

INVITED REVIEW

Neurologic music therapy: The beneficial effects of music making on neurorehabilitation

Eckart Altenmüller^{1,*} and Gottfried Schlaug²

¹*Institute of Music Physiology and Musicians' Medicine (IMMM), University of Music, Drama and Media, Hanover, Emmichplatz 1, D-30175 Hannover, Germany*

²*Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA*

Abstract: Making music is a powerful way of engaging a multisensory and motor network and inducing changes and linking brain regions within this network. These multimodal effects of music making together with music's ability to tap into the emotion and reward system in the brain can be used to facilitate therapy and rehabilitation of neurological disorders. In this article, we review short- and long-term effects of listening to music and making music on functional networks and structural components of the brain. The specific influence of music on the developing brain is emphasized and possible transfer effects on emotional and cognitive processes are discussed. Furthermore we present data on the potential of music making to support and facilitate neurorehabilitation. We will focus on interventions such as rhythmic auditory stimulation, melodic intonation therapy, and music-supported motor rehabilitation to showcase the effects of neurologic music therapies and discuss their underlying neural mechanisms.

Keywords: Music, Brain plasticity, Auditory-sensory-motor integration, Stroke, Aphasia

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1. MUSIC AS A DRIVER OF BRAIN PLASTICITY

Musical experience is one of the richest human emotional, sensory-motor, and cognitive experience. It involves listening, watching, feeling, moving and coordinating, remembering and expecting. It is frequently accompanied by profound emotions resulting in joy, happiness, bitter-sweet sadness or even in overwhelming peak experiences which manifest themselves in bodily reactions like tears in the eyes or shivers down the spine. A large number of brain regions across various domains contribute to this musical experience (for reviews see [1,2]).

Primary and secondary regions in the cerebral cortex for example are critical for any conscious perception of sensory information be it auditory, visual, or somato-sensory. However, music also changes activity in multi-sensory and motor integration regions in the frontal and parietal lobes. The frontal lobe is involved in guidance of attention, in planning and motor preparation, in integrating auditory and motor information, and in specific human

skills such as imitation and empathy which play an important role into the acquisition of musical skills and in the emotional expressiveness of music. Multisensory integration regions in the parietal lobe and temporo-occipital regions integrate different sensory inputs, from the ear, eyes, and touch sensors into a combined sensory impression; it is this combined sensory impression which constitutes the typical musical experience. The cerebellum is another important part of the brain that plays a critical role in the musical experience. It is important for motor coordination and in various cognitive tasks especially when aspects of timing play a role, for example in rhythm processing and tapping in synchrony with an external pacemaker such as a metronome. Finally, the extended emotional network (comprising the basis and the inner surfaces of the two frontal lobes, the cingulate gyrus and brain structures in the evolutionarily old parts of the brain such as the amygdala, the hippocampus and the midbrain) is crucial for the emotional perception of music and hitherto for an individual's motivation to listen to or to engage in any musical activity.

The brain as a highly dynamically organized structure can change and adapt as a result of activities and demands imposed by the environment. Musical activity has proven

*e-mail: eckart.altenmueller@hmtm-hannover.de

to be a powerful stimulus for this kind of brain adaptation, or brain plasticity, as pointed out by Wan and Schlaug [3]. Effects of plasticity are not restricted to musical prodigies, they occur in children learning to play a musical instrument [4] and in adult musical amateurs [5], albeit to a lesser extent. Thus, with the main topic of our article in mind, we suggest that music making induced brain plasticity may produce benefits not only by changing sensorimotor brain networks but also by influencing neuro-hormonal status as well as cognitive and emotional processes in healthy and neurologically diseased/disordered individuals, helping to improve various sensory, motor, coordinative or emotional disabilities.

In the following, we will first briefly review mechanisms of music making induced brain plasticity. We will then clarify the impact of music on emotion and neuro-hormones. Subsequently, we will demonstrate transfer effects of music exposure and music making to other cognitive and emotional domains and finally show examples of the potential of music making to support and facilitate neurorehabilitation. Here we will not give an exhaustive review, but focus on improving rehabilitation in basal ganglia disorders, aphasia and motor impairments following brain injury.

2. SOME MECHANISMS OF MUSIC INDUCED BRAIN PLASTICITY

During the past decade, brain imaging has provided important insights into the enormous capacity of the human brain to adapt to complex demands. These adaptations are referred to as brain plasticity and do not only include the quality and extent of functional connections of brain networks, but also fine structure of nervous tissue and even the visible gross structure of brain anatomy [6]. Brain plasticity is best observed in complex tasks, including temporo-spatially precise movements with high behavioral relevance. These behaviors are usually accompanied by emotional arousal and motivational activation of the reward system. Furthermore, plastic changes are more pronounced when the specific activities have started early in life and require intense training. Obviously, continued musical activities provide in an ideal manner these prerequisites of brain plasticity. It is therefore not astonishing that the most dramatic effects of brain plasticity have been demonstrated in professional musicians (for a classic review see [7], for more recent reviews [3,8]).

Our understanding of the molecular and cellular mechanisms underlying these adaptations is far from complete. Brain plasticity may occur on different time axes. For example, the efficiency and size of synapses may be modified in a time window of seconds to minutes, the growth of new synapses and dendrites may require hours to

days. An increase in gray matter density, reflecting either an enlargement of neurons, a change in synaptic density, more support structures such as capillaries and glial cells or a reduced rate of physiological cell death (termed apoptosis) needs up to several weeks. White matter density also changes as a consequence of musical training. This effect seems to be primarily due to an enlargement of myelin cells: The myelin cells, wrapped around the nerve fibers (axons) are contributing essentially to the velocity of the electrical impulses traveling along the nerve fiber tracts. Under conditions requiring rapid information transfer and high temporal precision, these myelin cells are growing and as a consequence nerve conduction velocity will increase. Finally, brain regions involved in specific tasks may also be enlarged after long-term training due to the growth of structures supporting the nervous function, for example blood vessels that are necessary for the oxygen and glucose transportation sustaining nervous function.

Comparison of the brain anatomy of skilled musicians with that of non-musicians shows that prolonged instrumental practice leads to an enlargement of the hand area in the motor cortex [9] and to an increase in grey matter density corresponding to more and/or larger neurons in the respective area [10]. These adaptations appear to be particularly prominent in all instrumentalists who have started to play prior to the age of ten and correlate positively with cumulative practice time. Furthermore, in professional musicians, the normal anatomical difference between the larger, dominant (mostly right) hand area and the smaller, non-dominant (left) hand area is less pronounced when compared to non-musicians. These results suggest that functional adaptation of the gross structure of the brain occurs during training at an early age.

Similar effects of specialization have been found with respect to the size of the corpus callosum. Professional pianists and violinists tend to have a larger anterior (front) portion of this structure, especially those who have started prior to the age of seven [11]. Since this part of the corpus callosum contains fibers from the motor and supplementary motor areas, it seems plausible to assume that the high demands on coordination between the two hands, and the rapid exchange of information may either stimulate the nerve fiber growth—the myelination of nerve fibers that determines the velocity of nerve conduction—or prevent the physiological loss of nerve tissue during the typical pruning processes of adolescence or during aging. These between-group differences in the midsagittal size of the corpus callosum were confirmed in a longitudinal study comparing a group of children learning to play musical instruments versus a group of children without instrumental music experience [4]. Another impressive adaptation of white matter structures has recently been shown by Halwani and colleagues [12]. They reported differences

in macrostructure and microstructure of the arcuate fasciculus, a prominent white-matter tract connecting temporal and frontal brain regions, between singers, instrumentalists, and non-musicians. Both groups of musicians had higher tract volumes in the right dorsal and ventral tracts compared to non-musicians, but did not show a significant difference between each other. Singers had higher tract volume and different microstructures of the tract on the left side as well when compared to instrumental musicians and non-musicians suggesting that the right hemisphere AF might show a more general effect of music making, while the left hemisphere AF had a stronger response to the specific aspects of vocal-motor training and control. The microstructure of the left dorsal branch of the arcuate fascicle was correlated with the number of years of participants' vocal training, suggesting that long-term vocal-motor training might lead to an increase in volume and microstructural complexity of specific white-matter tracts constituting the so-called aural-oral loop and connecting regions that are fundamental to sound perception, production, and its feedforward and feedback control. Similarly, Sarah Bengtsson and her colleagues [13] have found structural differences in the corticospinal tract, particularly in the posterior limb of the internal capsule, between musicians and non-musicians. This difference was related to measures of training intensity.

Subcortical structures also seem to be highly affected. In professional musicians, the cerebellum, which contributes significantly to the precise timing and accuracy of motor commands, is also enlarged [10,14].

In summary, when training starts at an early age (before about seven years), these plastic adaptations of the nervous system affect brain anatomy by enlarging the brain structures that are involved in different types of musical skills. When training starts later, it modifies brain organization by re-wiring neuronal webs and involving adjacent nerve cells to contribute to the required tasks. These changes result in enlarged cortical representations of, for example, specific fingers or sounds within existing brain structures. In the following we will more closely examine the emotional prerequisites for brain plasticity and the impact of music on emotions and neurohormones.

3. THE ROLE OF MUSIC INDUCED EMOTIONS FOR BRAIN PLASTICITY

An intriguing question is why music is such a powerful medium allowing it to induce physiological and anatomical effects on the brain which might underlie the beneficial effects of neurologic music therapy? This brings us to the specific motivational and emotional role of musical experience. Emotional responses to music are often cited when people describe why they value music and why they ascribe certain effects of music on health. Music is known

to have a wide-range of physiological effects on the human body including for example changes in heart rate, respiration, blood pressure, skin conductivity, skin temperature, muscle tension, and biochemical responses (e.g. [15], for a review see also [16]).

Joyful musical behaviors, for example learning to play a musical instrument or to sing is characterized by curiosity, stamina and the ability to strive for rewarding experiences in future. This results in incentive goal directed activities over prolonged time periods which are mainly mediated by the transmitter substance dopamine. Most nerve cells sensitive to this neurotransmitter are found in a small part of the brain which is localized behind the basis of the frontal cortex, the so-called meso-limbic system, an important part of the "emotional" brain. Dopamine is widely recognized to be critical to the neurobiology of reward, learning and addiction. Virtually all drugs of abuse, including heroin, alcohol, cocaine, and nicotine activate dopaminergic systems. So called "natural" rewards such as musical experiences and other positive social interactions likewise activate dopaminergic neurons and are powerful aids to attention and learning [17]. There is ample evidence that the sensitivity to dopamine in the meso-limbic brain regions is largely genetically determined resulting in the enormous variability in reward-dependent behaviour. The genetic "polymorphism" of dopaminergic response explains the different motivational drives we observe in children with a similar social and educational background. It is intriguing that there is a strong link of dopaminergic activity to learning and memory, which in turn promote plastic adaptations in brain areas involved in the tasks to be learned.

Serotonin is another neurotransmitter important for music induced brain plasticity. It is commonly associated with feelings of satisfaction from expected outcomes, whereas dopamine is associated with feelings of pleasure based on novelty or newness. In a study of neurochemical responses to pleasant and unpleasant music, serotonin levels were significantly higher when subjects were exposed to music they found pleasing [18]. In another study with subjects exposed to pleasing music, functional and effective connectivity analyses showed that listening to music strongly modulated activity in a network of mesolimbic structures involved in reward processing including the dopaminergic nucleus accumbens and the ventral tegmental area, as well as the hypothalamus and insula. This network is believed to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli [19].

Blood and Zatorre [20] determined changes in regional cerebral blood flow (rCBF) with PET-technology during intense emotional experiences involving sensations such as goose bumps or shivers down the spine whilst listening

to music. Each participant listened to a piece of their own favourite music to which they usually had a chill experience. Increasing chill intensity correlated with rCBF decrease in the amygdala as well as the anterior hippocampal formation. An increase in rCBF correlating with increasing chill intensity was observed in the ventral striatum, the midbrain, the anterior insula, the anterior cingulate cortex and the orbitofrontal cortex: Again, these latter brain regions are related to reward and positive emotional valence.

Taken together, these powerful music induced modulations of neuro-hormonal status may not only account for pleasurable experiences but may also play a role in neurologic music therapy.

4. RHYTHMIC AUDITORY STIMULATION AS ONE EXAMPLE OF NEUROLOGIC MUSIC THERAPY

Studies on neurological applications of music therapy have so far mainly dealt with examining the effects of efficacy in Basal Ganglia disorders, such as Parkinson's disease, and in stroke patients with aphasia or motor impairments. With respect to Parkinson's disease, Rhythmic Auditory Stimulation (RAS) has been proven to be particularly efficient. Parkinson's disease is a neurodegenerative disorder with movement related symptoms including tremor, rigidity and slowness of movements, particularly during walking. Stride-length and gait velocity are typically markedly diminished. These symptoms result from the loss of dopamine-generating cells in the Substantia nigra, a region in the midbrain which is part of the basal-ganglia loop, controlling motor behavior and automated movements.

Here, rhythmic auditory stimulation has profound effects as a coordinative sensory input to entrain timing functions of the basal ganglia loop and increase stride length and gait velocity (for a review see [21]). It is argued that time cues may be important facilitators to enhance the underlying physiology of temporal pattern formation in the basal ganglia, thus enhancing motor learning [22]. In order to evaluate the long-term use of rhythmic auditory stimulation in gait rehabilitation, Thaut *et al.* [23] used a two-armed parallel group design, comparing RAS to conventional gait training in physical therapy. Results demonstrated a statistically significant superiority of the RAS-group compared to the physiotherapy group with regard to the kinematic parameters gait velocity and stride length. This positive outcome has also been found by another research group [24].

Data on the differential use of metronome vs. rhythmic-auditory stimulation in a musical context are not consistent. Thaut *et al.* [25] have provided evidence that the temporal synchronization of a sensorimotor task is

more precise with rhythmically accentuated musical stimulation than with metronome clicks in healthy subjects. In relation to the improvement of the quality of gait in Parkinson's disease patients, Enzensberger *et al.* [26], however, found a superiority of metronome stimulation as compared to stimulation by rhythmically accentuated music.

5. FACILITATING RECOVERY FROM NONFLUENT APHASIA THROUGH A FORM OF SINGING

The ability to sing in humans is evident from infancy, and does not depend on formal vocal training but can be enhanced by training. Given the behavioural similarities between singing and speaking, as well as the shared and distinct neural correlates of both, researchers have begun to examine whether forms of singing can be used to treat some of the speech-motor abnormalities associated with various neurological conditions [27].

Aphasia is a common and devastating complication of stroke or other brain injuries that results in the loss of ability to produce and/or comprehend language. It has been estimated that between 24–52% of acute stroke patients have some form of aphasia if tested within 7 days of their stroke; 12% of survivors still have significant aphasia at 6 months after stroke [28]. The nature and severity of language dysfunction depends on the location and extent of the brain lesion. Accordingly, aphasia can be classified broadly into fluent or nonfluent. Fluent aphasia often results from a lesion involving the posterior superior temporal lobe known as Wernicke's area. Patients who are fluent exhibit articulated speech with relatively normal utterance length. However, their speech may be completely meaningless to the listener, and littered with jargon, as well as violations to syntactic and grammatical rules. These patients also have severe speech comprehension deficits. In contrast, nonfluent aphasia results most commonly from a lesion in the left frontal lobe, involving the left posterior inferior frontal region known as Broca's area. Patients who are nonfluent tend to have relatively intact comprehension for conversational speech, but have marked impairments in articulation and speech production.

The general consensus is that there are two routes to recovery from aphasia. In patients with small lesions in the left hemisphere, there tends to be recruitment of both left-hemispheric, perilesional cortex with variable involvement of right-hemispheric homologous regions during the recovery process [29–32]. In patients with large left-hemispheric lesions involving language-related regions of the fronto-temporal lobes, the only path to recovery may be through recruitment of homologous language and speech-motor regions in the right hemisphere [30,33]. It has been suggested that recovery via the right hemisphere may be

less efficient than recovery via the left hemisphere [29,31], possibly because patients with relatively large left hemispheric lesions are generally more impaired and recover to a lesser degree than patients with smaller left hemisphere lesions. Nevertheless, activation of right-hemispheric regions during speech/language fMRI tasks has been reported in patients with aphasia, irrespective of their lesion size [30]. For patients with large lesions that cover the language-relevant regions on the left, therapies that specifically engage or stimulate the homologous right-hemispheric regions have the potential to facilitate the language recovery process beyond the limitations of natural recovery [32–34]. Based on clinical observations of patients with severe nonfluent aphasia and their ability to sing lyrics better than they can speak the same words [35–37], an intonation-based therapy called Melodic Intonation Therapy (MIT) that would emphasize melody and contour and engage a sensorimotor network of articulation on the unaffected hemisphere through rhythmic tapping was developed [38–40]. The two unique components of MIT are the (1) intonation of words and simple phrases using a melodic contour that follows the prosody of speech, and the (2) rhythmic tapping of the left hand tapping which accompanies the production of each syllable and serves as a catalyst for fluency.

To date, studies using MIT have produced positive outcomes in patients with nonfluent aphasia. These outcomes range from improvements on the Boston Diagnostic Aphasia Examination (BDAE [41]; see also [42]), to improvements in articulation and phrase production [43] after treatment. The effectiveness of this intervention is further demonstrated in a recent study that examined transfer of language skills to untrained contexts. Schlaug *et al.* [33] compared the effects of MIT with a control intervention (speech repetition) on picture naming performance and measures of propositional speech. After 40 daily sessions, both therapy techniques resulted in significant improvement on all outcome measures, but the extent of this improvement was far greater for the patient who underwent MIT compared to the one who underwent the control therapy.

The therapeutic effect of MIT also is evident in neuroimaging studies that show reorganization of brain functions. MIT resulted in increased activation in a right-hemisphere network involving the premotor, inferior frontal, and temporal lobes [33], as well as increased fiber number and volume of the arcuate fasciculus in the right hemisphere [34]. These findings demonstrate that intensive experimental therapies such as MIT — when applied over a longer period of time in chronic stroke patients — can induce functional and structural brain changes in a right hemisphere vocal-motor network, and these changes are related to speech output improvements.

6. MUSIC SUPPORTED MOTOR THERAPY IN STROKE PATIENTS

Music supported therapy (MST) in the rehabilitation of fine motor hand skills was first systematically investigated by Schneider *et al.* [44]. Patients were encouraged to play melodies either with the paretic hand on a piano, or to tap with the paretic arm on eight electronic drum pads that emitted piano tones. It was demonstrated that these patients regained faster their motor agility, and improved in timing, precision and smoothness of fine motor skills. Along with fine motor recovery, an increase in neuronal connectivity between sensory-motor and auditory regions was demonstrated by means of EEG-coherence measures [45,46]. Therefore, establishing an audio-sensory-motor co-representation may support the rehabilitation process (see Fig. 1). This notion is corroborated by findings in a patient who underwent music-supported training 20 months after suffering a stroke. Along with clinical improvement, fMRI follow up provided evidence for the establishment of an auditory-sensory motor network due to the training procedure [47].

Undoubtedly, music-supported training is efficient and seems to be even more helpful than functional motor training using no auditory feedback, but otherwise similar fine motor training. A randomized prospective study comprising all three groups is presently under the way and will clarify the differential effects of functional motor training and music-supported training. With respect to the underlying mechanisms, there still remain a number of open questions. First, the role of motivational factors must be clarified. From the patients' informal descriptions of their experience with the music-supported training, it appears that this was highly enjoyable and a highlight of their rehabilitation process. Thus, motivational and emotional factors might have contributed to the success of the training program. Furthermore, according to a recent study by Särkämö and colleagues [48], music listening activates a wide-spread bilateral network of brain regions related to attention, semantic processing, memory, motor functions, and emotional processing. Särkämö and colleagues showed that music exposure significantly enhances cognitive functioning in the domains of verbal memory and focused attention in a music group compared to a control group. The music group also experienced less depressed and confused mood than the control groups. These mechanisms may also hold true for the music-supported training we applied.

Another issue is related to the auditory feedback mechanisms. Up to now it has not been clear whether any auditory feedback (e.g., simple beep tones) would have a similar effect on fine motor rehabilitation or whether explicit musical parameters such as a sophisticated pitch

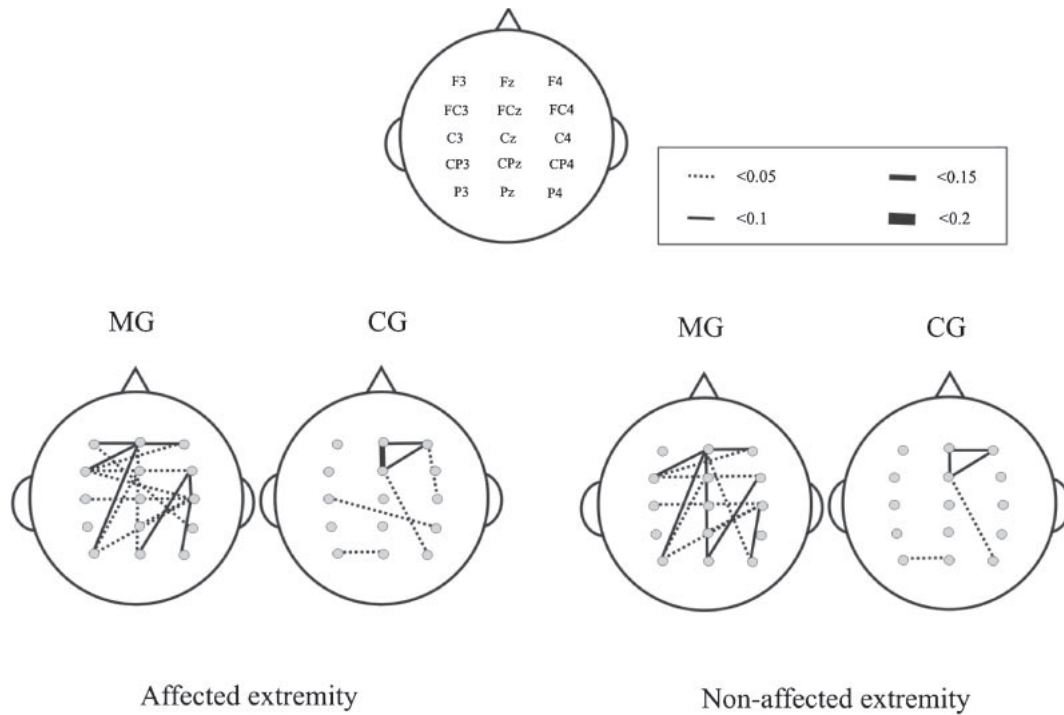


Fig. 1 Topographic task-related coherence maps for the Music group (MG) compared to the control group (CG) during self-paced arm movements for the drum pad condition in the beta band (18–22 Hz). Statistically significant increases in task-related coherence during the motor performance after 3 weeks and 15 sessions of music supported therapy on sonified drum pads are displayed. (From [45] with permission).

and time structure are prerequisites for the success of the training. This will be addressed in a planned study comparing the effects of musical feedback compared to simple acoustic feedback. With respect to the latter, according to a study by Thaut and colleagues [49], simple rhythmic cueing with a metronome significantly improves the spatio-temporal precision of reaching movements in stroke patients.

Furthermore, it is not clear, whether timing regularity and predictability is crucial for the beneficial effect of music supported therapy using key-board playing or tapping on drumpads. Although it has been argued that the effectiveness of this therapy relies on the fact that the patient's brain receives a time-locked auditory feedback with each movement, new results challenge this viewpoint. In a recent study, 15 patients in early stroke rehabilitation with no previous musical background learned to play simple finger exercises and familiar children's songs on the piano. The participants were assigned to one of two groups: in the *normal* group, the keyboard emitted a tone immediately at keystroke, in the *delay* group, the tone was delayed by a random time interval between 100 and 600 ms. To assess recovery, we performed standard clinical tests such as the nine-hole-pegboard test and index finger tapping speed and regularity. Surprisingly, patients in the delay group improved strikingly in the nine-hole-pegboard test, whereas patients in the normal group did not. In finger

tapping rate and regularity both groups showed similar marked improvements. The normal group showed reduced depression whereas the delay group did not [50]. Here we conclude that music therapy on a randomly delayed keyboard can significantly boost motor recovery after stroke. We hypothesize that the patients in the delayed feedback group implicitly learn to be independent of the auditory feedback and therefore outperform those in the normal condition.

Finally, the stability of improvements needs to be assessed in further studies, and the length and number of training sessions might be manipulated in future research. Additionally, the effect of training in chronic patients suffering from motor impairments following a stroke for more than a year will be assessed.

7. CONCLUSIONS

Emerging research over the last decade has shown that long-term music training and the associated sensorimotor skill learning can be a strong stimulant for neuroplastic changes in the developing as well as in the adult brain, affecting both white and gray matter as well as cortical and subcortical structures. Making music including singing and dancing leads to a strong coupling of perception and action mediated by sensory, motor, and multimodal brain regions and affects either in a top-down or bottom up fashion important sound relay stations in the brainstem and

thalamus. Furthermore, listening to music and making music provokes motions and emotions, increases between-subject communications and interactions, and — mediated via neurohormones such as serotonin and dopamine — is experienced as a joyous and rewarding activity through activity changes in amygdala, ventral striatum, and other components of the limbic system. Making music makes rehabilitation more enjoyable and can remediate impaired neural processes or neural connections by engaging and linking brain regions with each other that might otherwise not be linked together.

Music-based experimental interventions similar to other experimental interventions need to be grounded on a neurobiological understanding of how and why particular brain systems could be affected. The efficacy of these experimental interventions should be assessed quantitatively and in an unbiased way as one would require with any other experimental intervention. A neuroscientific basis for music-based interventions and data derived from randomized clinical trials are important steps in establishing neurologically-based music therapies that might have the power to enhance brain recovery processes, ameliorate the effects of developmental brain disorders, and neuroplasticity in general.

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Eckart Altenmüller (b. 1955) holds a Masters degree in Classical flute, and a MD and PhD degree in Neurology and Neurophysiology. Since 1994 he is chair and director of the Institute of Music Physiology and Musicians’ Medicine. He continues research into the neurobiology of emotions and into movement disorders in musicians as well as motor, auditory and sensory learning. From 2005–2011 he was President of the German Society of Music Physiology and Musicians’ Medicine.