Review

Musical Training as a Framework for Brain Plasticity: Behavior, Function, and Structure

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Musical training has emerged as a useful framework for the investigation of training-related plasticity in the human brain. Learning to play an instrument is a highly complex task that involves the interaction of several modalities and higher-order cognitive functions and that results in behavioral, structural, and functional changes on time scales ranging from days to years. While early work focused on comparison of musical experts and novices, more recently an increasing number of controlled training studies provide clear experimental evidence for training effects. Here, we review research investigating brain plasticity induced by musical training, highlight common patterns and possible underlying mechanisms of such plasticity, and integrate these studies with findings and models for mechanisms of plasticity in other domains.

It is now widely accepted that experience can modify many aspects of brain function and structure, yet we are still far from understanding the mechanisms underlying this plasticity. In neuroscience, this question is often addressed on the cellular, synaptic, and network level in animals, while in humans it is mostly addressed at the systems and cognitive level. The term plasticity has been used to describe various complex processes and represents a multifaceted phenomenon on different levels and different time frames. In the context of cognitive neuroscience, we use the term plasticity to describe changes in structure and function of the brain that affect behavior and that are related to experience or training; for a discussion of the processes occurring on the cellular and molecular level that may be associated with plasticity, see Buonomano and Merzenich (1998) and Zatorre et al. (2012).

In order to study human experience-related plasticity, we need adequate models and paradigms. One such model for cortical plasticity that has gained increasing interest in the past decades is musical training (Jäncke, 2009; Münte et al., 2002; Wan and Schlaug, 2010; Zatorre, 2005). Playing music involves several sensory systems and the motor system and makes demands on a wide variety of higher-order cognitive processes; this complexity creates challenges but also provides an excellent opportunity to study how sensory-motor systems interface with cognition and how different types of training influence these interactions, all within the same general model framework. Music requires fine-grained perception and motor control that is unlike other everyday activities, thereby reducing confounding influences of other types of experience. Also, the framework of musical training allows the study of both short- and long-term training effects. Studying expert musicians exploits the extraordinary amounts of time that they devote to their instrumental practice, and hence serves as an excellent model for long-term practice on a specific audio-motor task. On the other hand, auditory and/or motor training in a musical context is relatively easy and safe to administer in a lab or clinical environment for investigation of short-term effects of training. Finally, the behavioral consequences of musical training can be readily measured using both psychophysics and cognitive tasks, enabling the link to be made between brain function and structure with behavior.

In this review, we focus on the literature on musical and related training studies, with emphasis on longitudinal studies that allow conclusions about causal relationships. However, we also draw on cross-sectional studies in order to identify overlaps and differences between short- and long-term effects. In the first part of this review, we outline the literature on training effects on the auditory and sensorimotor systems and on their integration. Then, we attempt to relate musical training as a model for plasticity to other models of training and learning, focusing on some aspects of training-related plasticity that we believe yield particular insights to neuroscience, more specifically (1) how the multimodal nature of musical training might enhance plasticity, (2) how plastic effects on different time scales interact, and how this might relate to the concept of metaplasticity, (3) the role of interindividual differences for training success and plastic effects, and (4) how training-related plasticity changes over the life span. Lastly, we illustrate the potential of musical training in a clinical context.

Effects of Musical Training on the Auditory System

The auditory system is of course critical for music, and it is hence one of the systems that is most altered by musical training. Functional and structural changes due to musical experience take place at various stages of the auditory pathway, from the brainstem (e.g., Wong et al., 2007), to primary and surrounding auditory cortices (e.g., Bermudez et al., 2009; Schneider et al., 2002), to areas involved in higher-order auditory cognition (e.g., Lappe et al., 2008). Music has been used both as an active training protocol and as a stimulus in the context of purely auditory training. By comparing these different types of approaches we can shed some light on the extent of plastic changes due to passive and active types of training and the roles and interactions of the brain areas involved. Here, we will focus on neuroscientific findings in humans using behavioral and neuroimaging techniques. We provide a short overview of the advantages and disadvantages of the various imaging techniques in Table 1.

Table 1. Human Brain Imaging Techniques Relevant for Research in Training-Related Plasticity

Imaging Technique	Measures of Interest	Advantages	Disadvantages
Electroencephalograpy	Functional: - Evoked sensory responses (amplitude, latency) - Synchronization of neural activity (oscillations)	- Good temporal resolution - Relatively inexpensive and easily available - Lower susceptibility to movement - Silent - Relatively direct measure of neural activity	- Low spatial resolution - Less sensitive to deep and/or subcortical structures - Indirect localization of sources
Magnetoencephalography	Functional: - Evoked sensory responses (amplitude, latency) - Synchronization of neural activity (oscillations)	- Good temporal resolution - Acceptable spatial resolution for cortical sources - Silent - Relatively direct measure of neural activity	- Susceptible to subject movement - Less sensitive to subcortical structures - Sensitive primarily to tangential sources - Indirect localization of sources
Anatomical Magnetic Resonance Imaging	Structural: - Cortical thickness - Concentration of gray and white matter structures (VBM) - Deformation-based morphometry - White-matter integrity - Direction of fiber tracts (DTI; tractography)	- Good spatial resolution in cortical and subcortical structures - Whole-brain acquisition - Broad availability	- Indirect measures of anatomy - No direct relation between macro- and microstructural antomical variables
Functional Magnetic Resonance Imaging	Functional: - Blood oxygenation level-dependent (BOLD) response - Measures of functional connectivity, network properties	- Good spatial resolution - Similar cortical and subcortical sensitivity - Whole-brain acquisition - Broad availability	- Low temporal resolution - Acoustically noisy - Indirect measure of neural activity

While the many possible mechanisms underlying structure-function relationships with neuroimaging methods are far from being understood (Zatorre et al., 2012), the multimodal nature of the data in this domain provides many testable hypotheses.

It is well established from neurophysiological studies in animals that changes in auditory cortical responses can be elicited by either long-term or short-term exposure to specific, structured sounds. This literature is beyond our scope here, but it is important to point out some general features of these findings that are relevant to the cognitive neuroscience of music. First, it is well known that that there are long-term changes to map properties of auditory cortex as a function of exposure to specific stimuli (Ahissar et al., 1998; Bao et al., 2004; Bergan et al., 2005; Bieszczad and Weinberger, 2010; Gutfreund and Knudsen, 2006; Linkenhoker and Knudsen, 2002; Mercado et al., 2001; Polley et al., 2006). These changes take many forms depending on the behavioral paradigm used (classical conditioning, stimulus-response learning, perceptual learning, etc.) and can involve changes to both receptive field properties and to temporal aspects. Often an expansion is seen in specific tonotopically organized cortex, although reductions can also be elicited under some circumstances (Shetake et al., 2012). Second, such changes are typically quite task-specific even within the same cortical region (Ohl and Scheich, 2005; Polley et al., 2006). Third, reorganization is strongest when the auditory input is behaviorally relevant and if a task is actively trained (e.g., Fritz et al., 2005; Ohl and Scheich, 2005; Recanzone et al., 1993). Fourth, cortical remapping and adaptation of neural tuning are critically dependent on the reward value of the learned stimulus (Blake et al., 2006; David et al., 2012), which in turn is likely related to neuromodulatory influences arising from midbrain and forebrain nuclei (Bakin and Weinberger, 1996; Bao et al., 2001). Fifth, these changes are influenced by the maturational state of the nervous system, being generally greater during certain early periods of development (de Villers-Sidani et al., 2007, 2008). Finally, there are also short-term changes in neural response properties that reflect contingencies of a given task, and that are also quickly reversible (Fritz et al., 2005). The heterogeneous nature of these neurophysiological phenomena reflect the multifaceted nature of the cortical response to environmental inputs, and although this complexity poses a challenge for neurocognitive models, it also provides important knowledge that can be helpful in interpreting systems-level data obtained in the context of musical training studies. Parallels to some of these effects are numerous in the human literature.

Auditory Training
Cognitive processing of music is not in itself dependent on active or formal musical training, as even people without any special musical experience clearly have a good understanding of music, and show sensitivity to musical relationships like tonality (Krumhansl et al., 1982; Toiviainen and Krumhansl, 2003) and meter (Hannon et al., 2004). The evolutionary basis of music is still under debate (Fitch, 2006; Hauser and McDermott, 2003; McDermott, 2008), but there is no doubt that music originates very early in human history (Conard et al., 2009). Behaviorally, attention and sensitivity to music has been clearly demonstrated

in studies of infants, who consistently show precocious abilities to detect musical regularities and deviations from them, as shown for features such as tuning of chords (Folland et al., 2012), the pitch of the missing fundamental in complex sounds (He and Trainor, 2009), and musical phrase structure (Jusczyk and Krumhansl, 1993). The contingencies of musical relationships are believed to be learned implicitly through statistical learning at an early age via appropriate exposure, paralleling the way that native speech competence is acquired (Saffran et al., 1996). This suggests innate factors for the acquisition for both types of auditory information. Through exposure during the first few months and years of life, a quick narrowing to the relevant cultural sounds takes place, both for music (e.g., scale properties) and speech sounds (e.g., phonemes and prosody) (Kuhl, 2010).

Research in musically untrained people indicates that specific neural circuits respond to knowledge of musical rules acquired via exposure in every-day life. Koelsch et al. (2000) showed EEG evidence of sensitivity to violations of musical rules in chord sequences even in musical novices, indicating implicit learning of these rules. Relatedly, Tillmann et al. (2006) found that BOLD signal in frontal and auditory areas was modulated by the harmonic relationship of chords, indicating sensitivity to knowledge of musical structure. In a behavioral cross-cultural study, Wong et al. (2009) showed that the specific rules inherent in Western or Indian music are implicitly learned by people who grow up in either of these cultural environments. These results seem to indicate that passive exposure to music alone is sufficient to alter the neural response to musical sounds to some extent. These changes mostly happen at the later stages of auditory processing, where the complex relationships of harmonies and rhythms are being processed. There is less evidence that early stages of processing are already affected by such long-term passive auditory input for music, but some studies have shown effects of expectancies based on rules of chord progression (Marmel et al., 2011) and influences of more specific (musical) experience (Musacchia et al., 2007; Wong et al., 2007) on early brainstem processing for speech and nonspeech stimuli. Whether these changes in brainstem responses represent intrinsic modifications to brainstem circuitry and/or efferent modulation from cortical regions remains to be established, however. In auditory cortex, Pantev et al. (1999) reported that within as few as 3 hr of listening to music that had been bandpass filtered to remove specific frequencies, neuronal responses to tones that were within the filter band were diminished, while responses to frequencies outside the filter band remained unaltered. These responses always reverted to baseline overnight, indicating a fast, but short-lasting functional adaptation of the response properties of auditory neurons, similar to mechanisms of short-term and task-specific adaptation of auditory neurons in animal models (Ohl and Scheich, 2005). Whereas the effects of such passive short-term exposure could be explained by plastic changes mediated by local inhibitory circuitry from within auditory cortex, and perhaps via thalamic inputs, long-term effects on higher-order music cognition are most likely also mediated by interactions with top-down mechanisms; attention to the music of one's culture, which occurs from very early on (Trainor and Heinmiller, 1998), would no doubt be one such factor.

As with passive exposure, training effects in active auditory discrimination paradigms in humans can be found on different levels of processing. Short-term discrimination training of linguistic pitch contours and training to enhance speech in noise perception increase the fidelity of the neural encoding of pitch at the brainstem level (Carcagno and Plack, 2011; Song et al., 2008, 2012). At the level of the cortex, discrimination training in EEG/MEG studies results in improved pitch discrimination and increased auditory evoked potentials originating from secondary auditory cortex (Bosnyak et al., 2004; Menning et al., 2000) and increased synchronization of neural networks in secondary auditory cortex (Schulte et al., 2002). Similar effects of short-term training have also been found using speech material, where active discrimination training between subtle timing differences (Menning et al., 2002) or vowels (Alain et al., 2007) resulted in behavioral improvements and corresponding increases in evoked auditory responses from secondary auditory cortex. fMRI studies of perceptual learning with pitch tasks have shown both increases (Gaab et al., 2006) and decreases (Jäncke et al., 2001; Zatorre et al., in press) of activity in auditory areas, as is also the case with other types of perceptual learning (Kelly and Garavan, 2005). These global changes can be difficult to interpret as they may be linked to changes in task difficulty, attention, or other nonspecific factors that accompany learning (Poldrack, 2000). However, in one study perceptual learning decreased the slope of the function relating BOLD to pitch-interval size in microtonal stimuli (Zatorre et al., in press). Such specific reduction to a particular feature suggests that the outcome of learning under some circumstances may be that fewer neuronal units are needed to encode a given level of information, as also suggested for visual perceptual learning (Yotsumoto et al., 2008).

Findings of specific adaptations within a sensory system raise the question of the behavioral relevance and transfer to other, related tasks. However, pitch discrimination training for instance does not necessarily lead to improved vocal performance or associated neural changes (Zarate et al., 2010). Thus, transfer from sensory to motor domains cannot be assumed. It is important then to ask how active musical training that involves producing sound influences sensory responses and more generally what its effects are on the entire sensory-motor system.

Instrumental Musical Training

Several recent studies have looked at training that involves actively playing a musical instrument and that therefore involves the sensorimotor system in addition to the auditory system. Many studies on the effects of instrumental musical training are cross-sectional in nature, comparing groups of musicians and nonmusicians; since here we are mostly interested in training studies, we will emphasize those that pertain most to the results of later training studies. For example, musicians show enlarged auditory cortical evoked potentials to piano tones (Pantev et al., 1998), and this effect can be additionally modulated according to the timbre of their own musical instrument (Pantev et al., 2001), especially in the right auditory cortex (Shahin et al., 2003). Complementary fMRI findings were reported when comparing violinists and flutists (Margulis et al., 2009), where an experience-specific network encompassed auditory associations areas related to timbre processing, and also precentral and inferior frontal areas involved in

auditory-motor interactions and in musical syntax processing, respectively. More recently, instrument-specific tuning has been demonstrated as early as the brainstem level (Strait et al., 2012). Such instrument-specific effects provide good evidence for experience-dependent plasticity.

The effects of experience have been tested more directly in longitudinal studies that followed children taking instrumental lessons with the Suzuki method. The Suzuki method is particularly suited for systematic studies because it is standardized, because no preselection of students based on inherent talent takes place, and because the training focuses on playing by ear and learning by imitation. Although some studies have not provided conclusive proof for specific training effects in evoked electrical responses (Shahin et al., 2004), induced gamma-band responses reflecting binding of auditory features such as pitch and timbre did increase due to the training (Shahin et al., 2008), an effect that is similar to instrument-specific enhancements seen in adult musicians (Shahin et al., 2008). In another longitudinal study on 4- to 6-year-old children being trained with the Suzuki method (Fujioka et al., 2006), changes in amplitude and latency of several components of the auditory evoked fields to both a violin and a noise stimulus were evident in both groups, due to maturation, but the training group showed additional decreases in latency that were specific to the violin tone. These neural changes were accompanied by improvements on a behavioral musical test and also in a nonmusical working memory task, whereas no such changes were observed in the control group. However, people who enroll their kids are unlikely to be a random sample of the population, in particular with respect to musical exposure in the home, which may contribute to preexisting group differences.

The convergence of the results from adult musician-nonmusician comparisons and of the longitudinal studies shows that the auditory system can adapt to the specific relevant sounds in the environment, in agreement with the more controlled animal studies mentioned above. But as with the neurophysiological studies, the nature of the changes seems to vary, since different components of the auditory evoked response are affected in different studies, with either latency or amplitude also vary in their responses to training. Among the many factors that could influence the outcome of training is the potential interaction between the auditory input and the motor output required to produce it. Instrumental training could enhance the behavioral relevance of (and/or attention to) musical sounds, but it could also influence the reorganization in auditory cortex via sensory-motor interactions. Two recent studies (Lappe et al., 2008, 2011) have dissociated the effects of auditory exposure alone from active instrumental training by using two different paradigms: an auditory-sensorimotor and an auditory-only protocol. Whereas one group learned to play stimuli on a piano over 2 weeks, the control group only listened to the piano group's recordings attentively, detecting errors in performance to ensure attention. When compared to the control group on auditory discrimination, the piano groups showed better ability to detect incorrect pitch or timing after training, as well as larger increases in auditory mismatch negativity to these deviations in MEG measurements. These group differences indicate that the active sensorimotor input during the training shapes auditory responses, likely through interconnections between auditory and motor areas (Zatorre et al., 2007). Importantly, as the group assignment was random, the observed changes in behavior and neural responses could clearly be attributed to the piano training itself (Lappe et al., 2008, 2011). The increased auditory responses in the auditory-sensorimotor training group were similar to increases in auditory responses to unexpected tones in melodies that are observed in musicians compared to non-musicians (Fujioka et al., 2004). The fact that the gains in the auditory-only groups were very small seems to indicate that even attentive listening that involves a task, and thus gives the stimuli behavioral relevance, is not sufficient for measurable plasticity. However, 2 weeks might simply not be enough time for such changes, so controlled studies examining neural processing of specific sounds over a longer period of time would be valuable.

Further studies suggest that training-related changes in auditory cortex might not only take place on the functional level, as seen by blood oxygenation and auditory evoked responses, but also on the anatomical level. Several cross-sectional studies have demonstrated greater volume, concentration, or thickness of auditory cortices in trained musicians (Bermudez et al., 2009; Gaser and Schlaug, 2003; Schneider et al., 2002), although they differ in the precise cortical areas identified. Apart from the caveats mentioned earlier for cross-sectional studies, one important consideration in examining structure is determining its relation to function; without a clear demonstration of its functional significance, a structural difference is more difficult to interpret (Johansen-Berg, 2010). Schneider et al. (2002) reported that both the volume of Heschl's gyrus and amplitude of an early MEG response originating from primary auditory cortex were largest in professional musicians and smallest in nonmusicians, and were also related to behavioral performance. Foster and Zatorre (2010) found that cortical concentration and thickness in right auditory cortex and the intraparietal sulcus region bilaterally were predictive of performance on a musical transposition test. These two studies thus demonstrate that anatomical features can be linked to behavioral performance, implying that the structural effects reflect task-relevant adaptation. Converging results were seen in a longitudinal study of anatomical changes: children who received piano lessons over 15 months showed training-related changes in motor cortex, corpus callosum, and in right Heschl's gyrus, accompanied by correlated behavioral changes in motor sequencing and auditory discrimination, while a matched control group only showed the age-typical maturational changes (Hyde et al., 2009).

Effects of Musical Training on the Motor Network
Musical performance engages a distributed motor network that is specific to the type of action, with larger recruitment of hand areas in instrumental performance such as violin or keyboard playing (Lotze et al., 2003), versus representations of the vocal tract in singing (Kleber et al., 2007). Also, the auditory and sensorimotor systems are closely linked not only in actual instrumental practice, but also in mere perception of music (Zatorre et al., 2007), and coactivation of the respective other modality can be observed during listening, for example, to musical rhythms (Chen et al., 2008a; Grahn and Rowe, 2009), and during playing

on a silent piano keyboard (Baumann et al., 2007). There is a large literature on the acquisition of motor skills through training, suggesting different contributions of parts of the motor network in different phases of learning (Doyon et al., 2009; Hikosaka et al., 2002). Models of motor skill learning suggest that M1 and premotor cortices are particularly important for learning and storage of the representation of a specific motor sequence, whereas the basal ganglia are more strongly involved in initial stimulus-response associations, and the cerebellum is engaged in online error correction mechanisms, and in optimization of acquired motor sequences (Penhune and Steele, 2012). These models fit well with short- and long-term musical training effects, which have mostly been found for the cortical and cerebellar parts of this network, possibly related to the fact that in music learning fine-tuning of complex motor sequences is most relevant.

In a cross-sectional study of highly trained pianists, anatomical changes to motor-related pathways were seen in white matter micro-organization as measured with diffusion imaging (Bengtsson et al., 2005), such that amount of musical practice during childhood was associated with greater integrity of corticospinal tracts. Other parts of the motor network that differ anatomically between trained musicians and nonmusicians include the anterior corpus callosum (Schlaug et al., 1995), motor and premotor cortex (Bermudez et al., 2009; Gaser and Schlaug, 2003), and the cerebellum (Hutchinson et al., 2003). White-matter connections between auditory and anterior regions also appear to be anatomically more well-organized in musicians (Halwani et al., 2011), a finding which fits well with the more focal cortical thickness intercorrelations reported between temporal and frontal cortices among musicians (Bermudez et al., 2009).

Changes in the cortical representations within the motor network can also be related to the specific type of instrumental practice. Bangert and Schlaug (2006) showed that pianists' and violinists' brains can be distinguished even on the gross macroscopic level by examining the shape and size of the part of the motor cortex that contains the representations of the hands. Moreover, pianists and violinists differ regarding lateralization, with a left- and right-hemispheric enlargement, respectively, in line with the fine motor control required for their instruments. Elbert et al. (1995) showed that the cortical representations of the fingers of violinists' left hands, which are engaged in fine-tuned fingering of the strings during playing, are expanded as assessed by the amplitude and source location of tactile evoked responses measured in MEG, compared to their right hands' representations or to controls. Similar to the timbre-specific neuronal responses in different types of instrumentalists, such distinctions based on instrument played are a strong argument in favor of experience-related changes. What is less clear from this literature is how specific changes in certain portions of the motor networks are related to specific motor abilities, or to the nature of the motor abilities themselves (timing, sequencing, fine motor control, multijoint coordination, etc.) and what the underlying mechanisms of expansion of cortical areas on the cellular and molecular level are (Buonomano and Merzenich, 1998; Zatorre et al., 2012).

There is also evidence of structural changes in the motor network due to musical training from longitudinal training studies: in their training study, Hyde et al. (2009) also found effects of piano training on the primary motor hand area and on the corpus callosum, which were related to performance on a motor sequencing task, thereby again demonstrating the behavioral relevance of the observed cortical changes. The development of some motor skills might be particularly sensitive to early training (Penhune, 2011), but training effects can still be seen in adults, and on shorter time scales. These short-term studies show effects mostly regarding functional activity. Lahav et al. (2007) taught nonmusicians to play a familiar melody on the piano over the course of five days and measured their cortical activity using fMRI during listening to the trained and untrained melodies. Subjects showed increased activity in the motor network including ventral premotor and parietal areas during listening to the trained melodies compared to the untrained ones, presumably due to coactivation of motor areas during auditory perception reflecting new sound-action (piano-keystroke) associations. The roles of the ventral and dorsal parts of the premotor cortex in musical training were further elucidated in a recent study by Chen et al. (2012), in which participants learned to play a short melody on a piano within a single (albeit long) fMRI scanning session. The results revealed that dorsal premotor cortex, which is thought to be involved in abstract conditional sensorimotor associations (Hoshi and Tanji, 2007; Petrides, 1985), was only active after participants had successfully learned to play the melody and had established a representation of the key-sound mapping; the ventral part, which is typically involved in more direct sensory-motor mapping (Zatorre et al., 2007), showed decreased activity over the course of the training, in particular for the specific trained sequence, indicating its role in the initial learning of the motor sequence.

Multimodal Interactions and Integration in Musical Training

Because auditory and motor function are closely linked in musical performance, it seems plausible that training should not only affect those modalities separately, but also their interactions (e.g., Bangert et al., 2006; Chen et al., 2008a, 2008b; Haueisen and Knösche, 2001; Phillips-Silver and Trainor, 2007; Schulz et al., 2003; see also review by Zatorre et al., 2007). How does this functional link influence short-term training? Piano training results in increased auditory-motor coactivations already after 20 min of practice, and more stable effects are seen after 5 weeks, but only training with consistent finger-key mapping results in additional changes in right anterior frontal cortex (Bangert and Altenmüller, 2003), which is important for establishing new sound-action representations (Chen et al., 2012). The effects of cross-modal interactions on the motor domain after practice were also shown using transcranial magnetic stimulation (TMS) in pianists (D'Ausilio et al., 2006). After practicing a new piece of piano music, the excitability of motor cortex increased during the perception of the practiced piece, but not to a flute piece that the pianists were not able to perform. Both studies clearly show the effects of the auditory-motor interaction on short-term changes in the auditory and motor systems.

Music is an excellent framework to study the effects of uni- versus multimodal approaches. The fact that training involving
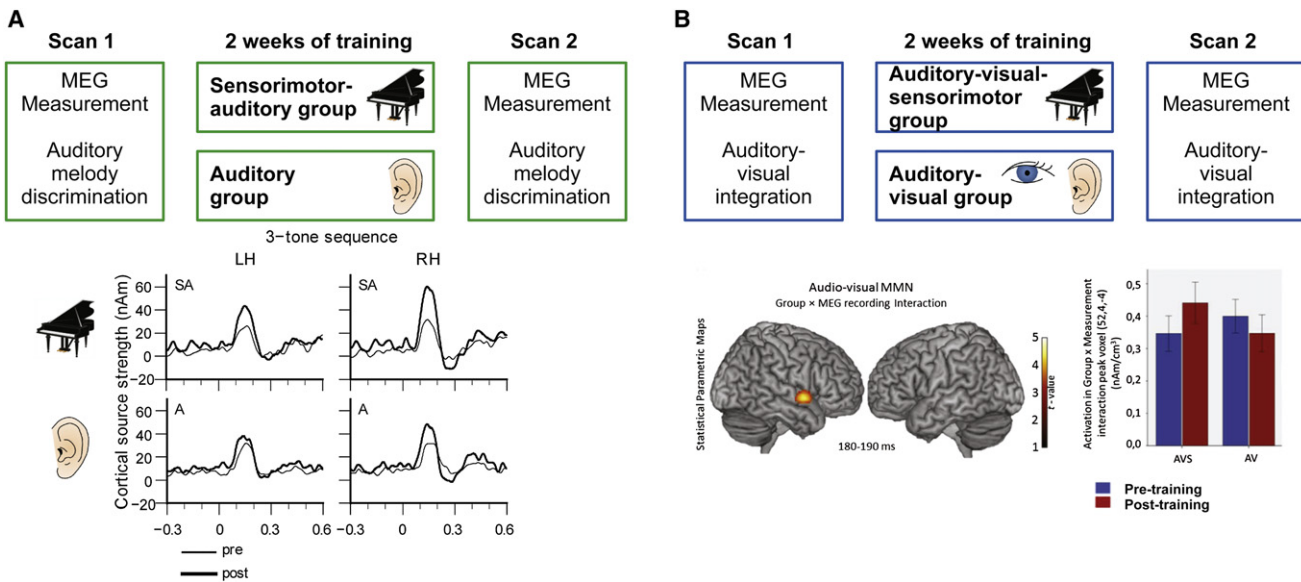
Figure 1. Neuronal Plasticity in Auditory and Association Cortices Due to Multimodal Training
Left panel: Piano training (sensorimotor-auditory, group "SA") compared to purely auditory training (group "A") resulted in a stronger enhancement of the auditory mismatch negativity to unexpected tones in a short melody after 2 weeks of training (adapted from Lappe et al., 2008). Right panel: Training to play short melodies on a piano based on simple visual notation (auditory-visual-sensorimotor, AVS group) resulted in stronger increases of responses to audio-visual incongruities (audio-visual MMN) than audio-visual training (AV group) that did not involve an active motor component (adapted from Paraskevopoulos et al., 2012).

more than one modality can lead to stronger plastic changes in auditory processing than training in the auditory modality alone (e.g., Lappe et al., 2008, 2011; Figure 1) can be interpreted in the context of the strong functional connections that exist between the auditory and motor system during music perception and performance (Bangert and Altenmüller, 2003; D'Ausilio et al., 2006; Lahav et al., 2007; Zatorre et al., 2007). This close functional connection suggests that Hebbian mechanisms based on the simultaneous inputs resulting in changes in synaptic strength are responsible for the multimodal plastic effects. The TMS study by D'Ausilio et al. (2006) supports such a mechanism, and other research indicates that the coactivation of cortical areas by a stimulus input (e.g., median nerve) and by a TMS pulse (e.g., to the hand region of motor cortex) results in local functional plastic changes (Stefan et al., 2000). After combined stimulation, the thresholds for motor evoked responses by TMS are modulated, depending on the delay between the stimuli and the pulse, which is interpreted as analogous to long-term potentiation and depression on the cellular level (Hoogendam et al., 2010). This paradigm has been applied in the auditory system using combined tones and TMS pulses on auditory cortex (Schecklmann et al., 2011), and in a cortico-cortical motor network using combined pulses on premotor and motor cortices (Buch et al., 2011). Although this technique has not yet been applied to test cross-cortical connections in musical training, the findings seem to indicate that plasticity based on simultaneous inputs in cortical networks might underlie the training effects observed during multimodal training. This phenomenon might be at the heart of some of the changes in white-matter pathways described above (Bengtsson et al., 2005; Hyde et al., 2009; Schlaug et al., 1995), since temporal synchrony in

distant cortical regions would be required to implement the necessary sensory-motor processes to play an instrument, which in turn would benefit from better-organized or more myelinated tracts (Fields, 2008).

Musical training also seems to affect the extent of cross-modal integration. In a successful musical performance, stimuli from several modalities have to be processed with high temporal precision. Audio-visual integration involving tones and lights can be demonstrated even in musically untrained subjects (Elmer et al., 2012). However, the integration of the senses seems to be enhanced by musical training in relevant domains, as shown in increased neural responses to simultaneous tactile and auditory input in trumpeters (Schulz et al., 2003), increased behavioral sensitivity and cortical responses to audio-visual asynchronies in musicians (Lee and Noppeney, 2011), and increased audiovisual integration in brainstem responses (Musacchia et al., 2007). Also, a recent multimodal training study showed that two weeks of piano training that involved visual, auditory, and sensorimotor modalities resulted in a stronger enhancement of audio-visual integration of stimuli in the posterior part of right STG than training that only involved the visual and auditory domains (Paraskevopoulos et al., 2012; Figure 1).

Recent models of multisensory integration in superior colliculus (SC) suggest that integration is achieved by feedback and feedforward synapses of the unisensory neurons with a multisensory area within the SC (Magosso et al., 2008). While additional mechanisms and more complex integration might be at work in the cortex, the role of feedforward predictions from one modality to the other, and evaluation of corresponding feedback between modalities has also been suggested as an important mechanism

for the efficacy of musical training for cortical plasticity (Lee and Noppeney, 2011). Research from animals and computational models indicates that multisensory inputs during development are crucial for the formation of the corresponding neural multisensory integration networks (Cuppini et al., 2011). Conversely, research in blind and deaf humans shows how sensory deprivation leads to functional reorganization of the sensory cortical areas, but that these areas maintain their organizational principles in the process and are probably to a large extent multisensory in nature to begin with (Voss and Zatorre, 2012). From anatomical work, it is furthermore known that even early sensory cortical structures are connected to other sensory and association cortices, and that the auditory cortex receives multisensory thalamic inputs (Budinger et al., 2006; Budinger and Scheich, 2009). These anatomical connections provide a good basis for the assumption that predictions and evaluations via cross-modal feedforward and feedback loops are an important mechanism in multimodal learning such as playing a musical instrument. In the example of playing a piano, the motor action of pressing a piano key will elicit a forward model of an expected sensation on the finger tip and a corresponding piano tone to which the actual sensory input from these modalities can be compared via feedback loops. In line with such a model, the role of auditory feedback for vocal performance and learning has been demonstrated in both humans and animals (Tschida and Mooney, 2012; Zarate and Zatorre, 2008). Similar models emphasizing interactions between motor and auditory areas have also been suggested for speech (Hickok and Poeppel, 2007; Rauschecker and Scott, 2009). Hickok and Poeppel suggest a model in which a dorsal processing stream linking auditory areas in the temporal lobe and motor areas plays a major integrative role. This auditory-motor interaction is assumed to be essential for speech production, in particular during development, since learning to speak requires that sensory input guide the tuning of motor speech production. This most likely involves both feed-forward models of the motor programs required to produce a specific sound or sound sequence, and feed-back monitoring mechanisms (Hickok and Poeppel, 2007). In a similar vein, Rauschecker and Scott (2009) propose feedforward and feedback loops for speech production between premotor and motor areas and posterior secondary auditory areas, with an integrating role of the inferior parietal lobule. The pathways and mechanisms involved for musical perception and production, as we have seen, bear some similarity to these models of vocal learning, leading to the speculation that both may have a common phylogenetic origin in a more general system for multimodal sensory-motor integration. In songbirds, interactions of motor and auditory brain structures are crucial for vocal learning and despite obvious and important differences in brain anatomy, the underlying mechanisms how auditory feedback and vocal exploration is used to shape motor output during learning might provide useful homologies (Doupe and Kuhl, 1999; Fee and Scharff, 2010). Further research will need to focus on the exact temporal mechanisms and loci of the integration during multimodal learning, in order to explain the enhanced plastic effects in uni- and multisensory processing observed after multimodal training in previous studies (Lappe et al., 2008; Paraskevopoulos et al., 2012).

The Role of Interindividual Differences

The longitudinal studies indicate that many of the differences observed in relation to musical training are indeed caused by the training, and thus are manifestations of experience-dependent plasticity. Furthermore, to the extent that some of these changes predict behavioral performance, it would seem that they reflect specific adaptations of neural networks to the exigencies of musical expertise. Thus, anatomical features within pitch-relevant auditory cortical areas, as measured via MRI, may reflect aspects of cortical organization that enhance local processing of pitch; similarly greater connectivity between auditory and frontal regions would likely reflect enhanced processing of working memory loops involving those structures, for example. But logically, the existence of experience-dependent effects does not rule out the presence of predispositional factors. For example, Foster and Zatorre (2010) noted that the cortical areas whose anatomy is related to performance were also sensitive to musical training, as expected based on an experiential model; however, the statistical relationship between anatomy and behavior remained even after accounting for musical training, suggesting that predispositions may also play a role (Figure 2). A role for predisposing factors in auditory cortex anatomy has similarly been proposed for speech. For example, in structural MRI studies of foreign speech sound training (Golestani et al., 2002, 2007) prelearning variability in left auditory cortical structure, or in related white-matter regions, predicted the ability to learn to distinguish the sounds. Similarly, Wong et al. (2008) reported that learning of pseudowords in a tone language is related both to left auditory cortex volume and musical training, but that the latter does not account for the anatomical relation. A related conclusion comes from a study of phonetic skill (Golestani et al., 2011), showing that gyrification of the left auditory cortex, a feature believed to be fixed prenatally, is greater in those with specific linguistic abilities. Heritability studies with twins indicate that whereas variability in some brain structural features has a large environmental influence (e.g., the corpus callosum; Chiang et al., 2009), genetic factors account for a large proportion of the variance in other structures, including the auditory cortex (Peper et al., 2007), and frontal and temporal areas (Thompson et al., 2001). Music may provide a fertile ground for future explorations of these nature/nurture interactions.

In musical training studies, interindividual variance in training success has not received much attention. However, a study by Gaab et al. (2006) showed that participants in an auditory discrimination training paradigm could be distinguished as slow or fast learners based on their behavioral scores, and that differential patterns of training-related changes could be seen between the two groups, with a stronger posttraining recruitment of the left supramarginal gyrus, and a trend for left Heschl's gyrus in the stronger learners (Gaab et al., 2006; Figure 2). Similarly, differential training-related changes in auditory areas were found for participants who improved on a frequency discrimination task and for those who did not (Jäncke et al., 2001). These findings seem to suggest that individual training rates can be related to differential changes in plasticity. Very few studies have yet made a connection between the initial functional or structural properties of auditory-motor networks and subsequent musical
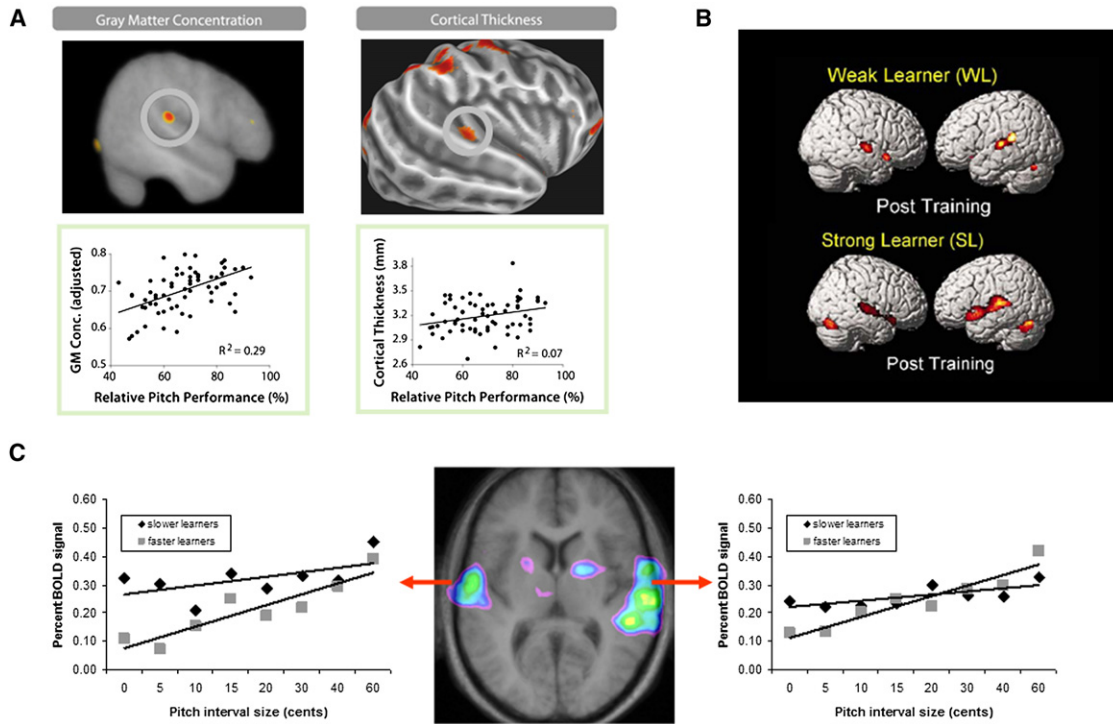
Figure 2. Interindividual Differences in Auditory Cortical Structure and Function
(A) Variability in auditory cortex gray matter concentration and cortical thickness predicted performance on a melodic transposition task (adapted from Foster and Zatorre, 2010).
(B) Different rates of behavioral improvement during pitch memory training were accompanied by differential training-related functional changes in secondary auditory areas (adapted from Gaab et al., 2006).
(C) BOLD signal covariation to increasing pitch size in microtonal melodies prior to training in both left and right auditory cortices was predictive of the speed with which learning occurred, such that those individuals who subsequently learned more quickly had an initially steeper response function (adapted from Zatorre et al., in press).

or auditory training success or training-related plasticity. One recent finding does point in this direction, however: using a micromelody task, Zatorre et al. (in press) found that individuals with a steeper BOLD response function in auditory cortex to pitch changes prior to learning subsequently learned more quickly (Figure 2). Also, in a recent study using speech-sound training, encoding of tones in the inferior colliculus in fMRI was related to subsequent learning rates (Chandrasekaran et al., 2012). The conclusion is that people may differ in the degree of sensitivity to certain stimulus features, and that these differences might influence learning. The extent to which variability can be explained by combinations of genetic, epigenetic, or environmental factors remains to be established; but individual differences will no doubt assume a greater importance in this literature, which to date has been focused almost exclusively on group-level effects (Kanai and Rees, 2011). It will therefore be an important, and challenging, task for future studies to disentangle how experience interacts with the initial status of relevant brain networks that influence learning.

Metaplasticity

An important higher-level phenomenon in the context of learning and plasticity is that long-term training can result not only in specific learning, but also creates greater potential for short-

term changes to occur quickly. Musical training not only changes the structural and functional properties of the brain, but it also seems to affect the potential for new short-term learning and plasticity. Such interaction effects of long- and short-term training have been demonstrated in the auditory (Herholz et al., 2011), in the motor (Rosenkranz et al., 2007) and in the tactile domain (Ragert et al., 2004; Figure 3). In the auditory domain, musicians have been shown to be faster to pick up regularities and abstract rules in tone sequences, as indexed by the mismatch negativity to violations of these rules (e.g., Herholz et al., 2009; van Zuijen et al., 2004, 2005). The emergence of this response during the acquisition of a new underlying rule can be observed even within a short time-frame, with musicians showing an increasing auditory evoked mismatch response to rule violations over ten minutes in contrast to nonmusicians (Herholz et al., 2011). Converging evidence comes from a study that used TMS to assess the excitability of motor cortex in musicians and nonmusicians by Rosenkranz et al. (2007). They applied stimulation to the median nerve paired with a TMS pulse over motor cortex and found that the resulting short-term changes in excitability were more pronounced in musicians, which can be interpreted as a greater potential for motor adaptation to new conditions. Additionally, it seems that long-term musical training enhances short-term plasticity within motor
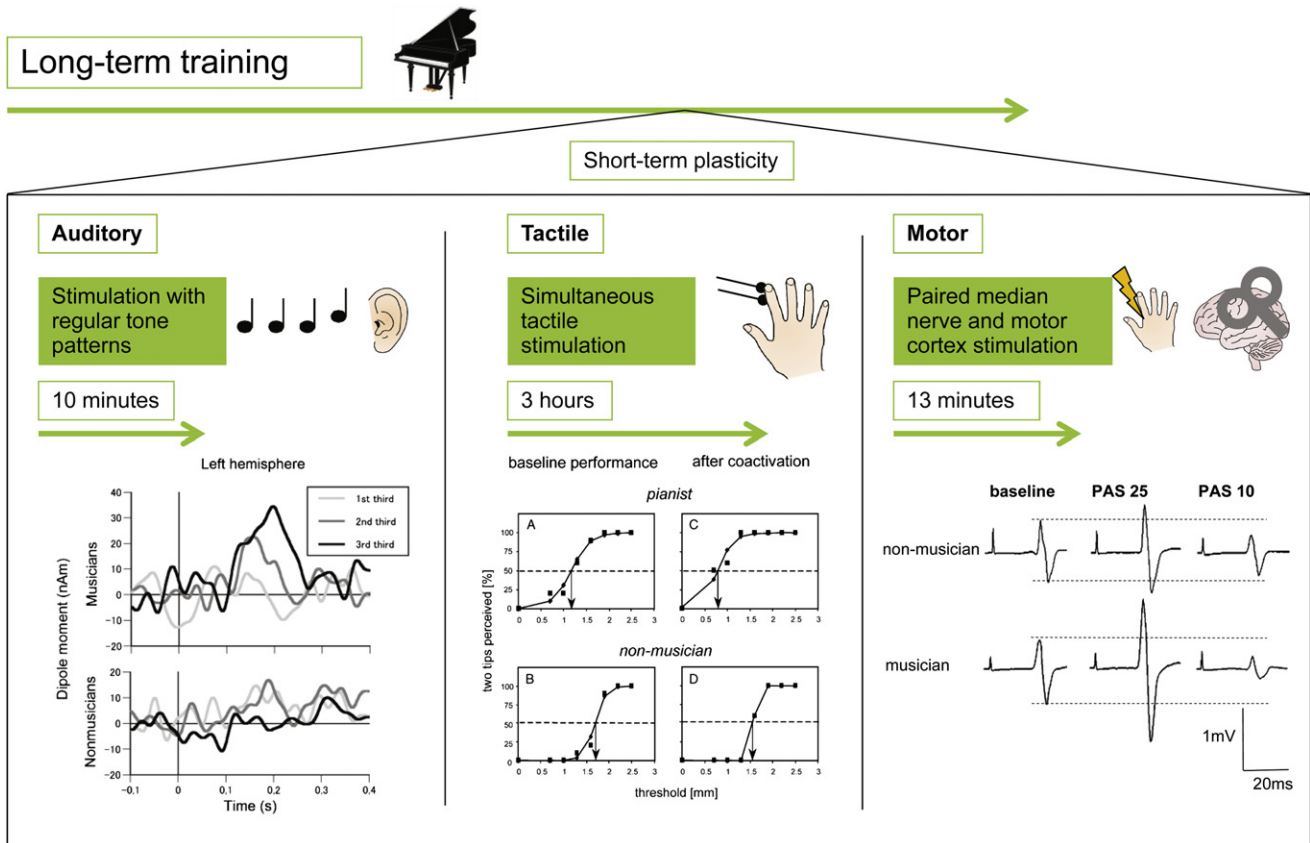
Figure 3. Metaplastic Effects of Musical Training on Various Time Scales
In the auditory domain (left), musicians compared to nonmusicians showed faster neural encoding of new auditory regularities within secondary auditory cortex. Musicians' auditory evoked responses to unexpected tone patterns increased within ten minutes of auditory stimulation, from the first to the third part of the MEG recording (adapted from Herholz et al., 2011). In the tactile domain (middle), musicians showed increased gains in tactile discrimination thresholds due to a 3 hr passive stimulation procedure intended to induce Hebbian learning of tactile perceptive fields (adapted from Ragert et al., 2004). In the motor domain (right), paired associative stimulation combining TMS pulses to motor cortex and electric median nerve stimulation resulted in stronger short-term plastic effects in the motor evoked potentials (enhancement with PAS 25 ms, decrease with PAS 10 ms) than in nonmusicians (adapted from Rosenkranz et al., 2007 and reproduced with permission of the Society for Neuroscience).

cortices and enhances motor performance and coordination on complex manual tasks. Pianists also showed faster learning in a nonmusical finger tapping sequence task, which was associated with stronger M1 activity compared to nonmusicians, and stronger decreases during learning in secondary motor areas, such as bilateral supplementary motor area, premotor, and cerebellar areas (Hund-Georgiadis and von Cramon, 1999).

Enhancement of short-term learning and plasticity by long-term training is an intriguing possibility that has great potential as an enhancing factor for applications of training protocols. These findings bear some conceptual resemblance to findings of increased plasticity on the cellular level due to pretreatment or previous learning or excitation history of the neurons involved, an effect termed metaplasticity to indicate that the rate of plasticity is altered on a higher-order level (Abraham, 2008; Abraham and Bear, 1996). While the concept of metaplasticity stems from cellular and molecular phenomena such as long-term potentiation (e.g., Huang et al., 1992), it has also been applied to explain features of experience-dependent plasticity in visual cortex (Bienenstock et al., 1982), and it can also explain enhanced

short-term plastic effects due to modulation of the involved networks by previous sensory experience or learning (Hofer et al., 2006; Zelcer et al., 2006). The framework of musical training offers an excellent possibility to explore the potential for metaplastic effects at higher levels of organization in the human brain. However, while the results so far clearly indicate that long- and short-term effects of musical training and other types of short-term plasticity interact and may enhance one another, more research is needed to reveal if the enhancement is due to top-down influences such as attention to relevant input, or if the properties of the sensory systems are also altered on lower levels of processing.

Musical Training and the Reward System
Although musical training can sometimes be very tedious and frustrating, as every professional musician can certainly confirm, the reward value and positive feedback associated with producing music might contribute to the observed efficacy of the approach in comparison to other, less rewarding training paradigms. Listening to certain musical passages has been
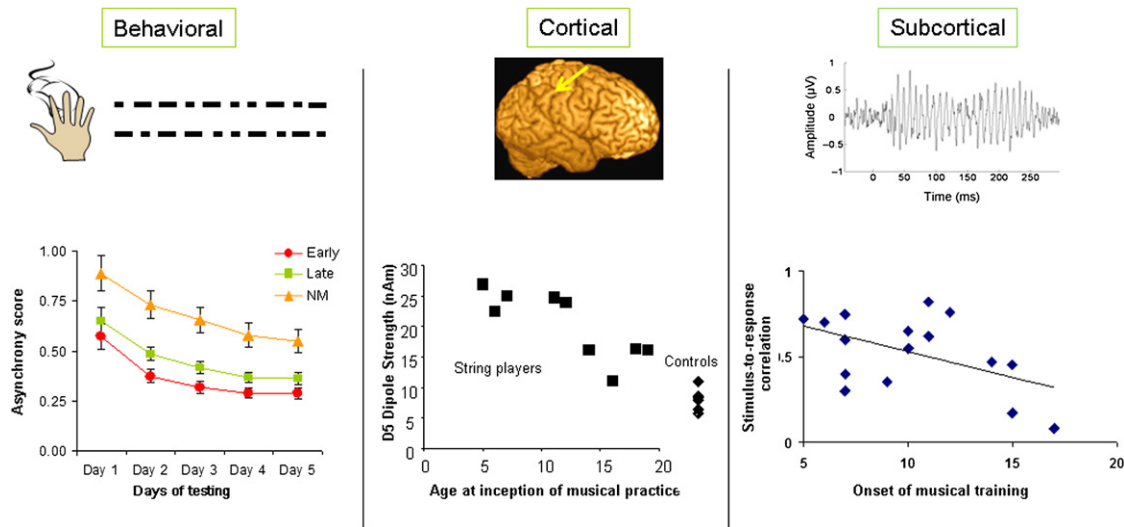
Figure 4. Enhancement of Musical Training Effects as a Function of Early Age Commencement
Left: Scores on a task requiring visuomotor temporal synchrony (lower score = better synchrony) across 5 days of learning were enhanced in early-trained (training commencing prior to age 7) compared to late-trained musicians, but both were better than nonmusicians (NM) (adapted from Watanabe et al., 2007). Middle: Size of evoked response in somatosensory cortex (yellow arrow) to stimulation of the fingers of the left hand was enhanced in string players compared to controls, but the enhancement was greater in those who began training at earlier ages (adapted from Elbert et al., 1995). Right: Fidelity of brainstem frequency-following response to a tonal stimulus was higher in musicians who began training earlier (adapted from Wong et al., 2007).

shown to engage the dopaminergic component of the reward system (Blood and Zatorre, 2001; Salimpoor et al., 2011). Therefore, another interesting aspect of musical training is the possible modulation of neuronal plasticity via the reward circuitry, in particular through aminergic systems, whose modulatory effects on cortical plasticity have been shown in animal models and to some extent also in humans (Gu, 2002; Thiel, 2007). For example, Bao et al. (2001) showed in rats that pairing a tone with stimulation of the ventral tegmental area, resulting in dopamine release to projections in the auditory cortex, enhanced responses to this tone and sharpened the neuronal tuning curve in A1 and secondary auditory cortex. In the context of music, the intrinsic or extrinsic reward of achieving a particular target sound, for example a particular timbre, might shape neural tuning to enhance the processing of these sounds in the future.

In humans, it is known that Levodopa administration can increase plasticity in the motor cortex (Kuo et al., 2008), while conversely plasticity in motor cortex is diminished in Parkinson's patients (Ueki et al., 2006). Behavioral studies have also shown that Levodopa can modulate both motor learning (Flöel et al., 2005, 2008; Rösser et al., 2008) and acquisition of an artificial language (de Vries et al., 2010). In a music training context, the produced sounds would provide direct feedback about accuracy of performance, which might be in part mediated through dopaminergic signals. While this has not yet been shown experimentally, the reward value of the immediate feedback might be important for the plastic effects that are observed due to training. Clearly this is an area ripe for more specific investigation.

Music also has some reward value beyond the pleasurable sounds and direct feedback—it also has an important role in social interactions, both in contexts of group listening and music making. While the effects of such interactions during music making have not been investigated to our knowledge, the role

of social influences and well-being on brain plasticity has been shown in other contexts (for a recent review, see Davidson and McEwen, 2012). Important aspects in the context of music and learning could include pupil-teacher interactions and imitation learning, social reward and influences on self-perception, but also negative influences like stress in professional situations and performance anxiety.

Training-Related Plasticity over the Life Span
Plastic changes can occur over the entire life-span, but early musical training seems to be particularly effective (Penhune, 2011), as is also true for other domains of learning, such as speech (Kuhl, 2010), development of absolute pitch ability (Baharloo et al., 1998; Zatorre, 2003), or the efficacy of cochlear implants (Nicholas and Geers, 2007). In turn, this phenomenon mirrors one seen in single-unit neurophysiology as mentioned earlier (de Villers-Sidani et al., 2007, 2008). Several musical training studies have found that long-term effects are modulated by the age at which the training began (Figure 4). Behaviorally, early musical training results in better visuomotor and auditory-motor synchrony (Pantev et al., 1998; Schlaug et al., 1995), even when controlling for amount of training (Bailey and Penhune, 2010; Watanabe et al., 2007). Anatomical changes in keeping with the idea of greater potential for plasticity as a function of age have also been described in the white-matter organization of the descending motor tracts in pianists (Bengtsson et al., 2005), in morphological features of the motor cortex (Amunts et al., 1997), and in the size of the anterior corpus callosum (Schlaug et al., 1995). Functionally, earlier age of training commencement is also associated with greater representation of the fingers of the left hand of string players (Elbert et al., 1995) and in greater cortical (Pantev et al., 1998) and brainstem responses to tones (Wong et al., 2007). These modulatory effects
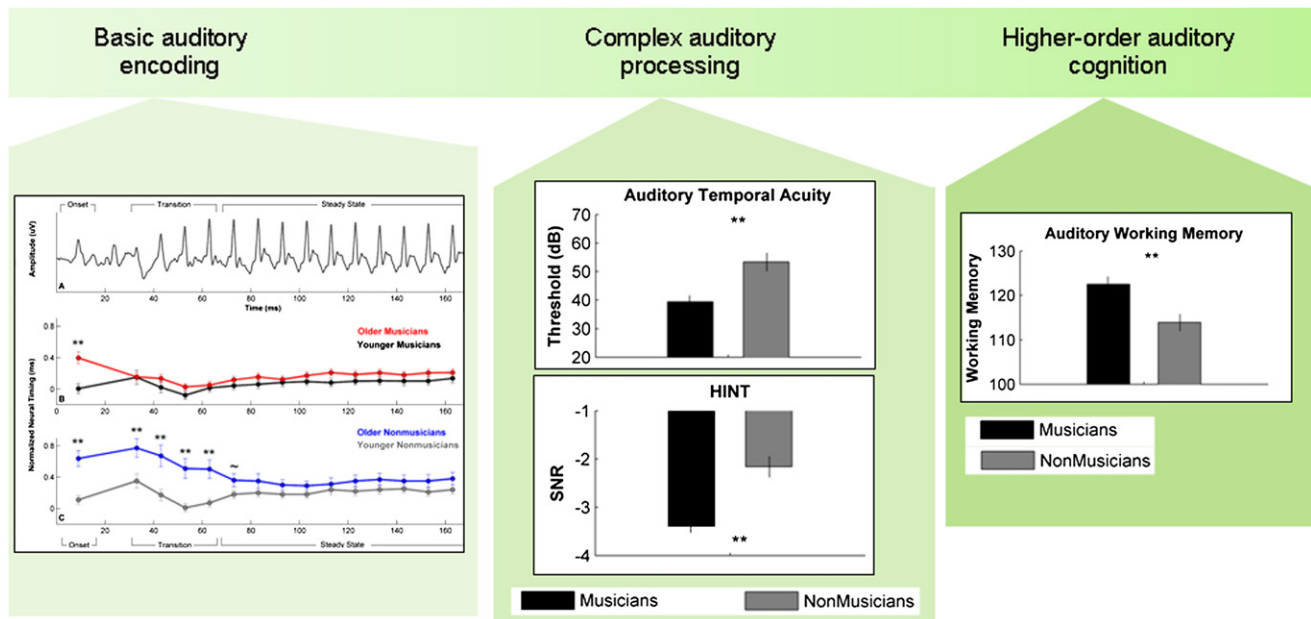
Figure 5. Possible Neuroprotective Effects of Musical Training in Aging at Different Levels of Auditory Processing
Cross-sectional comparisons of older musicians and nonmusicians showed: (left) enhanced fidelity of neural encoding of sounds in brainstem electrical recordings; (middle) better perception of speech in noise and enhanced auditory temporal acuity (adapted from Parbery-Clark et al., 2011), and (right) better auditory working memory capacities (Parbery-Clark et al., 2012).

of maturational state on experience-dependent changes likely emerge from an interaction of bottom-up and top-down mechanisms (Kral and Eggermont, 2007), which could include for instance finer tuning at sensory processing levels combined with stronger influences from attentional and other cognitive mechanisms (Penhune, 2011). The questions of developmental phases also pertain to the topics of interindividual differences and metaplasticity that are still open for investigation, for example, how musical training during childhood interacts with the array of developmental changes that are underway, how the initial status of the brain during childhood and musical training in different phases of life influence the potential for learning later on, and if the time windows for metaplastic effects are constrained by development and maturation. For example, metaplastic effects might differ depending on when the long-term training occurred.

Despite the fact that earlier training has more profound effects on brain plasticity, training changes brain structure and function at all ages, even in old age. For instance results from visuomotor juggling training in elderly adults show that anatomical changes can be observed even later in life (Boyke et al., 2008), although they are not as extensive. Cortical plasticity from unimodal motor training is however diminished in the elderly (Rogasch et al., 2009). This seems to suggest that exploiting the effects of multi-modality and reward that music might offer for plasticity might be especially beneficial in elderly adults. Since plasticity in the healthy and diseased aging brain is of particularly high relevance in aging societies, future research should explore the potential of musical training in these populations. While the focus of most larger studies is on general measures of physical and cognitive lifestyle, there are also some indications that specifically musical

training might mitigate some effects of aging in the brain (Wan and Schlaug, 2010). The evidence is good at the perceptual level that musical experience seems to delay the onset of age-related losses of neural encoding in the brainstem during speech perception (Parbery-Clark et al., 2012) and regarding auditory working memory capacity and the ability to understand speech in noisy environments (Parbery-Clark et al., 2011; Figure 5). Long-term musical practice may also reduce age-related declines in higher-order cognition such as nonverbal memory, naming, and executive processes (Hanna-Pladdy and MacKay, 2011), although confounding factors such as socioeconomic background or intelligence cannot be entirely excluded in such cross-sectional studies. An intervention study using physical exercise accompanied by music showed significant improvements in cognition in dementia patients compared to a control group (Van de Winckel et al., 2004). Active music therapy has also been shown more effective compared to physical therapy in Parkinson's disease in a randomized, controlled and double-blind prospective study (Pacchetti et al., 2000). Even passive music exposure has been shown to have beneficial effects on memory and mood in post-stroke patients (Särkämö et al., 2008). Such results are a promising basis for more research on the mechanisms of training-related plasticity in aging participants and age-related diseases.

Other Clinical Applications of Training-Related Plasticity
Knowledge derived from neuroscience studies of musical training in healthy people have promise for the application of this type of training in a clinical context. For example, melodic intonation therapy has shown considerable success at improving the

speech of nonfluent aphasics (Schlaug et al., 2010). As the name suggests, the approach teaches speech via a detour: singing. The patient is asked to sing back simple melodic contours based on normal prosodic contours in speech while tapping in synchrony. Whereas singing recruits the intact right-hemispheric homologous networks to the damaged left-hemispheric areas, the concurrent tapping with the right hand engages left-hemispheric motor areas, thereby strengthening the auditory-motor link and priming motor areas for articulation (Schlaug et al., 2008, 2010). Recent evidence suggests that the effects of this therapy can be enhanced by direct current stimulation applied over right posterior inferior frontal cortex (Vines et al., 2011), presumably because it modulates activity in a right-hemispheric network for articulation that is believed to engage in compensatory activity, especially through MIT, after lesions to left-hemispheric language areas. Therapy success is also accompanied by increases in the fiber density of the arcuate fasciculus connecting temporal and frontal areas within this network (Schlaug et al., 2009).

Musical training is also a successful approach in the rehabilitation of motor skill in the extremities after stroke. Schneider et al. (2007) used an electronic drum set to train gross motor coordination of arm movements, and a midi piano for training of more fine-grained motor control of hands and fingers in stroke patients. In comparison to a control group that only received the conventional treatment, patients in the music group showed improved motor control on standard test batteries. Importantly, those tests were not music related, indicating a transfer of the acquired motor skills to other every-day tasks. Electrophysiological evidence showed increased indices of motor cortex activation and reorganization in the motor network in the music therapy patients compared to the control group (Altenmüller et al., 2009). Both the behavioral and the neurophysiological effects might to some extent be explained by the additional, massed practice regime in the music group. However, comparison with other treatment strategies that involve similar if not higher amounts of practice, such as constraint-induced movement therapy, indicates additional mechanisms specific to the musical approach (Schneider et al., 2007). In a recent study using fMRI, it was shown that the gains in motor skills related to music-supported therapy in stroke patients are related to increased functional auditory-motor connectivity after therapy (Rodriguez-Fornells et al., 2012). The auditory-motor interactions that are specific to music (Zatorre et al., 2007), and the increased potential for plasticity in multimodal training paradigms (Lappe et al., 2008), might thus underlie the improvements seen in these music-based rehabilitation approaches. Additionally, it can be assumed that other aspects of the music treatments such as enjoyment of the therapy sessions, increased motivation and reward, and social aspects of the interaction during singing and music making contribute to the efficacy of the training approaches.

More recently, music-based therapy has also been successfully applied for tinnitus, a neurological condition that seemed untreatable for a long time. Research showing that the typical ringing noise that is perceived by tinnitus patients can be based on mal-adaptive cortical plasticity after deafferentation of cortical auditory neurons (Eggermont, 2007) on the one hand and research showing short-term plasticity of the tuning of audi-

tory neurons after band-passed noise on the other hand (Pantev et al., 1999) inspired a treatment approach aimed at reversing such maladaptive cortical plasticity (Okamoto et al., 2010). Listening to self-selected music that was notch-filtered to exclude the individual tinnitus frequency over 6 months significantly reduced perceived tinnitus loudness and annoyance as well as evoked auditory potentials to the tinnitus frequency, compared to a placebo control group. Based on findings from the animal literature (Eggermont, 2007), the treatment is assumed to take advantage of the lateral inhibition that occurs on the level of auditory cortex, and that counteracts the maladaptive reorganization that lead to the tinnitus percept in the first place. This shows that not only active music making, but also massed passive listening can lead to clinically relevant reorganization in the brain.

Conclusions and Outlook

Training-related plasticity in the human brain has been studied in a wide variety of experimental approaches and paradigms, such as juggling, computer games, golfing, and other training activities (e.g., Bezzola et al., 2011; Boyke et al., 2008; Draganski et al., 2004). We hope to have convinced the reader that musical training is a useful experimental framework that offers the possibility to compare studies using similar training activities, which facilitates the integration of findings across studies and modalities. The emerging patterns of findings can then be compared to mechanisms of plasticity in more basic experimental research such as direct measurements of plasticity in animal models and cellular biology, and to other models of learning and plasticity such as from the domain of language acquisition, as discussed in the previous sections. In most cases, methods available for study of human plasticity do not allow us to relate the observed changes directly to the diverse mechanisms on the cellular and molecular level; conversely, the invasive methods that allow more fine-grained descriptions cannot be applied to humans. For plasticity induced by training on complex tasks, bridging this gap is and will be difficult since tasks such as playing the violin will probably never have an equivalent in the animal literature, and many questions that we are interested in cannot be answered with simple training paradigms alone. Still, in order to make more direct inferences, we will need studies and experimental paradigms that intersect at the systems level, such as work that is done in parallel in human and animal studies (e.g., Sagi et al., 2012), in order to relate changes on the cellular and molecular level to changes observed in humans and on a macroscopic level.

The field has accumulated considerable and consistent evidence of training-related cortical and subcortical plasticity in the human brain. We believe that we are now at a point where we can move toward trying to understand the underlying mechanisms on a network level, for example regarding the role of multimodal interactions and coactivations during complex skill learning, and the role of within- and between-modality feedforward and feedback loops. It should be noted that neuroimaging techniques, despite their limitations, have the major advantage that they permit in vivo simultaneous whole-brain measures of multiple aspects of neural activity and of gray and white matter structure, thereby allowing network-level analyses of long-range

functionality. Contemporary neural models of cognition stress the idea of multiple interacting functional networks (Bullmore and Sporns, 2009), and it therefore behooves us to understand plasticity in those terms as well. The ability provided by neuroimaging methods to understand interactions across regions can also help inform the microstructural approaches of cellular and molecular techniques, to test network-level hypotheses that otherwise might not even be suspected. Furthermore, we should shift our focus from looking only at average training effects to also including interindividual differences in our models. This will allow teasing apart predisposing factors from general mechanisms of plasticity, with the future goal to tailor training, education, and rehabilitation approaches to optimally exploit the potential for learning and plasticity of the human brain.

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