limb amputations and finger syndactyly (Elbert et al., 1994; Flor et al., 1995; Mogilner et al., 1993; Yang et al., 1994).

During the last years music has increasingly been used as a tool for the investigation of human cognition and its underlying brain mechanisms. Music relates to many brain functions and therefore music is an ideal tool to investigate how the human brain is working. As described by (Zatorre et al., 2007), playing a musical instrument, for example the violin, is a highly complex task. The whole body and almost all sensory systems are involved and have to be coordinated at high degree of synchrony and accuracy. The arms support the violin and move the bow, the left hand fingers the strings, and feedback from the somatosensory perception about the body posture and from the fingertips is constantly integrated to fine-tune each and every movement. The auditory system analyses the correctness of the sounds and the auditory feedback is used to improve the sound quality. The visual system analyses the musical score and translates the musical symbols into meaningful information involved in the music production. Apart from the motor and sensory systems, memory and attentional as well as emotional systems are also involved. However, not only the brain of the performing musician is highly active but also the brains of the listeners. Even the passive act of listening to music activates a broad range of cortical functions: perception and analysis of the pitches, timbres, harmonics, rhythms, meter and of higher-order structures, attention and memory systems, and emotional responses to the music heard.

Over the last ten years enough scientific evidence has been accumulated demonstrating that musical training has pronounced effects on functional and structural human brain plasticity. On the structural level, larger brain volume has been demonstrated in musicians compared to non-musicians in several brain areas (auditory processing; Bermudez et al., 2009; Gaser and Schlaug, 2003; Schlaug et al., 1995b; Schneider et al., 2002), right superior parietal gyrus (visuo-spatial processing; Gaser and Schlaug, 2003), corpus callosum involved in motor control (Schlaug et al., 1995a), precentral gyrus (Bangert and Schlaug, 2006; Gaser and Schlaug, 2003) and cerebellum (Hutchinson et al., 2003). Not only in gray matter but also in white matter in different fiber tracts differences in nonmusicians and musicians have been found (Oechslin et al., 2010a). Also, a recent longitudinal study (Hyde et al., 2009) in children who received keyboard lessons over the course of 15 months showed anatomical changes in primary motor and auditory areas as well as in the corpus callosum, thus providing further support for the interpretation that such changes are indeed due to the musical training.

Also on the electrophysiological and functional level, fundamental differences between musicians and non-musicians regarding the processing of sounds have been demonstrated in various studies – on the level of simple tones as well as in the processing of complex melodic stimuli (Fujioka et al., 2004, 2005; Pantev et al., 1998; Tervaniemi et al., 2001); chord sequences (Koelsch et al., 2002b), non-melodic tone patterns (van Zuijen et al., 2004, 2005) and speech stimuli (Besson et al., 2007). Differences between musically trained and untrained persons cannot only be seen in the auditory, but also in the somatosensory and the motor domains (Elbert et al., 1995; Lotze et al., 2003).

However, not only processing within one modality but also interactions between modalities are enhanced in musically trained people (Schulz et al., 2003). The interplay and the integration of several modalities is a key element of musical training and performance, and the multimodal integration and co-activation of the cortical areas involved during the training might be an important mechanism supporting the training effects within each modality, which are observed after musical training (Zatorre et al., 2007).

As a complete review on all aspects of structural and functional plasticity through musical training is beyond the scope of this paper, we focus mainly on the electrophysiological literature on plasticity in the auditory modality caused by musical training (please refer to Jancke, 2009; Pascual-Leone et al., 2005 for two excellent reviews on brain plasticity with a broader scope). By means of EEG and MEG it is possible to observe electric potentials and magnetic field distributions, respectively, over the scalp surface, which result from neuronal activity mainly from cortical areas of the human brain. These techniques are very well suited to study auditory cortical processing, as the measurements are completely non-invasive and silent. In addition, the high temporal resolution is adequate to resolve the rapid processing of auditory signals. The recorded cortical evoked responses correspond to different major components of the auditory evoked fields: the wave N1, having a latency of about 100 ms after stimulus onset (Pantev et al., 1988), the mismatch negativity (MMN) with latency of 150–250 ms (Naatanen and Alho, 1995), the transient auditory evoked gamma-band fields (Pantev et al., 1991) as well as the auditory steady state responses (ASSR) that follow the modulation frequency of the auditory stimulus with a maximum around 40 Hz (Pantev et al., 1996). All these components display stimulus-related neuronal activity that occurs mainly in circumscribed auditory cortical areas. In many of our own studies, this activity as measured with MEG has been analyzed using equivalent current dipole (ECD) model, that can account for most of the variance of the observed magnetic field distributions. Subsequently, the source space projection technique (Tesche et al., 1995) is applied to compute the time course of the corresponding dipole moment, resulting in so-called source waveforms. Other analysis techniques such as distributed source models have also been developed and provide information about the underlying sources without assumptions about the number of sources. The amplitude of early auditory evoked responses can be used to measure differences in cortical source activity resulting from musical training as a parameter that indicates functional cortical plasticity. Such differences might result from newly formed synapses or newly recruited additional neurons or from increased neuronal activity corresponding to increased synchronization in an existing cortical network. Whereas structural measures of brain anatomy (e.g. voxel based morphometry, cortical thickness) have been used to investigate differences in long-term reorganization of the brain, but have rarely been used to assess short-term adaptation processes, functional measures do not distinguish between the different causes for increased or decreased cortical activity, but have been used to assess both long- and short-term plasticity changes.

Experiments on cerebral cortical organization in musicians demonstrated an astonishing plasticity. Results of such studies showing the influence of long-term and short-term musical training on the cortical reorganizational processes to complex musical sounds within the human auditory cortex are presented in this review. In general the plasticity of the auditory cortex in musicians due to their intensive musical training is a positive phenomenon. The training induced alterations in the cortical map correspond to perceptual correlates indicating superior performance, an example of the “bright side” of the cortical plasticity. However, the plasticity of the auditory cortex has also a “dark side”. It occurs when a peripheral lesion, by itself manageable, is triggered by an unusually intense and stressful experience to cause negative and even catastrophic auditory cortex reorganization, such as that underlying the tinnitus. At the end of this review the results of a study with modified notched music to reverse mal-adaptive cortical reorganization in tinnitus are presented.

2. Long-term cortical plasticity as result of long-term musical training

2.1. Increased auditory cortical representation in musicians for instrumental tones

In an early study on auditory cortex plasticity we investigated a group of musicians and compared them to a control group of nonmusicians matched in age. From each subject the N1 component of auditory evoked fields to piano tones and to pure tones with corresponding fundamental frequencies were recorded by means of MEG. The N1–P2 complex of auditory evoked responses reflects processing of stimulus features that can be modulated by factors such as task demands and attention. In this experiment (Pantev et al., 1998) we found a significant difference between musicians and nonmusicians in the strength of the cortical sources activated by the piano tones compared to the pure tones (Fig. 1). Both for musicians with absolute or relative pitch the cortical source strength (ECD) was by 21–28% significantly larger for piano tones than for pure tones. This effect was found although the two types of tones were matched for loudness. For the nonmusicians no significant difference was found in ECD between piano and pure tones. The increase in cortical source strength in musicians reflects either an expansion of the number of cortical neurons processing the musical tones, i.e. more neurons were engaged in the processing of these tones in skilled musicians, or increased synchronization of those neurons, or most probably both.

The observed increase in cortical source strength was correlated with the age at which the musicians began to practice. This result indicates that the younger the subjects started playing their instrument, the larger was the cortical representation for the piano tones compared to the pure tones.

This original finding was challenged by later studies that did not find such a differential effect in musicians compared to nonmusicians. Lutkenhoner et al. (2006) reported increased N1 responses to piano tones compared to sine tones both in musicians and nonmusicians. Meyer et al. (2006) investigated auditory evoked responses to instrumental (piano, trumpet and violin) tones versus sine tones using the analysis method of low-resolution electromagnetic tomography (LORETA) on EEG data, an alternative approach to ECD fitting that shows sources of evoked potentials without a priori assumptions about the number of sources. All of their participants were nonmusicians, but showed increased N1 and P2 responses to the instrumental tones compared to the sine tones nevertheless. Similarly, in one of our own studies (Shahin et al., 2005), no difference in N1 amplitude to instrumental tones compared to sine tones was found in musicians and nonmusicians. However, in this study, the musicians showed a stronger increase of P2 amplitude to instrumental tones vs. sine tones than the nonmusicians. This somewhat inconsistent pattern of findings might be partially explained by attentional effects. Depending on the context of the experiment, musicians might pay more attention to instrumental tones because they are of high professional relevance. This issue was recently addressed in a paper by Baumann et al. (2008). Again, they presented instrumental tones and sine tones to musicians and nonmusicians while the participants listened passively or attended to the tones. Both musicians and nonmusicians performed well on the detection tasks that controlled attention, and both showed increased amplitudes of the N1/P2 complex in their auditory evoked responses to the instrumental tones compared to the sine tones. Regarding the effect of musical training the authors reported enhanced N1 responses in musicians compared to nonmusicians while controlling for attention, thus excluding attention as a potential explanation for group differences, and partly confirming earlier findings of training-related enhancements of cortical representations of instrumental timbre. However, this group effect was nonspecific, as both responses to both instrumental and sine tones were enhanced in musicians, and therefore the controversy remains unsettled.

However, an alternative way of testing if musicians show an enhanced response to instrumental tones as a result of their training is to test if responses are more pronounced for the timbre of the specific instrument that they trained on.

2.2. Timbre-specific enhancement of auditory cortical representations in musicians

In a further study we investigated (Pantev et al., 2001) whether cortical representations for tones of different timbre (violin and trumpet) are enhanced compared to sine tones in violinists and trumpeters, preferentially for timbres of the instrument on which the musician was trained. Seventeen highly skilled musicians were recruited. Participants in both groups had practiced their instrument for 15 years on average, and had practiced intensely in the five years preceding the study. Importantly, they had never practiced the respective other instrument. The N1 component was recorded for violin and trumpet tones of corresponding pitches.

The time course of the N1 cortical source strength evoked by violin and trumpet tones is portrayed separately for the two hemispheres in Fig. 2a, for one representative violinist and one

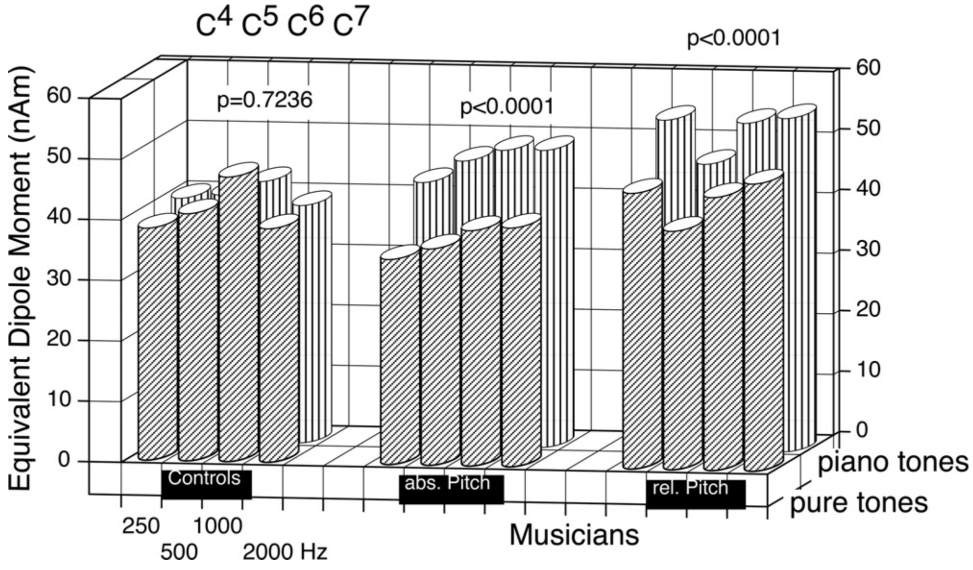

Fig. 1. Equivalent dipole moment (strength of neuronal activation during the N1 component of the auditory evoked field) as shown for pure tones and piano tones in control subjects and musicians with absolute or relative pitch (from Pantev et al., 1998).

representative trumpeter demonstrating clear timbre specificity. Group data are depicted in Fig. 2b, where it can be seen that in each hemisphere the N1 cortical strength was larger for timbres of the instrument of training.

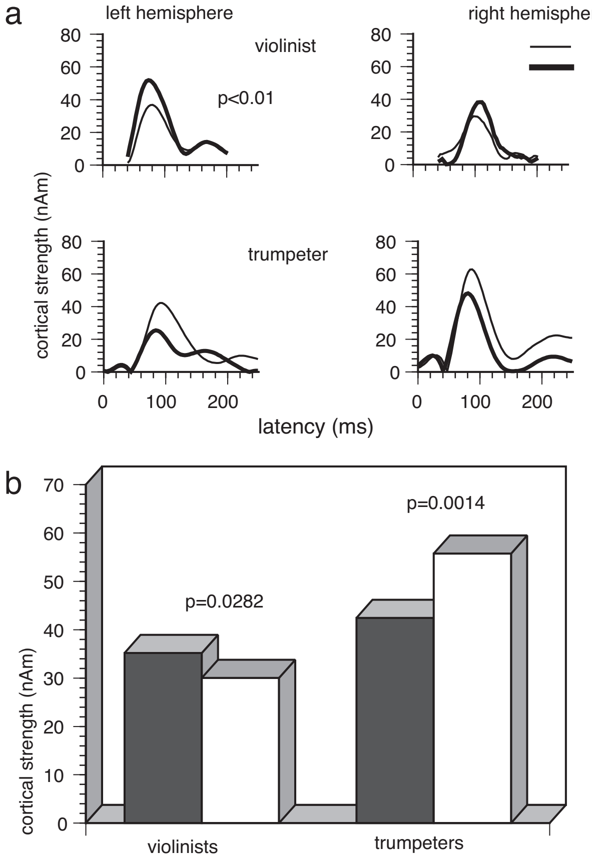

Fig. 2. (a) Timbre specificity. Cortical responses evoked by string tones (thick line) and trumpet tones (thin line) are shown for a representative violinist (upper panel) and trumpeter (lower panel) for the left and right hemispheres separately. (b) Mean ECD evoked by the string tones and trumpet tones are shown for the trumpeter and violinist groups (hemispheres combined) (from Pantev et al., 2001).

Complementary evidence of timbre-specific enhancements of cortical activity with different methods was also more recently reported in professional flute and piano players (Margulis et al., 2009), as well as in violin and piano players (Shahin et al., 2008). Using fMRI, Margulis et al. (2009) found activity in an extensive network of cortical areas that relate to processing of musical syntax (BA 44), timbre (auditory association cortex), and sound–motor interactions (precentral gyrus). Shahin et al. (2008) reported increases of induced oscillatory gamma band activity specifically in response to tones of the trained instrument in violinists and pianists that are interpreted to reflect highly learned perceptual template matching.

Taken together, these findings show that highly skilled musicians exhibit enhanced auditory cortical representations for musical timbres associated with their principal instrument, compared to timbres associated with instruments on which they have not been trained. Timbre specificity is predicted by neuroplastic accounts of brain development, when musical training has been specific to one or the other of these instruments. It is difficult to explain such differential effects on the basis of genetic disposition or environmental factors. In order to explain timbre specificity, nativistic accounts would have to be elaborated to propose that genetic mechanisms code for complex tones of specific spectral structure, and that the genetic code for spectral structure is sufficiently constraining as to determine who trains as a trumpeter and who as a violinist. Additionally, Shahin et al. (2008) also reported similar increases of induced oscillatory gamma band activity in 4- and 5-year old children before and after one year of piano training, whereas a age-matched control group of children who did not receive piano training did not show such an effect. Although in this case group assignment was not random, these data provide additional and compelling evidence for training-induced plastic changes of the auditory cortex.

These findings of timbre-specific enhancements of neuronal responses among musicians shed new light on the controversy about possible differences between musicians and nonmusicians that was discussed earlier, because the selection of musicians who took part in the studies might have influenced the results. Whereas in both our studies that found enhanced auditory evoked responses to instrumental tones in musicians most subjects played the piano (which was the instrumental timbre used) as principal or secondary instrument. In contrast, musicians in the studies by Lutkenhoner et al. (2006) and Baumann et al. (2008) played a variety of instruments. Based on the recent findings of selectively enhanced responses to the timbre of the instrument of training, it seems plausible that the partial discrepancy of presented timbres (piano timbre in Lutkenhoner et al.; trumpet, violin and piano in Baumann et al.) and participating musicians' instruments of training might account for the null-findings regarding differences between musicians and nonmusicians in these studies.

2.3. *Enhanced automatic encoding of melodic contour and interval structures in musicians*

In the studies presented so far we have focused on the processing of single tones. Meaning in music, however, involves how tones are put together. The question asked here concerns the effect of extensive musical training on the processing of sequences of tones or melodic information. From a perceptual point of view, melodic pitch structure has two aspects, a contour and an interval code. The contour representation consists of information about the up and down pattern of pitch changes, regardless of their exact size, and is common to both speech prosody and musical melody. The interval representation consists of more analytic structure of exact pitch distances between successive tones. Pitch interval is specific to music and is crucial for scales and harmony, where exact intervals define the structure. We investigated the effect of musical expertise on contour and interval processing as compared to nonmusicians. The stimuli were designed to clearly separate contour and interval encoding.

In this study (Fujioka et al., 2004) we have shown that musicians' automatic encoding and discrimination of pitch contour and interval information in melodies is specifically enhanced compared to non-musicians. Twelve musicians and twelve non-musicians matched in age participated in the experiment. The stimuli for both the contour and the interval melodic conditions were composed of sequences of 5-note standard and deviant melodies, with standard melodies occurring 80% of the time. Standard melodies in the contour condition were ascending, whereas the last note of deviant melodies in this condition was descending, thus altering the contour of the melody, which was noticeable regardless of the specific pitch interval.

In contrast, in the interval condition, the pitch of the last tone of deviant melodies was altered so that the contour was preserved but the interval between the last and second-to-last note changed. Factors of deviation in musical context involving out-of-key changes, familiarity of melody, and range of pitch leaps that might cause additional cognitive processing, were carefully controlled. The control condition, in which no difference between the groups was expected, consisted of two successive blocks of pure tones of two different pitches in a classical oddball paradigm where one tone occurs more often than the other. In all of the conditions, deviating tones were expected to elicit a MMN, a neuronal response that is elicited by unexpected violations of regularity in the auditory input, and that reflects auditory discrimination ability on a pre-attentive level of processing.

As shown in Fig. 3, after the onset of the fifth note, clear and significant MMN responses were observed in both hemispheres for both contour and interval conditions in musicians. In contrast, non-musicians showed no clear responses in both contour and interval conditions. However, in the single tone control condition both musicians and non-musicians have clear MMN responses to the frequency change of the stimulus, indicating that the lack of MMN in nonmusicians in the melodic conditions is not due to a general inability to discriminate pitches. The results of the behavioral tests that were also conducted showed better behavioral discrimination performance in the musicians and thus confirmed the MEG results. The findings strongly support the hypothesis that the musical experience of musicians leads to specific changes in the neural mechanisms for processing melodic information, and that long-term musical training particularly enhances the processing of pitch relations between the successive notes of melodies. These findings were confirmed and extended in a similar studies using polyphonic melodies, in which again musicians showed a larger MMN response to unexpected tones in short melodies compared to nonmusicians (Fujioka et al., 2005). Moreover, similar to findings regarding specificity to instrumental timbre, the individual training biographies of musicians also reflect in their processing of melodies. Seppänen et al. (2007) showed that musicians who prefer aural training strategies (such as playing by ear and improvisation) show better discrimination performance to contour and interval changes in short melodies compared to musicians who mainly use non-aural strategies (e.g. playing from sheet music), and that this is also reflected in a larger MMN amplitude to these changes after a short, focused (aural) training session.

Other recent studies have shown that musicians not only show enhanced processing of melodies, but also of rather abstract tonal material. van Zuijen et al. (2004, 2005) showed that nonmusicians and musicians show similar processing of relatively simple, unmelodic patterns of tones that were grouped according to similarity of pitch, or a temporal regularity (van Zuijen et al., 2004, 2005, respectively). However, musicians show enhanced mismatch responses to deviant and unexpected tones in slightly more complex patterns of tones that were based on Gestalt features (ascending tones; van Zuijen et al., 2004) or numerical regularities (van Zuijen et al., 2005). Also, in one of our own recent studies, we were able to show that musicians are better able than nonmusicians to extract temporal regularities from abstract sequences of tones based on global probabilities of patterns in tone sequences (Herholz et al., 2009), which complements evidence of enhanced and differently lateralized processing of musical meter in highly rhythmic, musical stimuli in musicians compared to nonmusicians (Vuust et al., 2005). Also, passive exposure to musical stimuli can modulate neuronal responses as early as the brainstem even in nonmusicians (Skoe and Kraus, 2010). Within 1.5 h of passive listening, auditory evoked brainstem responses to a five tone melody increased, indicating on-line plasticity based on global stimulus probabilities even on such an early processing level. Also, the response to a repeated note within the melody increased over time, suggesting an influence of local stimulus probabilities on subcortical auditory plastic changes as well. Most likely, such plastic changes in the responses in the brainstem are the result of modulation by cortical feedback via cortico-fugal pathways (Kraus and Chandrasekaran, 2010).

2.4. *Music imagery and cortical plasticity*

Although the influence of long-term musical training on the processing of heard music has been the subject of many studies, the neural basis of music imagery and the effect of musical expertise remain still insufficiently understood. In a recent experiment (Herholz et al., 2008) we compared the neuronal processing of imagined music in musicians and non-musicians, who listened to the beginnings (first six tones) of familiar melodies. Subjects were explicitly instructed to imagine the following six tones of the melody in their mind within the corresponding silent period. Then they judged via button press if an actually presented test tone was a correct further continuation of the melody or not. This could only be identified based on the preceding correct imagination of the individual melody and not solely on the basis of the first six tones. As expected, musicians were far better than non-musicians in the behavioral task. The MEG data showed that a significantly increased MMN, i.e. an enhanced negativity in response to the incorrect tones compared to the correct tones of the imagined melody was observed only in the musicians' group and this MMN-like response was termed imagery mismatch negativity (iMMN).

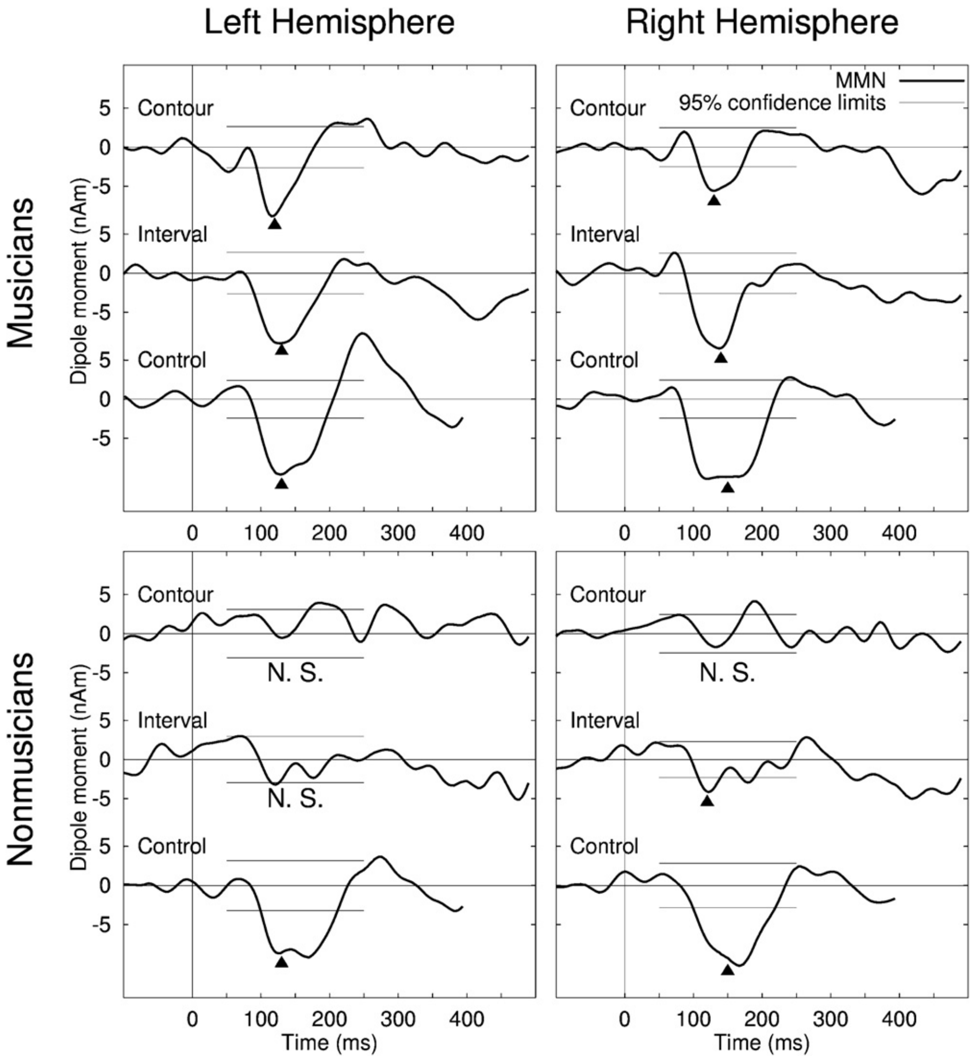

Fig. 3. The source space waveforms of MMN. For both contour and interval condition the time scale on the *x*-axis refers to the onset of the 5th note. The thick lines represents the MMN response and thin lines above and below zero line shows the upper and lower limit of the corresponding 95% confidence interval. The mean of confidence interval was subtracted from the response to adjust the baseline of MMN waveform to the zero line (from Fujioka et al., 2004).

Based on findings of largely overlapping activity during imagery and perception of music (cf. review by Zatorre and Halpern, 2005), we interpreted the observed difference between groups in both the behavioral and MEG data as further evidence that the intense musical training has modified cortical networks for auditory processing, resulting a superior ability for imagery of music in trained musicians.

2.5. Effects of musical training on the development of auditory cortical-evoked fields in young children

Although differences between musicians and nonmusicians are usually interpreted as evidence for plastic reorganization of the brain, and correlations with years of training or age of onset of training as well as training-specific effects such as the reported timbre-specific responses provide further support for this interpretation, such correlational evidence from cross-sectional studies is indirect and has been challenged (Monaghan et al., 1998). For example, musicians might be more likely to start and pursue a musical career, because they have better auditory or other relevant skills already before the training due to genetic factors or because they were more strongly exposed to music or encouraged in their practice due to socio-economical factors. Therefore, longitudinal studies and training studies are of high importance to provide conclusive causal evidence for training-induced effects.

In this vein, we addressed more directly the effects of musical training on neuronal correlates of musical processing. In a longitudinal study following Suzuki violin students over the first period of one year, we observed a stronger increase in the neuronal responses to violin as compared to noise stimuli, whereas such a differential effect was not found in a group of children of the same age, who did not take violin classes (Fujioka et al., 2006). Both groups were comparable regarding other extra-curricular activities, time spent on listening to music and parents' musical background. Auditory evoked responses to a violin tone A4 (fundamental frequency of 440 Hz) and a 500 ms noise-burst stimulus were measured by MEG in four repeated measurements over the one-year period. The corresponding cortical source strengths showed prominent bilateral peaks of various transient components of the auditory evoked field: P100, N250, P320, and N450 peaks (cf. Fig. 4), which in children has different configuration as compared to adults. Significant changes in the peak latencies of all components except P100 were observed over time. Larger P100 and N450 amplitude as well as rapid change of N250 amplitude and latency was associated to the violin rather than the noise stimuli. Larger P100 and P320 peak amplitude in the left hemisphere than in the right

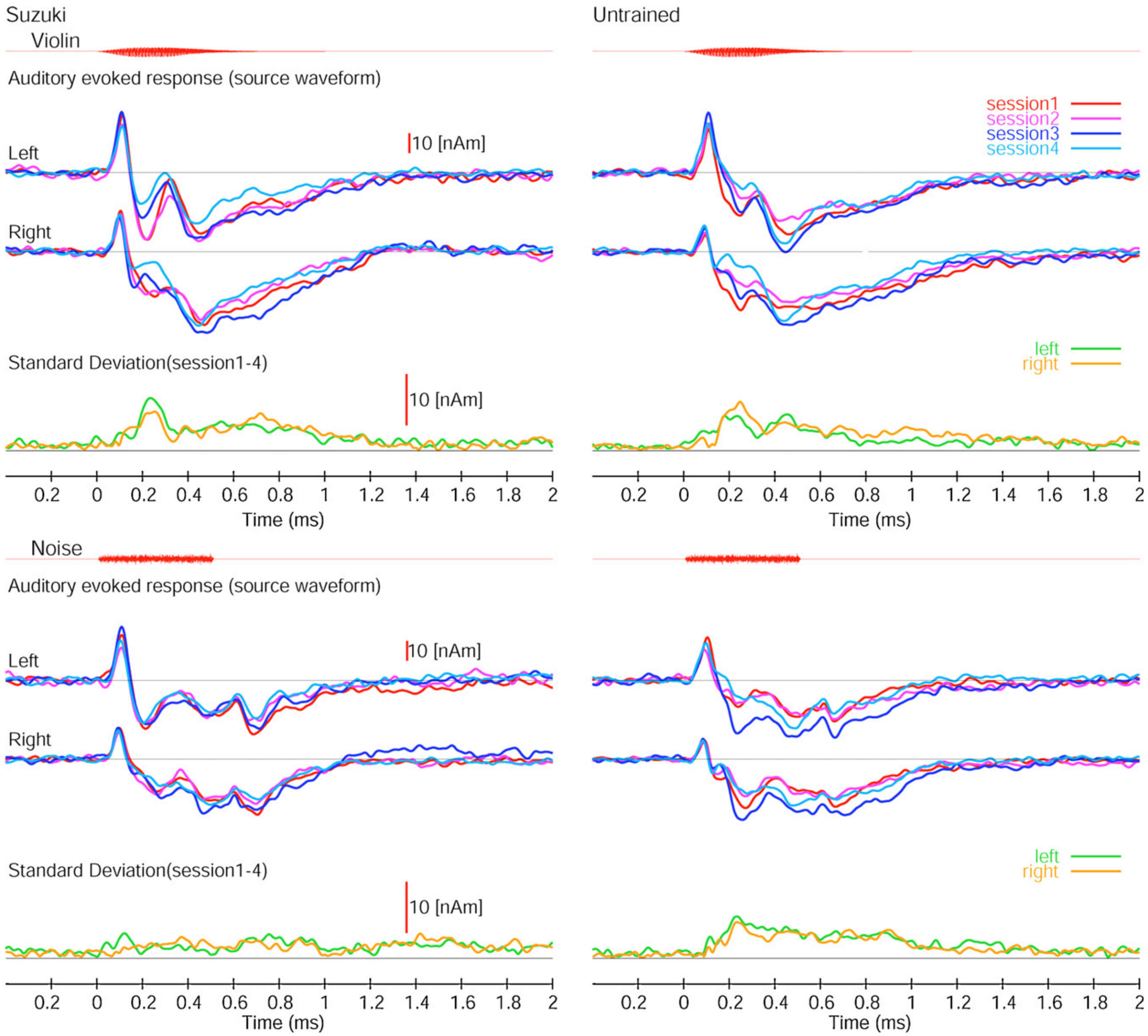

Fig. 4. Grand averaged source waveforms at each session with its standard deviation across all sessions in each hemisphere in response to violin and noise stimuli from (left) Suzuki-music-trained subjects and (right) non-musically trained subjects (from Fujioka et al., 2006).

were consistent with left-lateralized cortical development in this age group.

A clear musical training effect was expressed in a larger and earlier N250 peak in the left hemisphere in response to the violin sound in musically trained children compared to untrained children. This difference coincided with pronounced change in the waveform morphology during the time window between 100 and 400 ms, which was observed in musically trained children in response to violin stimuli only, whereas in untrained children a similar change was present regardless of stimulus type. This transition could be related to establishing a neural network associated with sound categorization and/or involuntary attention, which can be altered by music learning experience.

2.6. *Effects of musical training on pitch processing in language*

Music and language share cortical networks, and therefore it is plausible that the plastic changes caused by musical training affect language processing and acquisition as well (Koelsch et al., 2002a; Maess et al., 2001; Zatorre et al., 2002). One aspect of language processing that is highly related to music processing is pitch (please see review by Kraus and Chandrasekaran, 2010, for a discussion on effects of musical training on other auditory skills). Pitch cues are important not only in tonal languages such as Mandarin Chinese, but also in non-tonal languages to indicate sentence meaning via the pitch contour of the sentence (prosody). In a study investigating pitch processing of Mandarin pitch contours in speech stimuli, Wong et al. (2007) showed that musicians compared to nonmusicians have a more robust and faithful representation of pitch contours at a neuronal processing stage as early as the brainstem, as assessed in the frequency following response (FFR) in EEG. Significant correlations with years of musical training and age of onset of musical training again indicate a training-based effect. Also, learning success in learning an artificial language in which words had to be distinguished based on Mandarin-like pitch contours can be predicted by the volume of left-hemispheric Heschl's gyrus, the first cortical stage in which pitch is encoded (Wong et al., 2008), as well as by the amount of musical training of the participants (Wong et al., 2009a). Learning success is also related to bilateral activity in posterior superior temporal lobe during sound-pattern classification already before language training started.

This confirms the important role of auditory cortex in the analysis of pitch cues in language. In a very recent study, Marie et al. (2010) provided evidence that processing of pitch information in Mandarin words is enhanced in musicians compared to nonmusicians, and that this is related to event-related potentials in auditory cortex. Musicians and nonmusicians who did not speak Mandarin had to discriminate sequences of Mandarin words that differed in terms of their tonal or segmental (vowel or consonant, respectively) information. Musicians performed better than nonmusicians in both conditions, and also showed an increased and earlier N2/N3 component to tonal variations that reflects stimulus discrimination, as well as an earlier and enhanced P3b (categorization and decision processes; also modulated by task difficulty and confidence in response) to both variations. Importantly, the N3a component that reflects attention was similar in both groups, and therefore the group differences are likely not caused by different attention.

Another line of research indicates that musicians not only have enhanced processing for foreign language sounds, but also for pitch variations in their own language (Besson et al., 2007). A study on French speakers showed that musicians can better perceive subtle pitch incongruities in short melodies and in spoken sentences, where the fundamental frequency (F0) that corresponds to the perceived pitch was altered in the last tone or word (Schon et al., 2004). The superior detection performance for these weak incongruities was reflected in a larger positivity to weak compared to congruous endings, that was observed only in musicians.

Furthermore, in two longitudinal studies with kids, the effect of musical training was compared to the effect of a painting training. Importantly, children were comparable regarding intelligence and socio-economic status, and were randomly assigned to the trainings. In the first study that has been conducted in France, music and painting training of 8 weeks duration did not lead to clear differences regarding pitch processing in language between the groups behaviorally, but there was a reduction of late positivity to strong pitch incongruities in speech stimuli in the music group (Moreno and Besson, 2006). In a second study that has been conducted in Portugal and that involved music and painting training of 15 months duration, children in the music group, but not in the painting group, showed better detection of pitch incongruities in music and language, associated with enhanced N300 and P600 to subtle pitch incongruities (Moreno et al., 2009). As both trainings were comparable regarding the amount of time that children spent on the respective activity, and the motivation and joy they showed in the course of the training, these factors can be excluded as explanations for the observed effects. Another recent study by Oechslin et al. (2010b) reported somewhat contradictory results, as they found a deactivation in auditory areas in response to speech prosody in musicians compared to nonmusicians. This observation was interpreted by the authors as a sign of more efficient processing associated with higher proficiency in processing of auditory information. Different methodology, trainings, age groups and stimuli might lead to activity changes in different parts of auditory cortex. Further studies will have to reveal how interactions between different auditory areas during speech processing are modulated by musical training and how this changes in the course of brain development.

2.7. *Effects of passive exposure to music*

There is now evidence that even passive exposure to music in everyday life shapes the way we perceive and process music. Not only are even nonmusicians able to process complex musical syntax in chord progressions (Koelsch et al., 2000), but studies by Wong and colleagues also showed that implicit knowledge about musical scales and meters is specific to the listener's own musical culture (Wong et al., 2009a,b). Bimusical subjects, that is, persons who are familiar with two different musical cultures (Indian and Western style) show similar cognitive (recognition) and affective (tension judgements) responses to Indian and Western music excerpts, whereas monomusical subjects showed differential patterns, favoring the musical style that they were familiar with.

Passive exposure to music (in some cases during many years) may be sufficient for some level of musicality and plastic neuronal changes, but studies showing differences between musicians and nonmusicians seem to suggest that more fine-grained auditory discrimination skills can only be acquired through active training. In the following sections we will discuss studies that investigated the short-term effects of different types of training on auditory processing, from purely auditory to instrumental training.

3. Short-term cortical plasticity due to musical training

3.1. *Plasticity of the human auditory cortex induced by auditory training*

Most studies of musically induced plasticity of the auditory cortex have compared musicians with years of extensive training to non-musicians. However, the differences between musicians and non-musicians described above may, however, not only be the result of life-long training. Becoming a musician may also be related to innately driven musical talent, socio-economic factors or different learning skills (Monaghan et al., 1998). Therefore, training musically naive subjects in a laboratory environment and comparing different kinds of training is a method that is even better suited to directly evaluate the effects of training. Therefore, the question arises whether it is possible to induce plastic changes through specific and relatively short-term training. In a first study we investigated this question by having adults learn in the laboratory to discriminate ambiguous "virtual" melodies (Schulte et al., 2002). A short melody of eight harmonic complex tones with missing fundamental frequencies was composed. The perceived pitch of those complex tones corresponded to the beginning of the tune "Frère Jacques" (virtual melody) whereas the harmonics were chosen so that the spectral melody had an inverse contour to the virtual one. Perception of the virtual melody involves auditory binding of the harmonics into one auditory Gestalt.

Ten subjects who were initially only able to perceive the spectral pitch melody were investigated in this experiment. They were intensively trained over the course of several days until they gained the ability to perceive the virtual pitch melody, and we were able to investigate the involvement of plastic re-organizational processes in virtual pitch formation and perception in the auditory cortex (Fig. 5).

Auditory evoked fields were recorded over both hemispheres before and after training in a passive listening paradigm by means of MEG. In all 10 subjects, the training resulted in a sudden switch from the spectral to the virtual mode of pitch perception. The clear change in perception was accompanied by a distinct increase of the transient gamma band response that has been found to be associated with integrative cognitive functions, such as the binding process during object recognition, and by a medial shift of the underlying sources. Also, independent component analysis indicated higher synchronization of the cortical networks involved in the generation of the evoked gamma band activity after achieving the ability to perceive the virtual melody. In summary, the question of learning-induced plasticity in the perception of the virtual pitch of complex tones was directly addressed in this study. The enhancement of the auditory evoked responses can be interpreted either by higher synchronization, or by enlargement of the involved cortical networks, or most likely by both. As the latency of the transient gamma band response is about 30–70 ms after stimulus onset

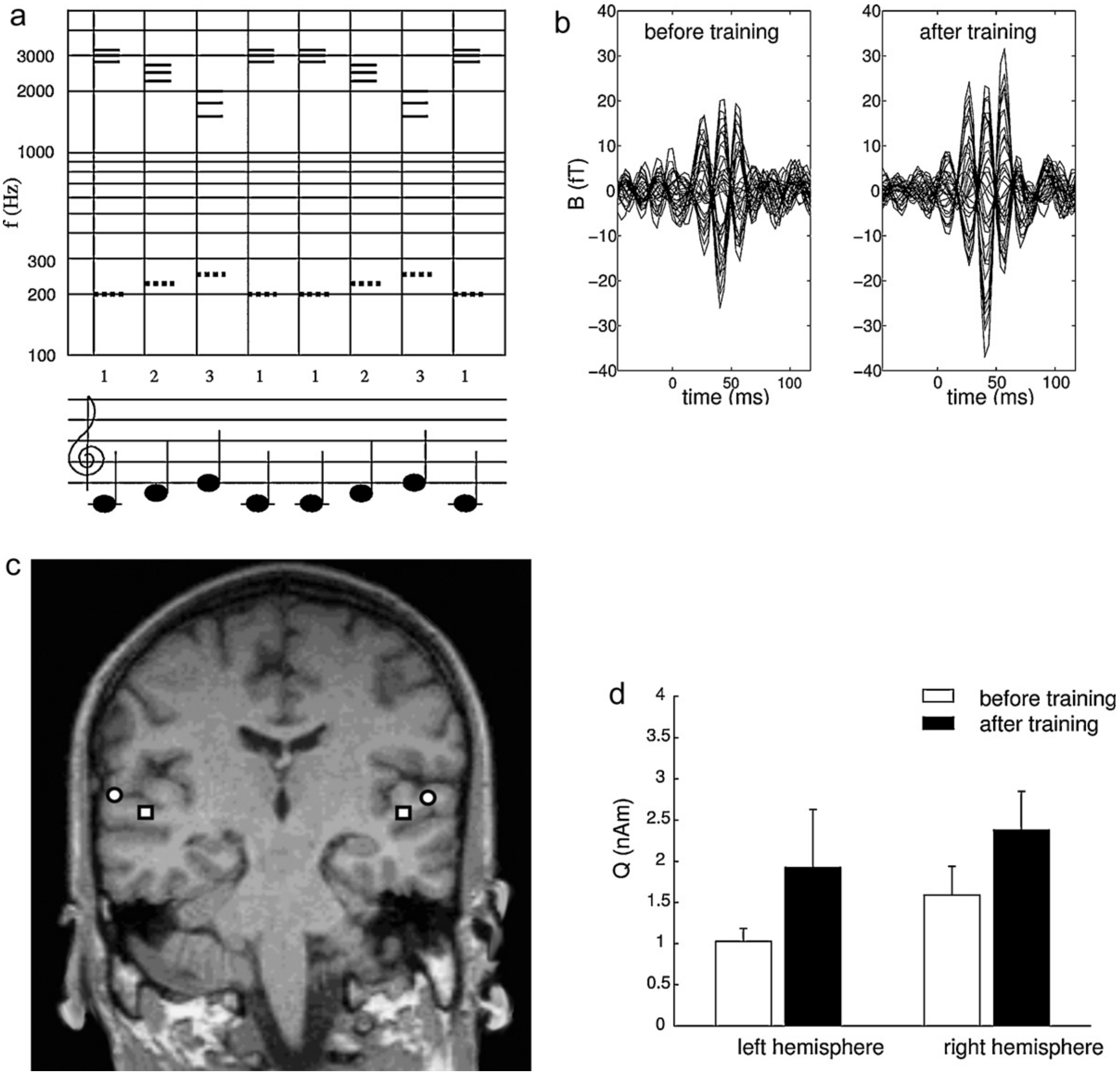

Fig. 5. (a) Stimulus sequence of the virtual melody. The sequence consists of three different complex tones played in the order 12311231. The fundamental frequencies (f_{0i}) were chosen as follow: f_{01}: 200 Hz; f_{02}: 225 Hz and f_{03}:250 Hz. The virtual melody follows the tune 'Frère Jacques' (shown by the dotted line), whereas the spectral melody given by the center frequencies of three harmonics, has an inverse pitch contour. (b) Averaged tGBF of about 600 epochs of one representative subject to tone 1 (band pass filtered: 24–48 Hz). Data are plotted together for the session before (left) and after training (right). (c) Location of the estimated cortical sources of the tGBF integrated into MRI overlay of one individual subject. Circles denote the source location before training and squares denote the estimated location after training. (d) Estimated tGBF cortical source strengths for the left and the right hemispheres, cross-averaged over all subjects. Black bars show the values after training and white bars before training. Error bars indicate the standard error of the mean (from Schulte et al., 2002).

this plastic reorganization of auditory neural networks is likely to take place at the level of the primary auditory cortex.

Several studies have now investigated the effects of pitch discrimination training (Jancke et al., 2001; Menning et al., 2000; Zarate et al., 2010). We showed that a frequency discrimination training over the course of three weeks led to fast behavioral improvements that were accompanied by enhanced N1 and mismatch responses to pitch deviations, thus showing fast plastic changes in auditory cortex (Menning et al., 2000). However, a follow-up measurement 3 weeks after the end of the training revealed that these changes are not lasting, as the amplitudes of the evoked responses decreased again. In a similar fMRI study two randomly assigned groups were compared, one of which received auditory discrimination training over the course of one week (Jancke et al., 2001). The results showed a differential pattern even for subjects within the training group. Subjects who improved in the course of the training and showed improved auditory acuity also showed decreased activity in auditory areas (planum temporale and superior temporal sulcus) in fMRI. Subjects who did not improve in the course of the training and the control group (no training) did not show different activity before and after one week. The seemingly contradicting finding of decreased activity after successful learning was interpreted by the authors as a sign for more efficient processing within auditory cortex and was also explained by differences in methodology (fMRI versus MEG/EEG in most other studies).

The studies reported so far investigated effects of auditory training on auditory perceptual skills. But does auditory training also lead to improvements in productive skills? Zarate et al. (2010) recently addressed this question in a study on the effects of auditory discrimination training on singing proficiency. Based on the hypothesis that poor singers might lack the auditory skill to match their own singing to the required pitches, they trained poor singers on an auditory discrimination task over the course of two weeks. However, whereas their auditory discrimination performance improved markedly, no improvements were seen in their

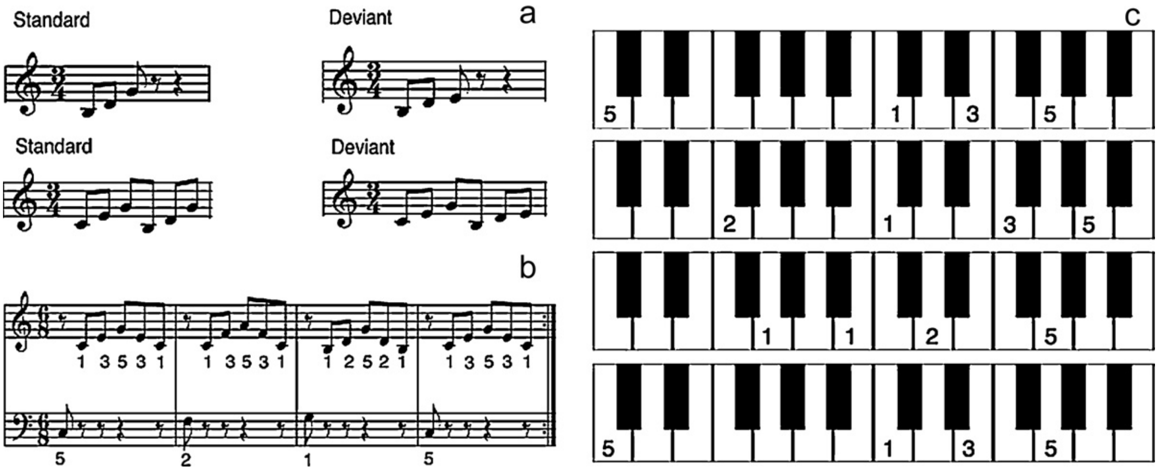

Fig. 6. (a) Tone sequences for the standard and deviant stimuli that were used in the MEG measurements before and after training. (b) Musical score of the I–IV–V–I chord progression in c-major in broken chords that was used as training sequence for SA and A training. (c) Visual templates for the SA training for each broken chord of the training sequence. Numbers represent the fingers (thumb, 1; index finger, 2; etc.) with which the subjects were supposed to press the corresponding piano keys. On each template, the image of the piano keyboard was depicted and the finger placement was marked. For each chord, the notes were to be played in ascending order first, and then descending again (compare score in b) (from Lappe et al., 2008).

vocal proficiency–participants still sang poorly after the training as assessed by a pitch singing and a melody singing task. Also, activity in the cortical network for audio-vocal integration during singing as measured with fMRI did not change before and after training. Thus, it can be concluded that (at least in a short timeframe of two weeks) mere auditory training is not sufficient, but that active vocal training is required to improve vocal accuracy and to change the underlying cortical networks.

As an interim conclusion, short-term auditory training leads to plasticity within auditory cortex regarding the task that is trained, but it might not be sufficient for other auditory functions, and the gained skills are not easily transferable to other tasks. As already described in the introduction, making music is all about multimodal integration of different sensory modalities and motor functions. Therefore, in a recent study we asked the question if it is this multimodal integration during active instrumental practice that makes musical training so effective for cortical plasticity.

3.2. Cortical plasticity induced by short-term uni-modal and multi-modal musical training

The interaction, as well as the integration among different sensory modalities is especially important when playing a musical instrument. Sensory modalities interact, functionally reorganize, and contribute to new qualities of perception that convey information not inherent in each single modality and therefore the strong effects of musical training on cortical reorganization might be due to this multimodal nature of the training. Specifically, we hypothesized that sensorimotor-auditory training in the context of piano playing leads to greater plasticity in the human auditory cortex compared with a mere auditory training. We investigated this using a paradigm that was similar to the melody MMN study by Fujioka et al. (2004) that was described above.

Twenty-three non-musicians with no formal musical training, except for their compulsory school lessons, participated in the study (Lappe et al., 2008). These subjects were assigned randomly to either the sensorimotor-auditory or to the auditory experimental group. The auditory MMN responses from all participants were measured before and after training. Training-induced plasticity was evaluated by comparing the MMN differences and the performance in an auditory melody discrimination test before and after training between the sensorimotor-auditory and auditory groups.

For the MEG measurements before and after training, we used a three- and a six-tone piano sequence (Fig. 6a). Deviant sequences differed regarding the last tone of the sequence. Whereas the three-tone sequence was included in the sequence that was subsequently trained, the three-tone sequence was not. During a two-week training, the sensorimotor-auditory group learned to play the I–IV–V–I chord progression (Fig. 6b) in broken chords using both hands from a visual template that was easy to read for musical novices (Fig. 6c).

In contrast, subjects in the auditory group merely listened to all of the training sessions of one randomly assigned subject from the sensorimotor-auditory group and the training sessions were scheduled in the same way. In order to ensure that the subjects of the auditory group also participated actively in the experiment and listened carefully they had to judge the correctness of the heard sequences.

As expected, auditory discrimination of short melodies improved more strongly in the group that received the piano training compared to the listening group, as assessed by the behavioral test and by the melody MMN to deviant melodies in the MEG. The group averages of the MMN source waveforms before and after training for both groups are displayed in Fig. 7. As can be seen from the waveforms, and as confirmed by the statistical analysis, the training effect, as seen in the increase from pre- to post-training sessions, was much larger in the sensorimotor-auditory group than in the auditory group. In line with a dominant role of the right hemisphere in pitch processing, the overall training effect was stronger in the right hemisphere. Interestingly, this was especially true for the longer six-tone sequence, although this sequence was not exactly contained in the training stimulus, indicating that the generalization of the training effect to other stimuli is especially right lateralized.

Most importantly, we showed that multimodal sensorimotor-auditory training in non-musicians results in greater plastic changes in auditory cortex than auditory-only training. Since MMN is primarily generated in auditory cortex (Picton et al., 2000), the results indicate strong effects of sensory-motor practice on auditory representations. In the present study, we manipulated experience in a well-controlled laboratory setting, group assignment was on a random basis, and auditory input was identical for both groups. Therefore, this study enables us to conclude that instrumental training involving both the sensorimotor and the auditory system leads to stronger functional changes in auditory cortical areas than mere auditory training. Certainly sensorimotor

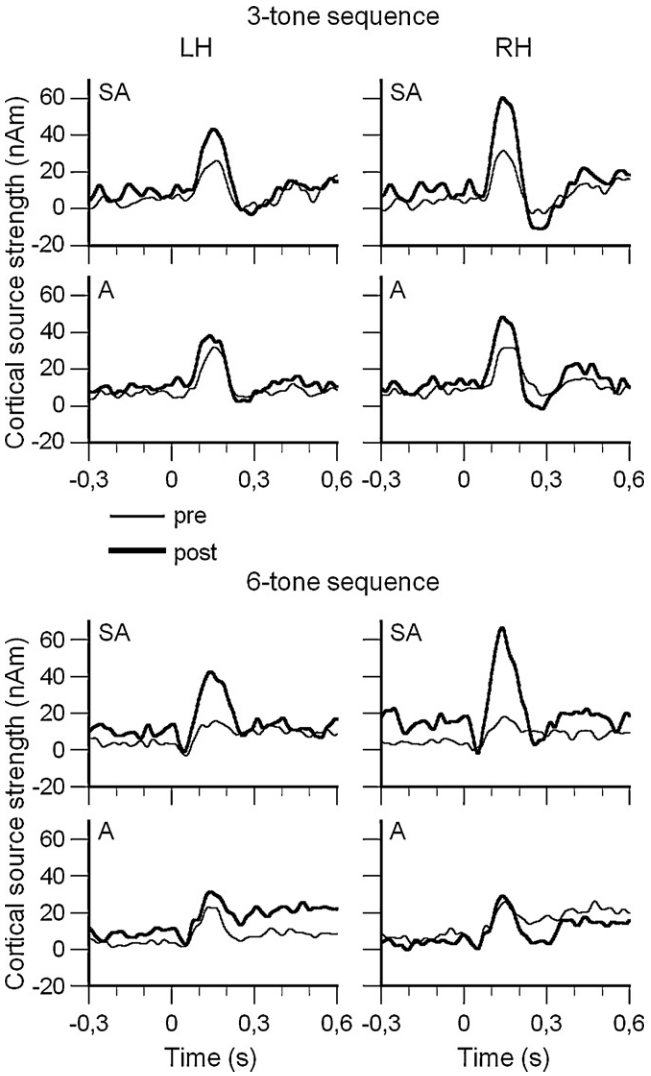

Fig. 7. Group averages of the source waveforms obtained after performing source-space projection before and after training for both groups, stimulus conditions, and hemispheres. Data for the three-tone sequences are shown in the top four panels and data for the six-tone sequences in the bottom four panels. Within each set of four panels, SA group data are shown in the top row, and A group data are shown in the bottom row. Data from the left hemisphere (LH) are presented on the left and those of the right hemisphere (RH) on the right. Thin lines indicate pretraining (pre) data and thick lines posttraining (post) data (from Lappe et al., 2008).

training is more demanding and motivating, causing more attentional resources to be spent on the perception of the tones. Thus, the increased value of attention during the sensorimotor-auditory training is a further factor leading to the increased neural activity in the auditory system.

Further research will have to address the questions of how far such short-term instrumental training generalizes on other auditory and higher cognitive abilities. Also, the respective effects of motivation, attention and the multimodality of the training should be further investigated. All the training studies so far had very different durations and training intensities, from long-term training over the course of many months to short-term training of as little as a week. In order to better evaluate the effectiveness of different types of training, more research on the optimal duration of training and on the long-term effects will be needed.

Plastic changes of the auditory cortex that have been observed in healthy kids and adults hold a lot of potential for therapeutic applications. We will now turn to one very recent example on how plastic reorganization of auditory cortex can help recovery from auditory disorders, specifically tinnitus.

4. Tinnitus: the dark side of the auditory cortex plasticity

Tinnitus is one of the most prevalent symptoms of hearing disorders in the industrialized countries (Heller, 2003; Lockwood et al., 2002) that can severely worsen a patient's quality of life (Eggermont and Roberts, 2004). The tinnitus perception arises in auditory cortex, and tinnitus generation and maintenance have been associated with maladaptive auditory cortex reorganization (Eggermont, 2006; Eggermont and Roberts, 2004; Saunders, 2007).

Maladaptive cortical plasticity in the motor system has been shown to be reversible by behavioral training (Elbert and Rockstroh, 2004; Taub et al., 2002). In this study, we developed and evaluated a customized music training procedure that aims at the reduction of subjective tinnitus loudness in patients suffering from chronic, tonal tinnitus (Okamoto et al., 2010). This training was intended to reverse maladaptive plastic processes in auditory cortex supposedly contributing to the tinnitus perception. For the training, the patients selected their favorite music. Then, the frequency spectrum of the music was modified for each patient individually by digitally filtering out the frequency band of one octave width centered at the individual tinnitus frequency (i.e., the frequency that sounds like the tinnitus). The patients were instructed to listen to their customized music regularly with pleasure.

The results of this training evaluation study demonstrated that those patients who had listened to their pleasant customized music (target group) daily for approximately 1–2 h over the course of 12 months experienced significantly reduced subjective tinnitus loudness. Moreover, subjective tinnitus annoyance as well as experienced handicapping by the tinnitus decreased significantly.

In contrast, matched patients who had instead listened to pleasant placebo music (placebo group) that had moving notch at a frequencies that did not correspond to the tinnitus frequency did not experience any significant changes in these variables over time, and the same holds true for matched patients of the monitoring group who listened to normal, non-modified music throughout this time period (monitoring group).

In order to complement and corroborate the subjective change measurements with neurophysiological data, we additionally measured tinnitus related evoked neuronal activity change from primary (ASSR) and non-primary auditory cortical areas (N1) corresponding to the individual tinnitus frequency by means of MEG (Fig. 8). After 12 months of training, tinnitus related neuronal activity was significantly reduced (Fig. 9) in the target group both regarding the ASSR and N1 responses, but did not significantly change in the placebo and monitoring groups. Additionally, perceived change of tinnitus loudness correlated with evoked neuronal activity change in primary auditory cortex. Patients in whom the tinnitus became less loud exhibited reduced tinnitus related primary auditory cortex activity, and patients in whom the loudness had not changed or had increased exhibited the corresponding change in tinnitus related primary auditory cortex activity.

The observed reductions in tinnitus loudness, annoyance and handicapping as well as the reductions of the evoked neural activity generated in primary and secondary auditory structures appeared cumulatively, indicating a long-term neuroplastic effect. There is evidence in humans that tinnitus is associated with a relative excitatory-inhibitory cortical neural network dysbalance, at the expense of the inhibitory system (Diesch et al., 2010). This loss of inhibition may lead to hyperactivity and/or spontaneous hypersynchrony of a certain cortical neuronal population, which would eventually contribute to the tinnitus perception (Weisz et al., 2005). By means of our customized music modification, we intended to

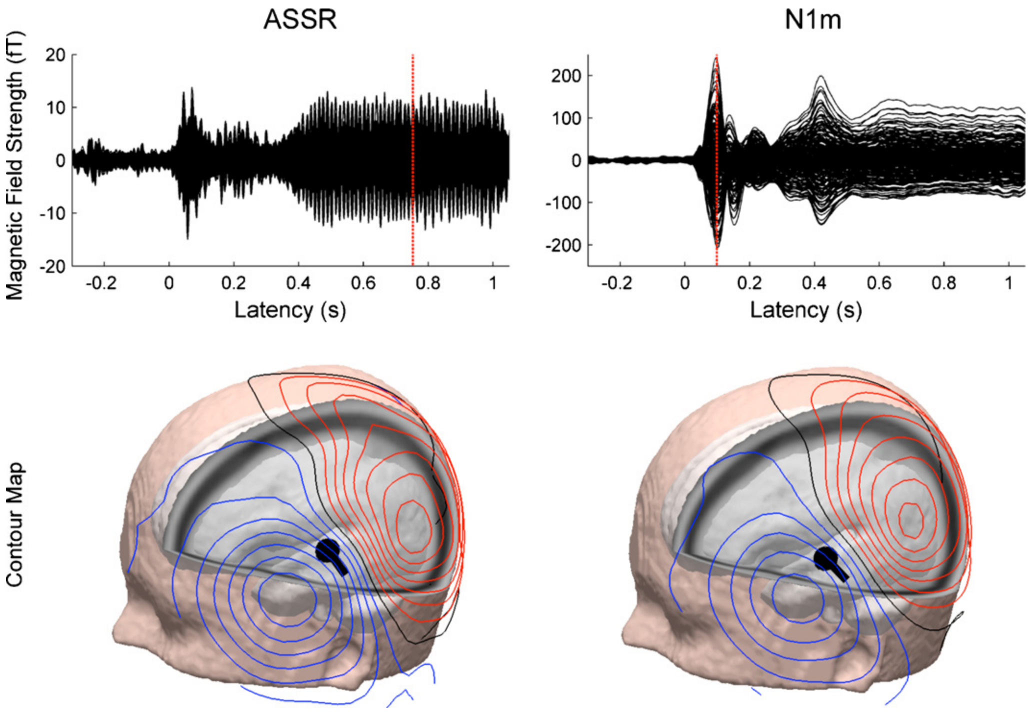

Fig. 8. Examples of measured auditory evoked magnetic fields and estimated underlying sources. *Top*: Examples of averaged measured auditory evoked steady-state response (ASSR, originating from primary auditory cortex) and N1 response (originating from non-primary auditory cortex). *Bottom*: Measured contour maps and estimated dipolar sources corresponding to the responses shown in the top.

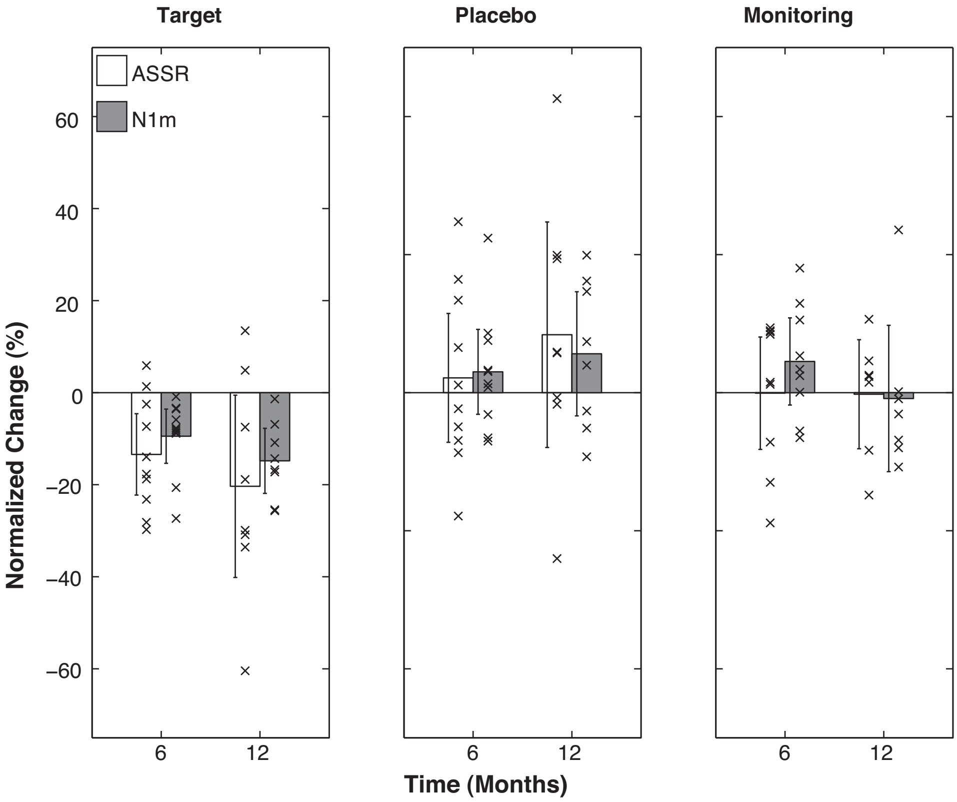

Fig. 9. Normalized tinnitus-related auditory cortex evoked activity change after 6 and 12 months of treatment (or monitoring) relative to baseline (0) for the three patient groups (target, placebo, and monitoring). Positive change values reflect increment, negative change values reflect decrement. The bars indicate group averages; each "×" indicates an individual data point. The error bars denote confidence intervals. ASSR change values are reflected by white bars, N1 change values are reflected by gray bars. The data were normalized as following: [(ASSR or N1_tinnitus frequency after 6 or 12 months/ASSR or N1_control frequency after 6 or 12 months)/(ASSR or N1_tinnitus frequency baseline/ASSR or N1_control frequency baseline) − 1] × 100. As indicated by the confidence interval bars, only the changes in the target group were statistically significant (from Okamoto et al., 2010).

"re-attract" lateral inhibition into these neurons in order to reverse their maladaptive hyperactivity and/or hypersynchrony. The consequence of this induced reversion is that the tinnitus related auditory cortex activity of the target group patients decreased, and correspondingly their tinnitus became less loud (and therefore less annoying and less handicapping). The customization of the training is in several aspects important. One aspect is the customization of the frequency spectrum of an acoustic stimulus in order to reverse maladaptive cortical plasticity. Additionally, it is evident that cortical plasticity benefits from focused attention and enjoyment (Polley et al., 2006). Therefore, it should be advantageous to motivate the brain to process the tailored acoustic input as actively and with as much pleasure as possible, requirements that music, and especially one's favorite music, meets perfectly, as it can absorb attention, and it can elicit positive emotions (Blood and Zatorre, 2001; Salimpoor et al., 2011).

5. General discussion

Musical training perfectly match the conditions that are necessary for studying brain plasticity in humans, since musical training is more complex and multimodal than most other daily life activities and the musicians perform the training with high attention and long-lasting commitment. Learning to play a musical instrument involves training of sensory and motor abilities as well as the coordination and integration of several modalities (Zatorre et al., 2007). Musical training has been shown to modulate uni-modal (Elbert et al., 1998; Pantev et al., 1998) as well as multimodal (Schulz et al., 2003) cortical processing and enhance neuronal co-activation of involved cortical structures such as auditory and motor cortices (Lahav et al., 2007). Investigating long- and short-term training effects in the musical domain yields important information about how the brain is constantly reorganizing itself when confronted with new demands or special environmental influences.

The results presented in this overview open perspectives for future studies, which should also answer open questions that could not yet be resolved. The fact that short-term training of a complex auditory function such as the analysis of melodies can be trained in an experimentally controlled setup is very promising for the study of training effects also on other complex auditory tasks. Comparisons of training effects resulting from short-term musical training and long-term training assessed in similar tasks will allow to differentiate the effects of laboratory training of a specific function and the more general effects of long-term training and to shed more light on the effects of "nature" and "nurture" in musical training.

In the presented studies, the focus of the investigation laid on neuronal processing within the auditory cortex. However, in such complex functions like melodic discrimination, imagery, and higher-order temporal analysis, other brain areas such as frontal areas play an important role as well, and plastic effects of musical training on areas other than auditory cortex can be expected. Using complementary neuroimaging methods like fMRI and multiple-source analysis methods in MEG will yield important information not only on activity in other cortical areas involved, but also on the interactions within the whole network supporting the instrumental performance. This will enhance our understanding about the mechanisms, through which the multimodal training exerts its effects on uni- and cross-modal processing.

The effects of training on cortical plasticity involving music hold promising prospects for neuronal rehabilitation, as shown in the last tinnitus study. By means of a multimodal training, auditory or motor skills impaired by lesions might be recovered more effectively compared to classic rehabilitation programs, for example for the recovery of motor function (Altenmuller et al., 2009; Schneider et al., 2007) or speech (Schlaug et al., 2009) after stroke, but see also the recent review by Koelsch (2009).

Apart from the fact that multimodal training seems to be more effective than uni-modal training, making music can be a very rewarding and positive experience, which might enhance motivation and cooperation of patients in the training, and consequently enhance the therapeutic effects.

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