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MULTISENSORY INTEGRATION AND NEUROPLASTICITY IN THE HUMAN CEREBRAL CORTEX

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Abstract

There is a strong interaction between multisensory processing and the neuroplasticity of the human brain. On one hand, recent research demonstrates that experience and training in various domains modifies how information from the different senses is integrated; and, on the other hand multisensory training paradigms seem to be particularly effective in driving functional and structural plasticity. Multisensory training affects early sensory processing within separate sensory domains, as well as the functional and structural connectivity between uni- and multisensory brain regions. In this review, we discuss the evidence for interactions of multisensory processes and brain plasticity and give an outlook on promising clinical applications and open questions.

Keywords

• Multisensory processing • Training-related plasticity • Training • Musical training

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Introduction

The human ability to perceive and understand the surrounding world relies essentially on multisensory integration, as incoming information from multiple senses is unified in order to form a coherent percept, or segregated in order to dissociate distinct events. Within the context of cognitive neuroscience and throughout the last decades, there has been an increasing interest in the study of the underlying brain mechanisms of multisensory integration, both on an anatomical and functional level [1,2]. Recent technological advances allow the study of brain structures and functions in human subjects, and have contributed immensely to a better understanding of multisensory integration [3,4]. In addition, there has been increased interest in the neuronal plasticity in the adult human brain. Several studies showed that intensive training of a cognitive or motor process induces plastic changes in underlying cortical structures and representations [5,6]. These parallel routes of research have not been extensively combined, and therefore learning-induced neuronal plasticity of multisensory integration still constitutes an auspicious field of research.

This review will focus on the intersection of the research areas of multisensory processing and learning-induced neuronal plasticity and will summarize recent research results. Initially, we will briefly describe the known anatomical substrates underlying multisensory integration in humans and the proposed functional frameworks, referring when necessary to animal research results. Subsequently, we will then survey how these frameworks relate to neuroplasticity by distinguishing between the mechanisms through which multisensory integration modulates the resulting plasticity (on a uni- and multisensory level) and the mechanisms through which learning-induced plasticity modulates multisensory integration. Additionally, the basic models and paradigms that are used in the study of multisensory plasticity will be outlined. Finally, we will describe the clinical relevance of multisensory-based interventions and the resulting plasticity with regard to the prevention and rehabilitation of known neurological deficits and age-related changes, and provide an outlook for possible avenues for future research.

The multisensory brain

Several anatomical structures that convey multisensory characteristics exist throughout the brain at cortical and subcortical levels. At the cortical level, the regions that are usually referred to as multysensory include the cortex along the superior temporal sulcus (STS), the cortex along the intraparietal sulcus (IPS) and the frontal cortex." Nevertheless, an increasing amount of data indicates that areas traditionally considered to be unimodal sensory (unisensory) also contain neurons with multisensory attributes [1,2]. Additionally, there are white matter pathways that connect different unisensory regions or a unisensory region with higher order association areas, and they are therefore also considered multisensory [7–9].

Evidence for the multisensory characteristics of the STS comes from several research approaches. Functional magnetic resonance imaging (fMRI) studies [10,11] have shown that the STS responds stronger to congruent audiovisual letter stimuli than to incongruent ones, a result that has been confirmed with other neuroimaging methods such as magnetoencephalography (MEG) [12].

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Intracranial recordings in humans [13] also show that audiovisual speech integration modulates the responses of the STS. Additionally, direct neuronal recordings in the cortical area of macaque monkeys that corresponds to the STS indicate that approximately 23% of neurons responsive to the sight of biological motion are significantly modulated by the corresponding auditory component [14].

The IPS has a role in multisensory processing of motion and space, integrating tactile, visual and auditory information [15]. An fMRI study by Bremmer *et al.* [16] indicated that the IPS region integrates visual, tactile and auditory stimuli in order to form a multimodal representation of motion. Similar results were seen in another fMRI study by Makin *et al.* [17], which revealed that the posterior IPS and lateral occipital complex represent hand-centered space in a predominantly visual manner, while the anterior IPS uses multisensory information to represent motion in space. This was also confirmed by a recent study that combined electroencephalography (EEG), Transcranial Magnetic Stimulation (TMS) and psychophysics [18]. Moreover, results from animal studies indicate that the sensory responses in the IPS can be driven by any input modality and are characterized by a complex task dependence [19–21]. The lateral occipital complex and posterior middle temporal cortex are also considered to respond to multisensory stimulation with a preference for shape representation and motion, respectively [22].

Prefrontal regions have also been related to multisensory integration [23]. A fMRI study by Noppeney *et al.* [24] indicated that the inferior frontal sulcus showed increased activity in tasks that relied on the combination of auditory and visual information. Importantly, it weighted its connectivity to auditory and visual regions according to its reliability and decisional relevance. Another study by Belardinelli *et al.* [25] indicated increased activity in the inferior frontal sulcus when subjects were confronted with incongruent audiovisual pairs. Similar effects are also present in a recent MEG study by Paraskevopoulos *et al.* [26], while direct recording primate studies confirm the multisensory characteristics of this region at a single neuron level [27–29].

Neurons that show multisensory characteristics have recently been found in cortical regions that were traditionally considered unisensory. Several fMRI [30–32] and MEG [33,34] studies have shown modulation of the auditory cortex via visual or somatosensory input, results that have been confirmed with intracranial recordings in macaque monkeys [14]. Similarly, neurons in V1 have been shown to modulate their response to a brief visual flash when concurrent auditory stimulation is presented [35] or during tactile Braille reading [36]. Additionally, multisensory responses have been shown in neurons in the primary somatosensory cortex [37].

When considering the cortical structures that underlie multisensory processing, one must distinguish between the regions that modulate their activity in response to bi- or multimodal stimuli, as the ones described above, and the regions that show supramodal characteristics, i.e. regions that execute a specific process independently of the input modality. Such regions may include Broca's area [38], subregions of the intraparietal cortex [39] and the anterior cingulate cortex [40].

Areas that respond to multisensory stimuli at a subcortical level include the superior colliculus [41], which integrates multimodal input in spatial maps [42]. The multisensory processes of the superior colliculus strongly depend on a top-down input from the neocortex [43]. Neurons in the claustrum also respond to multisensory stimuli [44], as well as in the striatum [45] and the amygdala [46]. Moreover, thalamic neurons seem to modulate their response to auditory stimuli depending on the congruency of visual co-stimulation [47]. Even at the level of the brainstem, research has shown that neurons modulate their response based on the congruency of audiovisual stimuli [48,49].

Apart from the anatomical structures and pathways that promote multisensory integration, oscillatory phase coherence of the relevant neuronal populations is considered an important index for multimodal processing on a functional level [50]. In a high-density EEG study by Senkowski *et al.* [51], it was shown that the behavioral benefit of processing bi-sensory stimuli (i.e. faster reaction times) could be predicted by correlated oscillatory activity over frontal, occipital, central, and sensory-motor regions in the β frequency range (13 – 30 Hz). It is now assumed that the correlated oscillatory activity of different cortical regions is important in modulating their communication, thus allowing perceptual binding [52].

One framework regarding the functionality of multisensory processing has proposed that initially each sensory stimulus is processed independently and only later is sent to multisensory convergence zones in a strictly hierarchical organization [53]. This notion has now been widely challenged as research results indicate that multisensory neurons exist throughout the processing hierarchy [1] and that unisensory regions may be bypassed in certain cases, and a stimulus can be directly and independently processed in multisensory areas [54]. Additionally, recent electrophysiological data show integration effects already around 15 – 30 ms after the onset of the stimuli, thus confirming some form of parallel processing [49]. These new results have led to differing views with regard to the processing steps of multisensory integration, highlighting either a parallel procedure throughout the processing hierarchy [55] or the critical role of feedback circuits from multi- to unisensory areas [2]. Therefore, it is important to note that we refer to functionality and not to location when discussing uni- and multisensory structures.

Multisensory plasticity

Models and paradigms for the study of multisensory plasticity

The recent interest in the study of neuroplastic changes related to multisensory processing in humans has led to the establishment of some basic models and paradigms in this field of research. With regard to developmental cognitive neuroscience, the basic approach focuses on the question of whether a specific multisensory function, such as a cross-modal correspondence, is developed in infants or not [56]. Another approach is the use of a cross-sectional studies to compare the efficacy of a multisensory function in specific maturational stages, such as early childhood and adulthood [57]. The neuroplastic effects of sensory deprivation and deafferentation in humans have also been extensively studied, mainly by investigating the function of the cortical areas that have been affected by the deafferentation and whether these regions subsequently contribute to different processes [58,59]. Within the field of multisensory processing, the McGurk effect constitutes a commonly used paradigm [60]. According to the McGurk effect, when a person hears the syllable "ga" but simultaneously sees a person's lips moving as if saying the syllable "ba", the auditory percept is altered, producing an illusionary auditory percept of the syllable "da".

Musical training has also been developed as a research framework for studying the effects of multisensory training in the context of cognitive neuroscience [61], because it offers access to a sample population (i.e. musicians) that has extensively trained a multisensory action (i.e. playing a musical instrument) and can be easily compared with controls. Short-term music training can be used in a longitudinal setting to compare behavior, brain function and structure before and after an applied training protocol [62–64]. This approach allows causal inference regarding the origin of the neuroplastic changes. When two or more trainings are compared that differ in relevant characteristics, this additionally provides the opportunity to disentangle the elements of the training and identify each element's specific contribution to the resulting plasticity. Moreover, several studies [95–97] investigated the pairing of new audiovisual associations using novel (artificial) objects that were paired via training with a specific sound. In the following section, studies from all of the above mentioned approaches will be discussed.

Experience-related plasticity effects in multisensory processing

Maturation effects

Recent research in the study of multisensory processing has focused on the modulating effects of different forms of experience, including training. There has been extensive investigation on how experiences during development affect multisensory processing (for an extensive review see [65]). Research indicates the critical role that the experience of cross-modal stimuli has in the developing multisensory brain [66]. For example, Wallace *et al.* [67] revealed that a multisensory region of the cat's cerebral cortex (i.e., the anterior ectosylvian sulcus) is underdeveloped during early postnatal life, and multisensory neurons lack the ability to synthesize the cross-modal information they receive, and it develops gradually thereafter only if the cat receives normal multisensory input [68]. The same seems to be true for subcortical multisensory regions such as in the superior colliculus [69]. Similar results have been obtained in human infants that show age-dependent effects on reaction times when tested in localization of auditory, visual or audiovisual stimuli [70]. Nevertheless, some basic multisensory processes seem to be in place quite early in human life as indicated by data from 5-month-old infants regarding the discrimination of visual, auditory or audiovisual rhythms [71] and processing of audiovisual correspondences between the height of a pitch and the height of a visual stimulus [56].

In addition to these cross-modal correspondences that seem to be innate or established very early in life, new ones are generated via learning through experience, such as observing a cat meowing or a cow mooing [72] or that a hammer hitting a nail will result in a "bang" sound while a hammer hitting a finger will result in an "ouch" sound [73]. The learning of these audiovisual correspondences modifies their cortical representation and thus, when violated, they produce a mismatch response generated in multisensory cortical regions such as the lateral occipital complex [72] and the superior temporal gyrus [73]. Results consistently show that cross-modal correspondences that rely on temporal or spatial relations of the stimuli are already present early in life, while the ones that rely on semantic relations are gradually developed later in life on the basis of exposure to relevant experiences [74].

Brandwein *et al.* [57] investigated the maturation of audiovisual integration by comparing behavioral and neurophysiological responses of subjects aged from middle childhood to early adulthood. Their behavioral results indicated a gradual tuning of multisensory facilitation on a simple audiovisual reaction time task that reached adult levels at the age of 14. These results were positively correlated with an increase in the amplitude of the neurophysiological responses in frontocentral scalp regions at a latency of around 100 – 120 ms, indicating that maturation induces both neural and behavioral benefits in multisensory processing.

Sensory deprivation / deafferentation

Studies on plasticity due to sensory deprivation have contributed significantly to our knowledge of experience-related neuroplasticity of multisensory processes, indicating that deprivation of a sensory modality results in reorganization of neurocognitive functions. In the visual cortex of blind subjects, cross-modal activations have been observed in tactile tasks such as Braille reading [75], and auditory tasks such as sound localization [76]. Moreover, TMS over occipital areas in blind subjects can lead to disruption of language production tasks such as word generation [77]. Conversely, Pekkola *et al.* showed that visual speech stimuli activate the primary auditory cortex in congenitally deaf subjects [78], a phenomenon also present in cochlear implant users [79]. A more comprehensive review of the relevant literature is out of the scope of this review (for more detailed reviews see [58,59]). Nevertheless, the above-mentioned results clearly indicate the extent of plastic changes that are possible at a cortical level after sensory deprivation, even in adults.

Long-term training effects in multisensory brain areas

In order to study the long-term effects of multisensory training, several studies used a cross-sectional approach comparing musicians with controls [80]. Schulz *et al.* [81] used MEG to compare multimodal integration of somatosensory and auditory information in trumpet players and controls. They presented a tactile stimulus on the participants' lower lip or index finger and a trumpet tone either alone or as a combined audio-tactile stimulus. Results showed that musicians exhibited a training-induced reorganization of the cortical processing of the combined stimuli, showing a response generated in the somatosensory cortex that exceeded the sum of the unimodal responses. This response was absent in the control group, revealing that musicians had a qualitatively different way of processing multimodal information that is relevant to their training. Bangert *et al.* [82] investigated auditory and motor coupling in professional pianists and controls using fMRI. The subjects of this study either passively listened to short piano melodies or pressed keys on a mute MRI-compatible piano keyboard. Musicians had increased activity compared to the non-musicians in a distributed cortical network that was activated in both tasks, thus revealing enhanced cross-modal integration. This integrative network included the middle/superior temporal gyrus, the STS and the supramarginal gyrus bilaterally and the left precentral gyrus. Long-term musical training also increases the coupling of auditory and visual input during passive observation. Moreover, by using fMRI, Haslinger *et al.* documented auditory activations in pianists that merely observed someone playing a piano [83]. Using MEG, Paraskevopoulos *et al.* [26] investigated the effects of long-term musical training on the audiovisual integration of abstract rules which relate auditory and visual information. Subjects in this study had to identify congruent and incongruent audiovisual stimuli according to the rule "the higher the pitch of the tone, the higher the position of a circle". Results revealed that musicians, compared to non-musicians, showed greater difference of activities between the congruent and incongruent stimuli in the right superior frontal gyrus, the right superior temporal gyrus and the right lingual gyrus, indicating that the long-term multimodal training of musicians affects audiovisual integration (Figure 1).

Changes in multisensory processes do not originate solely from multisensory training. Recent evidence indicates that unisensory visual training can also have an impact on multisensory processing in that it narrows the audiovisual temporal binding window [84]. Training-related effects on multisensory training can also be quite specific. Using fMRI, Lee and Noppeney [85] showed that musicians have enhanced processing of audiovisual asynchronies in a task related with music, but not in a language task. These authors also revealed that the multisensory training of musicians changes not only the cortical activity patterns that process multisensory stimuli, but also the functional connectivity between the STS, the premotor cortex and the cerebellum. Luo *et al.* [86] showed that the resting state activity of musicians' brains has significantly increased functional connectivity among the motor and multi-sensory cortices, reflecting the plasticity of multisensory and motor functional integration. Enhancement of the cortical connectivity due to multisensory training has also been revealed on an anatomical level using Diffusion Tensor Imaging (DTI). A cross-sectional study by Bengtsson *et al.* [7] indicated that the extensive multisensory training of pianists results in increased functional anisotropy of the white matter (i.e. stronger anatomical connectivity) in the corpus callosum (which connects the left and right cerebral hemispheres via commissural fibers) and the internal capsule (a region that contains ascending and descending fibers mainly connecting the cerebral cortex with subcortical regions). Changes in anatomical connectivity due to musical training have also been found in the longitudinal fasciculus [87] (a white-matter tract that connects temporal and frontal regions) as well as in the corticospinal tract [88], which is known to convey sensory-motor information.

Enhancement of multisensory processing due to extensive training has also been observed in subcortical regions of the brainstem. Recently, Musacchia *et al.* [89] used EEG to measure early brainstem responses of musicians and non-musicians to linguistic and musical auditory and audiovisual stimuli. Results indicated that 4 -10 ms after stimulus onset, for both auditory and audiovisual stimuli, musicians already exhibited increased electrophysiological responses. Moreover, the frequency following response (FFR, a sustained portion of the brainstem response to complex sounds) was also enhanced in musicians. Importantly, the effect of musical expertise is generalized to the linguistic task. These data also imply that when processes early in the hierarchy are affected by training, this may affect all further "downstream" processing.

Multisensory training effects in neuroplasticity

The above-mentioned studies used a cross-sectional approach to investigate multisensory

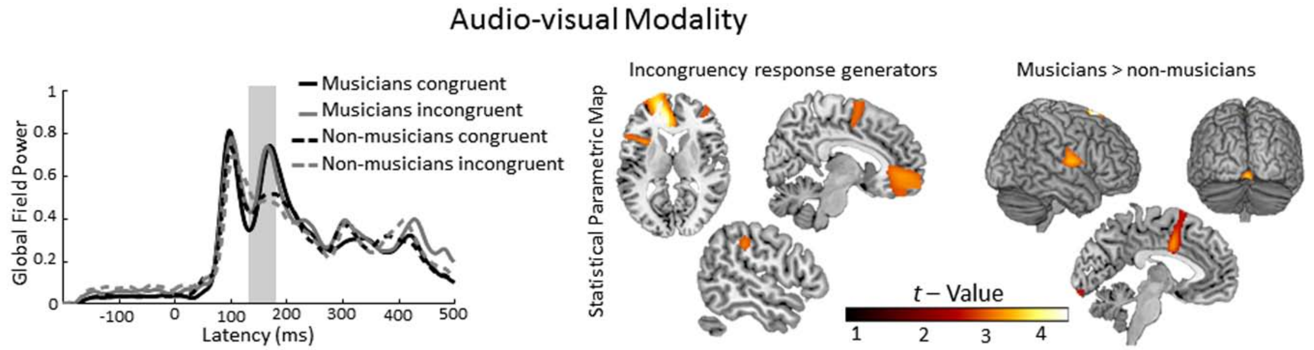

Figure 1. Effects of long-term musical training on audio-visual processing in a recent MEG study by Paraskevopoulos et al. [26]. Right side: statistical parametric maps of the audio-visual incongruity response and the musicians to non-musicians comparison. Musicians showed an increased difference of activity in the right superior frontal gyrus, the right superior temporal gyrus and the right lingual gyrus when they perceived stimuli with incongruent visual and auditory information compared to congruent audiovisual stimuli. Left side: grand average global field power for responses to congruent (black lines) and incongruent (grey lines) stimuli for musicians (continuous lines) and non-musicians (dashed lines). The time interval where the source analysis (right side) was performed is marked in grey.

neuroplasticity induced by experience. This approach can be highly informative with regard to the long-term effects of experience, but cannot be conclusive about the specific elements of the experience that drive these neuronal changes, nor does it allow causal inferences. In order to address these issues, several studies used a longitudinal approach with training protocols including specific, well-controlled multisensory elements. Training-related plasticity was then assessed by comparing neuronal activity before and after the training, or by comparing responses to trained versus untrained stimuli after the training.

Lahav *et al.*, [90] used fMRI to investigate neuroplastic changes in the audio-motor interaction system. They trained a group of non-musicians to play a melody on a piano and then monitored their brain activity while listening to the newly acquired piece or an equally familiar, but untrained piece. Results indicated that a network including Broca's area, the premotor region, the IPS, and the inferior parietal region was activated only when listening to the trained piece, indicating a task-specific training effect. Similar results have also been obtained using TMS by D'Ausilio *et al.* [91]. These authors used TMS to test excitability changes in piano players during auditory presentation of a rehearsed and a non-rehearsed piece. Their results showed increased motor excitability for the rehearsed, but not for the non-rehearsed piece. More recently, Chen *et al.* [92] used fMRI to study the formation of audio-motor interactions by measuring the brain activity before and after a piano training in a group of non-musicians. Their results showed that post-training subjects had reduced neural activity in the right superior temporal gyrus, and the left premotor cortex compared to pre-training, suggesting an increased efficiency in the unisensory processing of a multisensory trained stimulus.

Following a similar research approach, Bangert and Altenmüller [93] used EEG to show changes in cortical activation patterns of auditory and motoric tasks induced by short (20 minute) and medium term (5 week) piano training. In this study, co-activation of auditory and sensorimotor areas occurred within only 20 minutes, and the effect was enhanced after the completion of the 5-week training. Importantly, a stable key-to-pitch mapping throughout the training (compared to a varying one) was necessary to induce additional activity in the right anterior regions (since this effect was not present in an additional condition in which the keys were producing different pitches in each training session).

In two short-term musical training studies, Lappe *et al.* [62,63] used MEG to reveal that multisensory training is more beneficial for cortical plasticity than unisensory training, even for unisensory processing such as auditory melody [62] and rhythm [63] perception. Specifically, Lappe *et al.* first measured the auditory responses of 30 non-musical subjects in a 3-tone and a 6-tone melody mismatch negativity paradigm (MMN). The authors divided their subjects randomly into two groups that received different training over the course of 2 weeks. One group received auditory-sensory-motor training that involved learning to play a short musical piece on the piano, while the other group received only auditory training by listening to the recordings of the first group and expressing judgments about the correctness of the recordings. Hence, the two groups received identical input in the auditory modality and the contribution of the sensory-motor system differentiated the trainings. After 8 sessions of training, the subjects' auditory MMN responses were measured and compared with pre-training measurements. Results revealed that, after training, both groups had increased responsiveness of the auditory cortex to unexpected melodic changes in the auditory stimulation. Importantly, this increase was greater for the auditory-sensory-motor group than the auditory group.

Another recent training study using MEG [64] argued that plasticity due to short-term multisensory training alters the function of separate multisensory structures, and not merely the unisensory ones, along with their interconnection. In this study, musically naïve subjects were trained to play tone sequences from visually presented patterns in a music notation-like system (audio-visual-somatosensory training), while another group received audio-visual training only, which involved viewing the patterns and attentively listening to the recordings of the first group's sessions. The cortical responses of an audiovisual, an auditory and a visual MMN response were assessed before and after the training. The results of this study revealed an enhancement of the audiovisual MMN, while there was no significant effect on the auditory and visual mismatches. This finding indicates that a region in the right superior temporal gyrus was affected by input from all three modalities during the training procedure in such a way that the neuroplastic effect of short-term multisensory training modified its function.

In two fMRI studies, Butler *et al.* [94,95] investigated how new audiovisual associations of novel objects are established and the role that active motor involvement has in this process. They used a training protocol in which the subjects learned visuo-auditory-motor associations between novel objects and the sounds they produced; either through self-generated actions on the objects or by observing an experimenter produce the actions (passive learning). After the training, behavioral and fMRI measures were obtained while the subjects perceived the objects in uni- or multisensory mode. The results indicated that the additional use of the motor system during learning led to faster learning and more accurate recognition of audiovisual associations than when only the auditory and visual modalities were used (trained). On a neural level, greater activation during both the perception and recognition of actively learned associations in motor, somatosensory, and cerebellar regions were found. Also, functional connectivity between visual- and motor-related processing regions was enhanced during the presentation of actively learned audiovisual associations.

Naumer et al. [96] also investigated the facilitation of new audiovisual associations through training. They used fMRI to measure brain activity during the presentation of novel (artificial) audiovisual objects before and after a short-term audiovisual associative training process. The post-training results showed extended integration-related inferior frontal cortex activation bilaterally and a recruitment of additional regions bilaterally in the STS and IPS, indicating that these structures changed their activity due to the training.

Neuroplastic changes due to multisensory training have also been observed in brain structure. Using DTI to measure the integrity of white matter tracts after training, *Scholz et al.* [97] trained subjects on a visuo-motor training task (juggling). They were able to show that 6 weeks of multisensory training induced white matter changes that were not found in a group of controls who did not perform any training. Post-training changes in the fractional anisotropy were located within the white matter underlying the right IPS. Importantly, these changes remained elevated relative to the baseline after a period of four weeks juggling, indicating a long-lasting effect.

Functional frameworks

The architecture of the mechanisms upon which changes in multisensory integration rely still remains unclear [58]. The proposed frameworks emphasize either the role of feed-forward and feedback circuits between the multisensory and the unisensory regions, [97,98] or the changes occurring independently within the multisensory or unisensory structures [2,99]. These different frameworks are illustrated in Figure 2. However, the increasing evidence that neurons with multisensory functionality exist within the brain regions that were traditionally considered unisensory limits conclusions regarding the strict structural localization to uni- and multisensory brain regions. Since evidence exists for changes at all levels, it seems that multisensory training alters the processing at both lower and higher levels in the sensory processing streams, at the same time changing their functional and structural connections.

Evidence for the important role of feedback and feed-forward connections between the unisensory and the multisensory structures come from several studies. As discussed above, a multisensory training study by Scholz *et al.* [97] indicated alterations in white matter tracts due to several weeks of multisensory training. In an interesting animal study, Jiang *et al.* [43] demonstrated that disrupting the feedback circuit from a cortical multisensory region to the superior colliculus in cats eliminates the multisensory characteristics of the superior colliculus neurons, while strengthening the same thalamocortical connections seems to facilitate multisensory processing during maturation [100]. This notion is further supported by several studies on cortical functional connectivity [50,101–104].

Other studies highlight the changes occurring within multisensory structures. A recent MEG study by Paraskevopoulos *et al.* [64] indicated that the plasticity caused by short term multisensory training altered the multisensory structures involved in the training and not the unisensory ones and their interconnection. The results showed that salient multisensory stimuli may bypass primary sensory cortices and may be processed directly in multisensory regions. This highlights the possibility that multisensory regions are those which change through experience [54]. Complementary evidence for this model comes from the fMRI training studies that indicate plasticity in structures traditionally considered as multisensory [94,96,105].

The critical role of changes occurring within unisensory areas is emphasized by studies of perceptual learning [99]. In this context, it is hypothesized that the unisensory representation that is trained lowers the neural threshold needed for the activation of these structures [106] and, as a result, the "downstream" multisensory structures receive enhanced input. This finding is further supported by studies indicating plastic effects due to multisensory training within unisensory processes, such as the studies on the effects of multisensory piano training on auditory processing by Lappe *et al.* [62,63] discussed previously.

On a functional level the proposed mechanisms do not have to be mutually exclusive. Indeed, the different mechanisms may account for different forms of learning or they may even co-exist at different hierarchical levels [101]. Future research should focus on the way these different models of multisensory plasticity are induced by various types of training protocols and on clarification of the present results. Disentangling the differential effects of task or procedural characteristics of multisensory training on the resulting plasticity can also be of high importance for the elucidation of its clinical relevance.

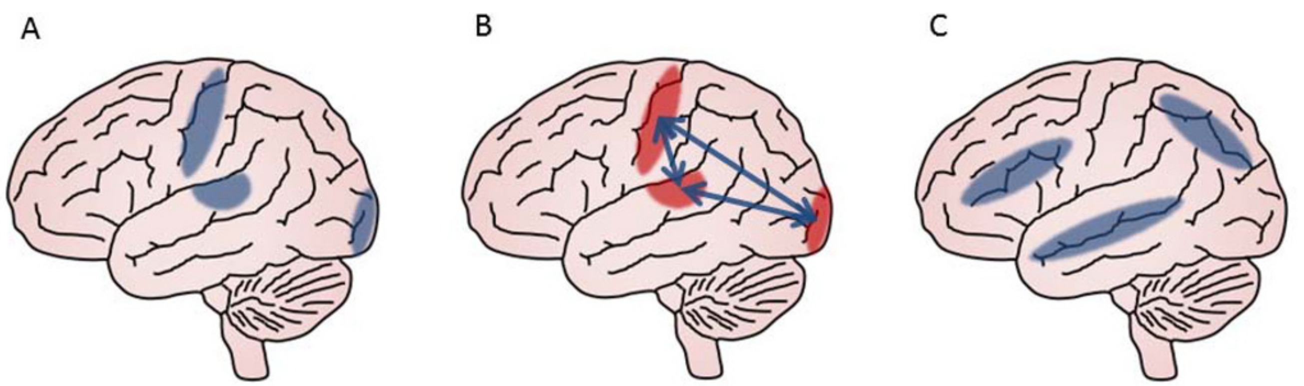

Figure 2. Illustration of different models and functional frameworks for multisensory plasticity. Structures that are modified by training structures are colored blue. A: Multisensory training modifies the unisensory structures, allowing for enhanced unisensory processing, which in turn send their output to the higher-order multisensory regions. B: Multisensory training modifies the feed-forward and feedback connections between the unisensory structures, allowing for better communication between the different modalities. C: Multisensory training modifies the multisensory structures directly, allowing for enhanced multisensory processing.

Clinical relevance of multisensory training

Rehabilitation approaches that use complex, multisensory training tasks have become increasingly widespread, with musical training as one of the most studied types of interventions. In stroke rehabilitation, musical approaches have been developed to train coarse movements of the upper and lower extremities using an electrical drum set programmed to play tones and to train manual and finger movements using piano practice [107]. Both in behavioral outcomes and underlying physiological neuroplasticity, the music-supported multisensory therapies are superior to traditional motor rehabilitation approaches [108].

Music-based interventions have become a popular intervention for patients suffering from Parkinson's Disease (PD), ranging from walking exercises accompanied by music [109,110] to dance lessons [111,112]. In these studies, both music-accompanied walking exercises and diverse dancing styles, like tango and ballroom, improve gait, posture and balance parameters in PD patients. Music-based interventions have recently been summarized in a meta-analysis [113] that finds further evidence for improvements of motor control and movement initiation from gait training with music rather than from dance practice. However, the benefits of the social aspect of dance practice should not be underestimated [112], and more systematic interventions will be needed to investigate the underlying neuronal mechanisms of behavioral improvements for both kinds of auditory-sensorimotor interventions. Indications that PD patients also benefit from multisensory cues for more basic motor control comes from a study showing that audiovisual training improves postural control in PD [114]. However, since the control group did not receive any training, the specificity of the audiovisual component of the training remains unclear.

In the literature, making music tends to be a more common intervention for acquired brain injuries, while dancing is frequently reported as a rehabilitation strategy for PD patients. This might be due to the emphasis on different types of movements (upper limbs and fine motor control in music-making versus whole-body movement, gait and posture in dancing) and has most likely emerged from practical considerations and target functions to be improved by the training (for a review see [113]). While both music-making and dancing are multisensory activities in that they involve sensorimotor, proprioceptive, auditory and visual domains, there is an important difference: while dancers synchronize with auditory input, musicians actively produce the sounds. Based on models of multisensory learning, especially with regard to use of feed-forward and feedback across modalities, both types of activities would be expected to build on different underlying learning processes. To what extent this reflects in training-related neuroplastic effects represents an exciting avenue for research with practical impact on rehabilitation approaches.

Insights in the mechanisms of neuroplasticity due to multisensory training also offer new perspectives for healthy cognitive aging and rehabilitative approaches for Alzheimer's disease (AD) [8]. Multisensory processing does not show as much age-related decline as unisensory processing, and is, in some cases, even enhanced in old compared to young individuals [115]. In the course of neurodegenerative processes, multisensory integration does not seem to be strongly affected by dementia, at least up to mild to moderate stages of the disease. Even AD and mild cognitive impairment (MCI) patients show intact multisensory integration, albeit delayed compared to controls [116]. Two arguments speak for a more widespread application of active, complex, multisensory activities to promote healthy aging: firstly, due to the increased benefits and preserved processing of multisensory input in aged individuals and dementia patients, activities that involve integration of several modalities might be expected to be more effective than trainings that focus on only one domain (e.g. visual attention trainings). Second, as discussed above, multisensory activities tend to result in neuroplastic changes not only in cortical sensory regions, but also in higher-order association areas. These are typically among the first to be affected in dementia and MCI, and are thus target regions for rehabilitation efforts. Longitudinal and cross-sectional studies suggest that an active lifestyle with leisure activities like dancing, music-making, sports and social activities, [117,118] and education, in combination with stimulatory experiences in late life [119], might be protective against MCI and several forms of dementia and neurodegenerative diseases [120]. An intervention study using physical exercise accompanied by music showed significant improvements in cognition in dementia patients compared to a control group [121]. However, it is yet unclear to what extent the multisensory nature of such activities contributes to global effects on cognition and quality of life.

For some cognitive functions, more specific associations between long-term training and behavioral benefits in aged individuals have been reported: aged individuals who had practiced music extensively showed better nonverbal memory, naming, and executive processes than non-musician peers in a cross-sectional study [122]. Similarly, middle-aged musicians show better speech-in-noise perception and better working memory than age-matched non-musicians. Interestingly, only verbal working memory was better, with no group differences for visual working memory, indicating that benefits of predominantly auditory-motor training don't easily generalize to other sensory domains [123]. These behavioral effects are partly based on differences in the neural hardware: musicians' long-term experience might delay the onset of age-related losses regarding neural encoding during speech perception as early as on the brainstem level [124]. Such results are a promising basis for more research on the mechanisms of training-related plasticity in aging participants. Still, due to the limitations of cross-sectional comparisons in most studies it remains unclear whether the training itself is protective against cognitive decline or whether musicians exhibit protective brain characteristics even before they start training.

Future directions

Better understanding of the role of multisensory integration in neuroplastic changes in the brain will be crucial for improving our models of underlying mechanisms. For this, well-controlled experimental training studies with direct manipulation of multisensory training components in healthy and patient populations are needed. The large variety of multisensory trainings that are used to study neuroplasticity, ranging from lab-based audio-visual-motor paradigms (e.g., [63]) to naturalistic approaches using leisure activities (e.g., [125]), creates challenges for the integration of findings across studies, because trainings and effects are difficult to compare directly. In order to identify task- or stimulus-specific and general aspects of multisensory trainings that drive behavioral improvements and neuroplastic effects, we will need new approaches for cross-study integration. Also, direct comparison of trainings within studies and the choice of appropriate control groups will be extremely helpful to disentangle the contributions of different task characteristics to neuroplastic effects.

Within the last few years, the focus of neuroscience research in humans has begun to shift from group comparisons and average effects to individual differences in behavior, brain function and structure [126]. White matter tracts, especially long-range connections relevant to conveying information across cortical areas during multimodal integration and processing, show significant inter-individual differences [127]. This may not only be related to the variability seen in plasticity effects in multisensory training studies of white matter tracts (e.g., [97,125]), but existing cortical functional and structural connections (and other relevant brain characteristics) might predetermine to what extent an individual can benefit from a multisensory training intervention. For example, the strength of existing connections between visual and auditory areas or between auditory and motor areas might predict how fast a participant may learn an auditory-visual or auditory-motor task, respectively. Lab-based training studies would allow investigation of the functional and structural predisposing factors for plasticity, but this has so far rarely been exploited. Findings of functional and structural characteristics that partly determine auditory [128–130] and visual learning [131] point in a promising direction. Due to the importance of cross-cortical and subcortical connections especially for multisensory learning, and their natural variability in the population, one might expect even stronger predetermining effects in complex multimodal training paradigms. Such effects are not only interesting for basic cognitive neuroscience, but consideration of individual strengths and predispositions could improve the selection of rehabilitation and educational strategies.

Finally, the interactions of individual maturation and changes of multisensory processing in early development, adulthood and aging with multisensory training-related plasticity are an exciting avenue for future research. In musical training, correlational data show that earlier onset of training results in stronger functional and structural changes. For example, the cortical expansion of finger representation in string players correlates negatively with training onset [132] and increased thickness of the corpus callosum connecting the hand areas in musicians is particularly prominent in musicians who started to train early in life [133]. This and other data speak for the existence of sensitive periods in development [134] during which the brain is especially susceptible to auditory-motor learning, which is further corroborated by the independence of age of onset effects from the overall duration of training [135]. To what extent the potential for multisensory learning changes with normal and pathological aging has not been extensively studied, but some recent studies in elderly individuals using golfing [125] and juggling [136] support the notion that the brain remains plastic into old age, and that multisensory activities might be particularly effective and rewarding. These questions have important implications for educational and clinical rehabilitation strategies and merit further investigation.

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