Chapter

The Use of Music and Brain Stimulation in Clinical Settings: Frontiers and Novel Approaches for Rehabilitation in Pathological Aging

Mariangela Lippolis, Francesco Carlomagno, Fulvia Francesca Campo and Elvira Brattico

Abstract

Aging is a phase of life characterized by the increasing risk of occurring neurodegenerative pathologies, as well as stroke and physical decline. Patients in such clinical conditions are known to benefit from programs able to promote the improvement of associated cognitive, functional, and behavioral disorders. In recent times, growing empirical evidence showed the efficacy of active and passive music-based interventions to be the highest when used for healing these diseases. Additionally, very latest research found the combination of electrical neurostimulation with music to have potential utility for clinical older adult populations, as it may amplify the impulse to neuroplasticity and, by consequence, the rehabilitation gains. Reiterating of active music making induces changes in multiple brain regions bringing to the enhancement of cognitive and sensorimotor skills, while merely listening to pleasurable music stimulates dopaminergic regions of the brain improving cognition, motivation, and mood in a variety of neurological diseases. The versatility of music-based interventions in combination with new technologies allows an effective application of innovative therapeutic techniques. Moreover, their easy implementation in healthcare settings and their positive effects on both recovery and patients' quality of life makes the integration of music-based interventions with conventional rehabilitation approaches highly desirable.

Keywords: aging, music-based interventions, neuroplasticity, rehabilitation, brain stimulation

1. Introduction

Over the years, thanks to the scientific research progress applied to medicine, lifestyle, and awareness of risk factors, our society has witnessed an exponential increment in the elderly population (age > 65 years), and the maximum duration of life has undergone a significant increase compared to the past. As a consequence, the number of people over the age of 60 years has risen up to 1 billion in 2019 and will more than double by 2050 [1]. Reasonably, this poses crucial issues for economies and welfare systems. Moreover, efforts to promote health in the elderly population lag far behind the current situation, making the decline in quality of life (QOL) in older people a major social problem. In particular, physical aging and its consequences are harmful to psychological health and cause the onset of negative emotional states and disabling problems, thus posing a threat to older people's autonomy in everyday life and mental health. Due to these emergencies and to the lack of effective treatments for neurodegenerative diseases, the scientific community has been stimulated to explore the validity of a wide range of rehabilitative and psychosocial interventions defined as nonpharmacological treatments [2]. In addition, while brain reorganization capacity was previously thought to be limited to early childhood, the discovery that neuroplasticity continues with age has led to the development of tools and techniques to promote it even during aging in order to cope with functional and cognitive decline and strengthen already existing skills [3].

Among the interventions able to benefit older people, music started to be widely explored in recent years in order to be included in programs for the promotion of psycho-physical health and to aid the rehabilitation of specific pathologies. By consequence, the beneficial effect of music-based training and treatments has become an object of study in relation to a variety of clinical populations together with healthy individuals [4, 5]. The interest toward music as a means to support the rehabilitation process and its use in clinical settings find reason in the intrinsic power of music to generate plastic changes in the brain and its possibility to act upon the cellular level in both humans and animals. In fact, similarly to sport, music training and listening are able to activate the body and the reward system in the brain [6]. Mostly, the reiteration of these activities triggers the neurotrophic factors (i.e., biomolecules that help both young and adult neurons to grow, survive, and differentiate) including the brain-derived neurotrophic factor (BDNF), a pivotal molecule involved in neuronal plastic changes related to learning and memory [7]. Taking into account the results already obtained from animal studies [8, 9], music could be contemplated as a promising option for improving human brain functioning through fostering the production of the BDNF, which levels are important to be adequate in both normal and pathological aging, and therefore stimulating the neuroplasticity process [10].

According to the recent findings from network science, the neuroplastic changes are considered both from a structural and functional level of adaptation; additionally, the two of them are interrelated as functional reorganization implies structural reorganization [11, 12]. On the one hand, thanks to several neuroimaging studies, music training is well known to be able to provoke anatomical as well as structural plastic changes even in the adult human brain [13]. A plethora of structural differences, manifested as increased gray matter volume, have been seen throughout literature in somatosensory areas, premotor cortex, inferior temporal and frontal regions, and in cerebellum in the brains of musicians compared to nonmusicians; results from longitudinal studies, in particular, showed a link between the duration of musical training and the degree of structural change in white matter pathways, such as the corpus callosum, highlighting the importance of reiterating the training over the years to see the long-term effects clearly [14–17]. Moreover, diffusion tensor imaging studies show greater structural connectivity after music training in other areas, such as in structures connecting visual and auditory brain areas located in the left inferior fronto-occipital fasciculus and connecting auditory and motor regions (e.g., arcuate fasciculus) as well as multimodal integration regions [18, 19]. In line with this, anatomical brain differences have been also found in auditory and motor cortices in relation to music training [13]. These findings reveal music-trained people to have specific brain areas that appear different compared to the starting age of music training. For example, a study with magnetic resonance imaging identified the left superior temporal gyrus, bilateral putamen (extending also to hippocampus and amygdala), and right thalamus as the regions linked with music training, in terms of cumulative hours of music lessons [20].

On the other hand, subtle functional changes, intended as deep modifications of synaptic strength in spread cortical networks, can be detected at a macrostructural and microstructural level after having music training or musical experience [12]. This brain adaptation through neurogenesis leads to changes also in behavioral performance, as demonstrated by studies showing correlations between brain changes and enhanced skills, i.e., auditory discrimination, motor sequencing, and speech skills [21, 22]. In sum, structural and functional changes due to musical experience take place at various stages of the auditory pathway, from the brainstem to primary and surrounding auditory cortices, to areas involved in higher-order auditory cognition [23]. This is confirmed by evidence that older people who have received long-term music training early in life have faster neural performance and timing on cognitive tasks, as well as increased auditory attention and executive functions [24, 25]. Similarly, an active music-based intervention is able to involve more analogous components to music training and learning, as it consists of the repeated practice of movements accompanied by auditory feedback and extensive cognitive processing. This explains the inclination of an active musical intervention to act as a multisensory stimulus, which makes it a useful tool for rehabilitation and prevention [11].

Findings on listening to music effects on the brain have been also useful to implement its use in healthcare environments. In particular, neurochemical research has revealed neurotransmitters' role on the affective components of listening to enjoyable music, namely their release of dopamine in the mesolimbic striatal system, as well as sensory regions for auditory reception together with peaks in autonomic nervous system activity [26, 27]. This may probably help to explain why music is so used for mood regulation and to achieve short-term enhancement of certain abilities in clinical settings. Indeed, even just exposure to listening to favorite music or songs with certain structural characteristics (e.g., fast pace and major mode) induces a state of greater activation capable of temporarily expand emotional resources and improving cognitive and motor performance (such as psychomotor speed, verbal fluency, and episodic memory) also in older people [28].

However, music listening can also lead to longer-term beneficial effects. Importantly, the neuroplastic modifications are not limited to the regular motor practice with an instrument, as merely listening to music during days, or even hours and minutes, can result in alterations of the brain functioning. This is due to the fact that listening to music under certain conditions (e.g., during aware and nonpassive listening where music is not used as a mere background) is characterized by the activation of dorsomedial prefrontal and occipital areas, thus eliciting an attentive internal state that allows for the initial reactions to sounds to become available for conscious evaluation [29]. Furthermore, music listening involves the drive to move and the memory process provoking network changes in the temporo-frontal brain areas and the hippocampus. As a result, when we listen, an automatic processing of repeated melodic and rhythmic patterns occurs together with the subsequent recognition [30].

Besides music, other forms of rehabilitative interventions able to induce neuroplastic changes have been recently explored. Similarly to musical interventions, noninvasive brain stimulation techniques have demonstrated the ability to modulate the neuronal excitability with a view to influencing plasticity mechanisms inherent in the central nervous system and temporarily improving a range of functions [31]. There are several forms of noninvasive brain stimulation, although the most widely adopted in the clinical setting is transcranial electrical stimulation (tEs). This technique consists of delivering a small (1–2 mA) current via two electrodes placed on the scalp. According to the stimulation parameters, tEs affects neural excitability and provokes plastic effects mediated by NMDA receptors [32]. These currents, cathodic (−) or anodic (+), generate an electric field able to modulate spontaneous neural activity by interfering with the membrane potential of the underlying neuronal structures and thus inducing hyperpolarization (inhibiting effect) or depolarization (facilitating effect), respectively [33]. Again, as for music-based interventions, it is important to underline that the brain changes produced become more stable and lasting (long-term effects) when the stimulation is repeated several times, likewise according to the principles of neuroplasticity [34, 35]. The most recent studies make a hybrid use of music and brain stimulation techniques to cope with cognitive decline. The results show the combination of tEs and music-based interventions give a greater boost to neuroplasticity than each of them can give individually and thus represent a functional, complementary solution to other types of therapy [36, 37].

2. Music as a nonpharmacological treatment in pathological aging: from the most well-known interventions up to novel approaches

As known, music has been extensively tested as a nonpharmacological intervention due to its effectiveness, its being inexpensive, and its possibility to be widely and easily applicable to clinical settings for the rehabilitation of a variety of age-related pathologies. Thanks to the awareness of the effects of music on neuroplasticity, a number of active and passive innovative music-based interventions, such as those of Neurologic Music Therapy (NMT) [38] and similar methodologies, also combined with new technologies, have risen in the last decades in order to promote brain reorganization after trauma and vascular problem or handle with cognitive decline during neurodegeneration. So far, its most significant application as a rehabilitation tool has been with post-stroke and dementia patients. This is because the urgency dictated by the compelling diffusion of these pathologies inevitably has led to the implementation and search for strategies to limit the discomfort of patients in their daily lives. In fact, stroke and dementia are two of the most occurring diseases during old age as well as the leading causes of neurological disability and death worldwide [39]. Specifically, every year 14 million people suffer a stroke, a number expected to increase by 34% up to 2035 [40, 41]. As regards dementia, and especially for Alzheimer's disease (AD), the number of people living with dementia was estimated to stand at 55 million in 2019 and is expected to rise up to 139 million in 2050 [42].

Findings from studies investigating non-degenerative disease related to brain traumas or vascular problems indicate music to be an effective means mostly for motor and language rehabilitation [28]. As mentioned, behavioral outcomes and brain functioning are related to each other; this means that altered behavior is a reflection of altered brain circuits, necessitating neurological renormalization or strengthening of substitute, relatively unharmed networks. The neuroplasticity capacity of the brain, able to provoke reorganization at both cortical and subcortical level, thus serves as the foundation for musical approaches to neurorehabilitation. Indeed, through the use of numerous pertinent neural circuits that are largely still guarded in the individual, music, which is a multimodal entity that engages perception, cognition, and motor control in the brain, serves as an effective medium for rehabilitating impaired neurologic functions [43].

In the specific case of motor rehabilitation after stroke, the aim is to enhance motor functions and induce and modulate plasticity through two main approaches: task-specific training (i.e., therapeutic interventions requiring the patient actively engage in motor skill re-learning guided by a therapist) and enriched environment; this latter consists of creating an engaging environment that promotes multimodal sensory processing as a result of physical, cognitive, and social activities [44]. Music-based active interventions for motor rehabilitation, which basically consists of playing musical instruments, encompass both approaches. Among them, one of the most investigated in recent times is the Music-Supported Therapy (MST) [45]. MST requires an electronic keyboard and an electronic drum set to train fine (keyboard) and gross (drums) movements, respectively. It is based on the principles of massive repetition, auditory-motor coupling and integration (i.e., reinforcement of motor effects due to immediate auditory feedback), shaping, tailoring the training to each individual's progress and emotion-motivation effects, which aids the rehabilitation process by engaging the reward-learning system. Several studies have proven its effectiveness in both acute and chronic stroke patients [46, 47]; see Grau-Sánchez et al. [48] for a review. These results, moreover, match with further experimental studies reporting brain changes in stroke patients after MST, therefore confirming and explaining the reasons behind the favorable outcomes of this technique from the neuroplasticity point of view. In particular, an increase in the excitability and a cortical motor map reorganization in the sensorimotor cortex was found [49] together with an intrahemispheric reorganization within the lesioned hemisphere after the training [50] indicating a re-establishment of functional connectivity between auditory and motor regions.

Another often compromised post-stroke area is that of language. Indeed, up to 40% of stroke patients experience post-stroke aphasia, a severe condition that affects speech production and/or understanding. It has a catastrophic effect on individuals, as it leads to lower quality of life more than any other stroke-related impairment due to patients' reduced participation and involvement in a range of life activities when in such condition, with a consequent predisposition to depression [51]. Among the most used music-based intervention designed for speech and language rehabilitation is the NMT technique named "Melodic Intonation Therapy" (MIT). In MIT, differences and commonalities between singing and speaking are used for a therapeutic scope: patients gradually shift from singing to speaking by intoning or singing common phrases while tapping their left hand rhythmically, and the musical prosody of the functional phrases or brief statements they sing or intone closely resemble the verbal utterance's typical speech inflection patterns [38]. The effectiveness of MIT has been proven by several RCTs, e.g., [52, 53]. It certainly depends, first of all, on the constructive use of the functions shared between speaking and singing during the intervention, i.e., the acoustical perception and production features as well as the ability of both systems to embed communicative functions in the auditory modality [54]. Secondly, MIT power comes from its ability to induce neuroplasticity in the damaged left hemisphere, together with greater activation in the right fronto-temporal regions and an increased functional connectivity between motor and right homologous language regions [55–57]. Hence, according to these findings, MIT is able to recruit undamaged homologous networks, compensating for affected speech function and help functional recovery of the compromised area. As already proposed by other authors [28, 58], both MST and MIT are optimal rehabilitation strategies able to promote behavioral benefits in elderly patients that still need to be grounded within a neurobiological understanding, as they are based on central nervous adaptations related to brain plasticity, therefore to neurobiological mechanisms underlying these beneficial effects.

In addition to MIT, a novel approach for language rehabilitation based on a passive music-based intervention for this type of patients, consisting in listening to vocal music, has been explored by more recent research [59, 60]. Previous pivotal studies on listening to music in post-stroke patients had already reported an enhancement of a range of cognitive abilities through the increase of gray matter volume in frontolimbic regions [61, 62]. In the case of vocal music listening, an interesting hypothesis is that it induces neuroplasticity effects on the language network in those brain areas linked to connected speech after stroke, such as the left frontal regions and their underlying white matter tracts [63]. Initial findings from the first studies on this topic are confirming this hypothesis: by one side, vocal music listening compared to audiobook listening would enhance the structural connectivity frontal aslant tract, i.e., an important tract for speech production [59]. On the other side, it would improve verbal memory by inducing changes in the longitudinal functional connectivity in the language network [60]. These discoveries corroborate the theory that language network engagement can be modulated by music and add new information on the empowering effect provoked by listening to music with sung lyrics. Thus, according to these findings, vocal music would be able to connect linguistic and musical information into a unified representation, through involvement by vocal music of bilateral frontotemporal areas in a more extensive way than speech alone. In general, given the encouraging results coming from research so far, it would be highly desirable to incorporate these techniques into post-stroke rehabilitation programs. Starting from the broad plastic potential for the brain language areas up to the involvement of motivation and reward circuits useful for enhancing motor functions, they constitute an excellent tool for functional, cognitive, and behavioral recovery of patients after stroke.

Considering tactics to promote brain plasticity in clinical settings could make a significant contribution to intervention strategies for healing and enhancement of functions; this could also provide people with hope for personal empowerment, as modern neuroscience largely shows the possibility for enhancing brain plasticity [64]. However, in the case of neurodegenerative pathologies like AD, halting cognitive decline is not feasible. Although, it is possible in any case to implement nonpharmacologic strategies to alleviate the symptoms and improve the life quality of demented patients, through stimulating leisure activities able to aid their cognitive and emotional capacity. Indeed, so far music-based interventions with AD patients have been implemented to deal with a variety of related disorders: progressive cognitive decline, memory impairment, visuospatial ability, executive function, language and speech production as well as behavioral and psychological symptoms, i.e., depression, anxiety, apathy, agitation, emotional control deficits, and sleep disorders which often lead to have problems living independently [65, 66]. One of the most effective and implemented music-based interventions with AD patients consists in a passive intervention of listening to familiar, popular, or autobiographical music in order to recall music-evoked emotions and music-evoked autobiographical memories [67–69] and to help patients to restore their sense of identity. This is because musical memory, intended as a special type of semantic memory, appears to be relatively preserved in

AD patients, differently from verbal and episodic memory. By consequence, patients experiment with a sense of familiarity for a melodic progression regardless of timbre, starting pitch and memory of a past event where the melody was heard, being able to recognize a particular musical piece in any key and at any tempo [70, 71]. Hence, during a music therapy session, it is possible to play the music they prefer both through technological means and/or by singing or playing musical instruments, since the mode difference will not affect the melody retrieval in memory.

At a neuroplastic level, as mentioned, listening to music is an intervention type with a great positive effect on cognitive function as it integrates perception of sounds, rhythms, and lyrics and the response to the sound requiring attention to an environment, which implies the simultaneous activation of cortical brain areas [29, 30, 65]. Furthermore, two more studies carried out with AD patients showed specific brain changes after several times of listening to preferred or long-known music. In one of them, the authors found an activation of brain regions involved in autobiographical memory (e.g., bilateral network of prefrontal, emotional, motor, auditory, and subcortical regions like cerebellum, putamen, and limbic structures) providing a potential mechanism by which the repeated activation of such areas can preserve musical memory and lead to improvements in overall memory [72]. In the other one, increases in functional connectivity in corticocortical and corticocerebellar networks have been found after the presentation of preferred musical stimuli, suggesting the possibility of improvements in brain network synchronization [73].

Music therapy has been included in the last Alzheimer's Disease International report [42] within the section named "Current and future non-pharmacological intervention in dementia." In the document, a distinction between mild and advanced stages of the disease is operated according to the different relaxing or stimulating facets of music. This dual quality of music brings to music-based intervention an extraordinary support to neurodegenerative diseases. During the mild stage of dementia, when distress, depression, and anxiety are associated with the decrease of cognitive performances, passive interventions as receptive music therapy to achieve psycho-musical relaxation techniques are considered useful to reduce these disorders. On the contrary, in the advanced stage, when verbal communication declines and apathy becomes one of the biggest behavioral symptoms to contend with, music interventions such as singing workshops and choirs are considered very pertinent to fight against apathy and to stimulate verbal communication. Thus, at all stages of the pathology, receptive, or active musical interventions have complementary impacts. The course of symptoms is obviously a consequence of the progressive neurodegeneration. Along the degenerative process, BDNF levels change with an increase in the early stages and then a decrease in the late stages, reflecting a starting compensatory neuronal repair mechanism followed by an increased neuronal loss and the consequent severity of dementia [74]. Previous studies carried out in BDNF on mice suggest that music exposure induces a relaxing and anxiolytic effect by increasing BDNF levels in the hippocampus [75]. It can therefore be deduced that music exposure would be able to increase the BDNF concentration and the activation of BDNF downstream signaling also in humans, but at the moment it is a mere speculation awaiting confirmation and empirical evidence. In that case, it would be possible to provide a molecular explanation for the role played by music in dementia and better understand the molecular mechanisms behind music effects on brain plasticity and AD, as well as giving more solid ground to the design of treatments [76].

Thus far, repeated music-based interventions have been observed to have long-term effects in both stroke (3 months) and dementia (2 months) [61, 77, 78]. This is because a stimulation repetition, including music stimulation, allows for persisting change in the strength of the synapse. This change takes place due to brief high-frequency stimulations enhancing the synaptic activity between two neurons. This causes a mechanism of long-term potentiation (LTP), which is mediated by NMDA glutamate receptors and leads to the strengthening of neuronal circuits at synaptic level. Specularly, the opposite effect has been defined as long-term depression (LTD), also involving NMDA receptors and occurring during longtime low rate stimulation. Contrary to LTP, LTD leads to decreased synaptic activity and weakening of synaptic connections [79, 80]. Both of these processes are neural mechanisms that underlie learning and memory and mostly occur in the hippocampus, which has been discovered to have indirect functional connections with the central auditory pathway, the fronto-medial cortex and, of course, with the remaining components of the limbic system [81]. These networks are involved in the formation of auditory memory and, in turn, auditory cues are involved in the formation of spatial memories [43, 82]. In sum, repeated sound stimulation and music are able to induce the LTP process, leading to an increase of BDNF levels and thus enhancing learning and memory abilities, which will be crucial for a comprehensive recovery of functional, cognitive, and behavioral aspects. Such awareness should therefore lead to a novel model of music therapy based on neuroplasticity, as claimed by a previous theoretical work by Stegemoller explaining how music therapy works on the brain through dopamine increase, neural synchrony, and a clear signal in contrast to noise [83]. In this regard, it is necessary to advance the production of empirical evidence and experiment new approaches capable of reinforcing and making the efficacy of music in clinical contexts even more evident.

2.1 Music and brain stimulation: when unity is strength

The principle of neuroplasticity through repetition is obviously applicable to other types of stimulation besides music. Periodical noninvasive brain stimulation is able to induce excitability changes of the cortex similar to the long-lasting LTP and LTD mechanism. On a behavioral level, these neuroplastic changes can be observed in a temporary improvement of some skills' performance [84–86]. This especially applies to transcranial direct current stimulation (tDCS), one of the noninvasive brain stimulation approaches that increasingly gather attention as a means for increasing or decreasing cortical excitability, depending on the delivery of anodal or cathodal stimulation to the cerebral cortex. This method has advantages over other transcranial stimulation techniques, such as its ease of application, the lower cost, and more prolonged modulating effect on the cerebral cortex; studies on its efficacy in post-stroke patients are emerging [87], as well as initial evidence on the positive effects on cognitive and psychiatric of patients with dementia [88, 89]. Some pioneering studies had shown a positive relationship between tDCS and auditory, motor, and visual processing, thanks to induced changes in the auditory cortex [90, 91]. Even newer are the applications of brain stimulation in hybrid rehabilitation approaches, especially in combination with music. Two recent studies with elderly participants combining tDCS and passive music-based intervention hypothesized that listening to autobiographically salient music is able to amplify the effects of tDCS on cognitive skills and corresponding brain functions [36, 37]. Specifically, in their study, Chow et al. [36] found personalized music to have the power to amplify the effects of tDCS for working memory (WM). Indeed, the combination may modulate neural processing of recognition memory when memory demands are high. Similarly, the study by Bidelman et al. [37] showed that tDCS paired with music listening can be a viable intervention to boost cognitive and WM performance, and in turn, receptive communication skills that decline during the lifespan. Listening to music and particularly to songs that evoke autobiographical memories would be then able to enhance responsivity to the effects of tDCS for older adults. This larger effect of the combination music+tDCS than music or tDCS alone supports previous findings in the literature demonstrating an advantage of combining tDCS with other cognitive tasks to maximize neuroplastic effects [92]. Although participants in these two studies were healthy elderly people, these findings are promising as they may have potential utility for clinical older adult populations who demonstrate a need for novel cognitive rehabilitation strategies, especially for individuals with AD and other dementias.

Further investigations also tried to combine tDCS with a range of music-based interventions, including active interventions. Two studies investigated the neuroplastic changes induced by tDCS by combining repeated sessions of anodal stimulation of the left temporal cortex with sound therapy (tailor-made notched music training) [93] or hearing aids [94], but neither study found any additional effect of tDCS to the audiological treatment [95]. Many other studies investigated the use of tDCS on the left temporoparietal cortex to treat the chronic subjective tinnitus [94, 96, 97] but were also negative. Other studies were designed to target the dorsolateral prefrontal cortex, which is involved in the tinnitus pathophysiology [98, 99] as well as major depression, which is a frequent comorbid disorder in tinnitus [100]. In a study by Moossavi et al. [101], they combined tDCS and tailor-made notched music training [102], a technique based on the hemostasis mechanism which induces the asynchrony in neural activities by lateral inhibition of neurons coding the notch area of the tinnitus frequency [103], which reduces the auditory cortex hyperactivities [102]. In their research, they found that tDCS, in combination with the tailor-made notched music training, was effective to reduce the loudness, awareness, and annoyance caused by tinnitus in the short term for up to more than a month after the end of the treatment. Additionally, this combined method revealed improvement of cognitive abilities such as auditory divided attention, auditory selective attention, and WM [101]. Music therapy and electric stimulation have been also used in the rehabilitation of aphasia. In their paper, Aravantinou-Fatorou et al. [104] divided their aphasic patients into three groups: group A, who did not perform music therapy and had no tDCS; group B, with only music therapy; and group C, which had a combined treatment with daily music therapy and tDCS. They found that when music therapy and tDCS were added to the rehabilitation program, the group C (32.6%) recovered to a greater extent than those patients in groups B (24.4%) and A (6.1%) [104]. A similar result has been achieved by Vines et al. [105] by combining MIT with a tDCS applied to the posterior inferior frontal gyrus of the right hemisphere in patients with Broca's aphasia. Results of their study show a greater improvement of language fluency in patients with a combined MIT + tDCS than those who had MIT + sham tDCS.

Overall, despite the little empirical evidence still available, it can be deduced that the synergy between music-based interventions (both active and passive) and brain stimulation represents an added value to more traditional therapeutic approaches. The capacity of both to promote neuroplasticity, together with the enriched environment and the rewarding stimuli provided by music therapy in clinical setting, able of creating an engaging environment and promoting multimodal sensory processing, can really constitute a resource and a model of therapy, based on neurobiological foundations, for the well-being of the elderly person.

2.2 Music meets technology: a glimpse into the future of rehabilitation

The inclusion of new technologies in active and passive music therapy sessions is actually already well known. With the evolution of technology and the need to find alternative therapeutic approaches to different disorders, the combination of traditional and innovative therapeutic techniques has become an important research approach. Starting with the implementation of music therapy interventions by the means of electronic devices [106], music technology has developed further in recent years providing both post-stroke and demented patients a variety of tools for rehabilitation, intersecting different research areas such as music psychology, neuroscience, music therapy, music information retrieval, music technology, medical technology, and robotics [107]. Such tools give the chance, for example, to combine sensors with MIDI converters to engage and stimulate consistent motor performance within improvisation as part of motor rehabilitation after stroke. Often, the movement location is translated to pitch height, offering an extra awareness of reach distance. In some other cases, percussion feedback sounds on bespoke instruments are used, allowing stroke patients to rehabilitate by drumming along to their own preferred music [108]. Recently, for AD patients, the effectiveness of interactive music exergames has been also explored to improve or maintain their physical condition while recovering past memories and an interest in social interaction [109].

The most significant innovation, probably, comes from another type of technological intervention, increasingly used in clinical settings and investigated by research in recent times, i.e., that based on virtual reality (VR), also indicated as an effective tool for older adults and able to induce neuroplasticity [110]. The progress and development of new devices to produce VR and augmented reality (AR) allow therapeutic interventions for a wide range of disorders [111]. Moreover, the customization and the possibility of using this type of technology make it possible to obtain low-cost and widely used therapeutic hardware and software. Some of the research areas in which the combination of music therapy and VR has produced greater results concern the management of anxiety states and in the palliative care of pain [112–114]. The results from these studies show how the combination of music therapy (in particular, the use of musical pieces linked to the preferences of the individual subjects) and VR has proved to be a feasible, usable, and acceptable tool for the improvement of states of anxiety and pain, highlighting more in general an improvement in the mood of the subjects. Furthermore, a use of these hybrid techniques has approached the treatment of neurodegenerative disorders, with particular interest in the different forms of dementia. The results show how the use of VR and music therapy can be a functional and complementary solution to other nonpharmacological therapies [115, 116]. Similarly to this approach, one of our team's research interventions will involve the use of VR in combination with music therapy on patients with different levels of cognitive impairment. In detail, the subjects will take part in a virtual environment experiment with familiar auditory and visual stimuli. Subjects will also undergo various tests to measure cognitive reserve before and after the intervention [117]. The principal aim is to evaluate neuroplastic processes and their modulation through the combination of musical and technological strategies, with a view to cope with cognitive decline and for a functional life.

3. Not only rehabilitation: the importance of prevention with music for a good elderly life

As known, the early stages of life are pivotal to maximize brain development in order to promote lifelong neuronal enrichment and accumulate what is referred to as "cognitive reserve." Nevertheless, it is important to promote brain plasticity throughout the life span. In this regard, researchers are starting to focus on the opportunity to induce neuroplasticity in the critical period of aging and underline how crucial it is to design engaging environments for the elderly that include activities able to support lifelong brain plasticity, emotional well-being, social bonding, and autonomy in everyday life [58]. A number of studies already exist on healthy older adults, e.g., [36, 37], providing both strategies for rehabilitation and findings on the potential cognitive protection of music. However, it is necessary to start thinking about elderly age not only from a rehabilitation perspective but also from a preventive point of view. In fact, there is a gap in research exploring the potential implications of music's long-term influence on neuroplasticity and music as a preventive measure to protect against impairment [11].

A good starting point in order to follow this direction is the literature available so far indicating that both music listening and active musical making, done regularly and frequently, have positive effects on the overall life of sick and healthy elderly. Music listening can facilitate cognitive, emotional, and neural recovery after stroke and support cognitive functioning, mood, and quality of life (QOL) in demented patients [61, 65]. Active music making, like playing an instrument, singing, and dancing have been shown to enhance executive functions, mood, and QOL in aged adults [118–122]. As seen, on the one hand, listening to autobiographical music restores the elderly's sense of identity and helps him/her to access memory through the emotions evoked by music. On the other hand, musical activities help older adults to connect with other people, increasing their self-esteem and decreasing feelings of isolation and loneliness; they have an influence on levels of hormones such as cortisol and affect the autonomic nervous systems by decreasing stress-related activation [123]. If regularly practiced, all musical activities offer great opportunities to maintain better mood and QOL and compensate for the gradual cognitive and neural decline associated with normal aging, potentially having a neuroprotective effect for neurodegenerative diseases. To transmute these deductions into empirical evidence, long-term studies with many years of follow-up, which are currently still lacking, and more research are needed on the topic.

4. Conclusions

Aging is a delicate phase of life characterized by psycho-physical decline and the onset of a variety of diseases provoked by neurodegenerative and vascular problems. According to research carried out mostly on clinical populations, such as on post-stroke and dementia patients, both active and passive music-based interventions have great rehabilitative potential and can constitute an optimal nonpharmacological treatment to be combined with traditional therapies. Moreover, neuroplasticity is now a well-established topic when studying the effects of music on the brain. Repetition over time of music listening and making is known to be able to induce neuroplastic changes and thus to provoke enhancement of a range of abilities on the behavioral level. Likewise, electrical brain stimulation techniques, including tDCS which is one of the most used, are able to induce long-term neuroplastic changes if repeated over time. A combination of music and brain stimulation, as well as music and other technology-based training like VR, is highly desirable in clinical settings with a view to innovative and more stimulating therapeutic offer. Moreover, it is important to ground the therapy with music on the model of neuroplasticity and, therefore, on the knowledge of neurobiological functions to a more effective implementation in healthcare environments. The hope is that music, with its positive functional, cognitive, emotional, and social influences and its innumerable possibilities of application, will be used as a stable tool for the well-being of the older person, not only in illness but also as a preventive and protective measure against impairment.

Acknowledgements

ML: Main writing of manuscript. FFC: Contribution to Section 2.1. FC: Contribution to Section 2.2. EB: Conception and contribution to overall writing and revision of the work.

Funding: Center for Music in the Brain (MIB) is funded by the Danish National Research Foundation (Project Number: 117). This research was supported by EU funding within the MUR PNRR A novel public-private alliance to generate socioeconomic, biomedical and technological solutions for an inclusive Italian ageing society (project n. PE00000015, AGE-IT).

Author details

Mariangela Lippolis[1], Francesco Carlomagno[1,2], Fulvia Francesca Campo[1,2] and Elvira Brattico[1,2]*

1 Department of Education, Psychology, Communication, University of Bari Aldo Moro, Bari, Italy

2 Department of Clinical Medicine, Center for Music in the Brain (MIB), Aarhus University and The Royal Academy of Music Aarhus/Aalborg, Aarhus, Denmark

*Address all correspondence to: elvira.brattico@clin.au.dk

References

[1] World Health Organization. International Day of Older Persons. 2022. Retrieved from: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

[2] Gramaglia C, Gattoni E, Marangon D, Concina D, Grossini E, Rinaldi C, et al. Non-pharmacological approaches to depressed elderly with No or mild cognitive impairment in long-term care facilities. A Systematic Review of Literature. Frontiers in Public Health. 2021;**9**:685860

[3] Toricelli M, Pereira AAR, Souza Abrao G, Malerba HN, Maia J, Buck HS, et al. Mechanisms of neuroplasticity and brain degeneration: Strategies for protection during the aging process. Neural Regeneration Research. 2021;**16**(1):58-67

[4] Satoh M, Ogawa J-i, Tokita T, Nakaguchi N, Nakao K, Kida H, et al. The effects of physical exercise with music on cognitive function of elderly people: Mihama-Kiho project. PLoS One. 2014;**9**(4):e95230

[5] Ferreri L, Moussard A, Bigand E, Tillmann B. Music and the aging brain. In: Thaut MH, Hodges DA, editors. The Oxford Handbook of Music and the Brain. Oxford, UK: Oxford University Press; 2019. pp. 623-644

[6] Maes PJ, Buhmann J, Leman M. 3Mo: A model for music-based biofeedback. Frontiers in Neuroscience. 2016;**10**:548

[7] Murray PS, Holmes PV. An overview of brain-derived neurotrophic factor and implications for excitotoxic vulnerability in the hippocampus. International Journal of Peptide. 2011;**2011**:654085

[8] Xing Y, Xia Y, Kendrick K, Liu X, Wang M, Wu D, et al. Mozart, Mozart rhythm and retrograde Mozart effects: Evidences from behaviours and neurobiology bases. Scientific Reports. 2016;**6**(1):1-11

[9] Chikahisa S, Sei H, Morishima M, Sano A, Kitaoka K, Nakaya Y, et al. Exposure to music in the perinatal period enhances learning performance and alters BDNF/TrkB signaling in mice as adults. Behavioural Brain Research. 2006;**169**:312-319

[10] Brattico E, Bonetti L, Ferretti G, Vuust P, Matrone C. Putting cells in motion: Advantages of endogenous boosting of BDNF production. Cell. 2021;**10**(1):1-16

[11] Schneider CE, Hunter EG, Bardach SH. Potential cognitive benefits from playing music among cognitively intact older adults: A scoping review. Journal of Applied Gerontology. 2019;**38**(12):1763-1178

[12] Reybrouck M, Vuust P, Brattico E. Music and Brain Plasticity: How Sounds Trigger Neurogenerative Adaptations. London, UK: Neuroplasticity—Insights of Neural Reorganization; 2018

[13] Olszewska AM, Gaca M, Herman AM, Jednoróg K, Marchewka A. How musical training shapes the adult brain: Predispositions and neuroplasticity. Frontiers in Neuroscience. 2021;**15**(Mar):1-16

[14] Moreno S, Bidelman GM. Examining neural plasticity and cognitive benefit through the unique lens of musical training. Hearing Research. 2013;**308**:84-97. DOI: 10.1016/j. heares.2013.09.012

[15] Barrett KC, Ashley R, Strait DL, Kraus N. Art and science: How musical

training shapes the brain. Frontiers in Psychology. 2013;**4**:713

[16] Miendlarzewska EA, Trost WJ. How musical training affects cognitive development: Rhythm, reward and other modulating variables. Frontiers in Neuroscience. 2014;**7**(8 JAN):1-18

[17] Criscuolo A, Pando-Naude V, Bonetti L, Vuust P, Brattico E. An ALE meta-analytic review of musical expertise. Scientific Reports. 2022;**12**:1-17

[18] Møller C, Garza-Villarreal EA, Hansen NC, Højlund A, Bærentsen KB, Chakravarty MM, et al. Audiovisual structural connectivity in musicians and non-musicians: A cortical thickness and diffusion tensor imaging study. Scientific Reports. 2021;**11**:1-14

[19] Schlaug G. Musicians and music making as a model for the study of brain plasticity. Progress in Brain Research. 2015;**217**:37-55

[20] Vaquero L, Hartmann K, Ripollés P, Rojo N, Sierpowska J, François C, et al. Structural neuroplasticity in expert pianists depends on the age of musical training onset. NeuroImage. 2016;**126**:106-119

[21] Hyde KL, Lerch J, Norton A, Forgeard M, Winner E, Evans AC, et al. Musical training shapes structural brain development. Journal of Neuroscience. 2009;**29**(10):3019-3025

[22] Bidelman GM, Villafuerte JW, Moreno S, Alain C. Age-related changes in the subcortical–cortical encoding and categorical perception of speech. Neurobiology of Aging. 2014;**35**(11):2526-2540

[23] Herholz SC, Zatorre RJ. Musical training as a framework for brain plasticity: Behavior, function, and structure. Neuron. 2012;**76**(3):486-502

[24] Bidelman GM, Alain C. Musical training orchestrates coordinated neuroplasticity in auditory brainstem and cortex to counteract age-related declines in categorical vowel perception. Journal of Neuroscience. 2015;**35**(3):1240-1249

[25] Sihvonen AJ, Särkämö T, Leo V, Tervaniemi M, Altenmüller E, Soinila S. Music-based interventions in neurological rehabilitation. The Lancet Neurology. 2017;**16**(8):648-660

[26] Zatorre RJ, Salimpoor VN. From perception to pleasure: Music and its neural substrates. Proceedings of the National Academy of Sciences of the USA. 2013;**110**:10430-10437

[27] Belfi A, Loui P. Musical anhedonia and rewards of music listening: Current advances and a proposed model. Annals of the New York Academy of Sciences. 2020;**1464**:99-114

[28] Särkämö T. Cognitive, emotional, and neural benefits of musical leisure activities in aging and neurological rehabilitation: A critical review. Annals of Physical and Rehabilitation Medicine. 2018;**61**(6):414-418

[29] Reybrouck M, Brattico E. Neuroplasticity beyond sounds: Neural adaptations following long-term musical aesthetic experiences. Brain Sciences. 2015;**5**(1):69-91

[30] Bonetti, L. Brattico, E. Carlomagno, F. Cabral, J. Stevner, A. Deco, G. Whybrow, P.C. Pearce, M. Pantazis, D. Vuust, P. et al. Spatiotemporal brain dynamics during recognition of the music of Johann Sebastian Bach. bioRxiv 2020;**165191**:1-44

[31] Filippetti M et al. Tecniche di stimolazione cerebrale non invasiva: la stimolazione elettrica transcranica. Revisione Narrativa Della Letteratura.

Giornale italiano di Medicina Riabilitativa. 2021;**36**(3):23-29

[32] Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clinical Neurophysiology. 2003;**114**(11):2220-2222. author reply 2222-3

[33] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology. 2000;**527**(Pt 3):633

[34] Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. Journal of Neuroengineering and Rehabilitation. 2009;**6**(1):1-13

[35] Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. Journal of Speech, Language, and Hearing Research. 2008;**51**:S225-S239

[36] Chow R, Gandon AN, Moussard A, Ryan JD. Effects of transcranial direct current stimulation combined with listening to preferred music on memory in older adults. Scientific Reports. 2021;**11**(1):1-13

[37] Bidelman GM, Chow R, Noly-gandon A, Ryan JD, Bell KL, Rizzi R, et al. Transcranial direct current stimulation combined with listening to preferred music alters cortical speech processing in older adults. Frontiers in Neuroscience. 2022;**16**(July):1-13

[38] Thaut MH, McIntosh GC. Neurologic music therapy in stroke rehabilitation. Current Physical Medicine and Rehabilitation Reports. 2014;**2**(2):106?113

[39] Avan A, Hachinski V. Stroke and dementia, leading causes of neurological disability and death, potential for prevention. Alzheimer's Dement. 2021;**17**:1072-1076

[40] Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurology. 2019;**18**:439-458

[41] Stevens E, Emmett E, Wang Y, McKevitt C, Wolfe C. The Burden of Stroke in Europe. Brussels, BE: Stroke Alliance for Europe; 2017

[42] Gauthier S, Webster C, Servaes S, Morais JA, Rosa-Neto P. World Alzheimer Report 2022: Life after Diagnosis: Navigating Treatment, Care and Support. London, England: Alzheimer's Disease International; 2022

[43] Chatterjee D, Hegde S, Thaut M. Neural plasticity: The substratum of music-based interventions in NeuroRehabilitation. 2021;**48**:155-166

[44] Liebermann DG, Buchman AS, Franks IM. Enhancement of motor rehabilitation through the use of information technologies. Clinical Biomechanics. 2006;**21**(1):8-20

[45] Schneider S, Schönle P, Altenmüller E, Münte T. Using musical instruments to improve motor skill recovery following a stroke. Journal of Neurology. 2007;**254**(10):1339-1346

[46] Rodriguez-Fornells A, Rojo N, Amengual JL, Ripolles P, Altenmuller E, Munte TF. The involvement of audio-motor coupling in the music-supported therapy applied to stroke patients. Annals of the New York Academy of Sciences. 2012;**1252**:282-293

[47] Ripollés P, Rojo N, Amengual JL, Càmara E. Music supported therapy

promotes motor plasticity in individuals with chronic stroke. Brain Imaging and Behavior. 2016;**10**(4):1289-1307

[48] Grau-Sánchez J, Münte TF, Altenmüller E, Duarte E, Rodríguez-Fornells A. Potential benefits of music playing in stroke upper limb motor rehabilitation. Neuroscience and Biobehavioral Reviews. 2020;**112**(February):585-599

[49] Grau-Sánchez J, Amengual JL, Rojo N, de Las V, Heras M, Montero J, et al. Plasticity in the sensorimotor cortex induced by music-supported therapy in stroke patients: A TMS study. Frontiers in Human Neuroscience. 2013;**7**:494

[50] Ripollés P, Rojo N, Grau-Sánchez J, Amengual JLL, Càmara E, Marco-Pallarés J, et al. Music supported therapy promotes motor plasticity in individuals with chronic stroke. Brain Imaging and Behavior. 2016;**10**(4):1289-1307

[51] Lam JMC, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. Medical Care. 2010;**48**:380-387

[52] Van Der Meulen I, Van De Sandt-Koenderman MWME, Heijenbrok MH, Visch-Brink E, Ribbers GM. Melodic intonation therapy in chronic aphasia: Evidence from a pilot randomized controlled trial. Frontiers in Human Neuroscience. 2016;**10**:1-9

[53] Van Der Meulen I, Van De Sandt-Koenderman WME, Heijenbrok-Kal MH, Visch-Brink EG, Ribbers GM. The efficacy and timing of melodic intonation therapy in subacute aphasia. Neurorehabilitation and Neural Repair. 2014;**28**(6):536-544

[54] Thaut M, Koshimori Y. Neurorehabilitation in aging through neurologic music therapy. In: Music and the Aging Brain. Cambridge, MA, USA: Academic Press; 2020. pp. 351-382

[55] Breier JI, Randle S, Maher LM, Papanicolaou AC. Changes in maps of language activity activation following melodic intonation therapy using magnetoencephalography: Two case studies. Journal of Clinical and Experimental Neuropsychology. 2010;**32**(3):309-314

[56] Schlaug G, Marchina S, Norton A. From singing to speaking: Why singing may lead to recovery of expressive language function in patients with Broca's aphasia. Music Perception. 2008;**25**(4):315-323

[57] Bitan T, Simic T, Saverino C, Jones C, Glazer J, Collela B, et al. Changes in resting-state connectivity following melody-based therapy in a patient with aphasia. Neural Plasticity. 2018;**2018**:1-13

[58] Altenmüller E, James CE. The impact of music interventions on motor rehabilitation following stroke in elderly. In: Music and the Aging Brain. Cambridge, MA, USA: Academic Press; 2020. pp. 407-432

[59] Sihvonen AJ, Ripollés P, Leo V, Saunavaara J, Parkkola R, Rodríguez-Fornells A, et al. Vocal music listening enhances poststroke language network reorganization. ENeuro. 2021;**8**(4):1-10

[60] Sihvonen AJ, Pitkäniemi A, Leo V, Soinila S, Särkämö T. Resting-state language network neuroplasticity in post-stroke music listening: A randomized controlled trial. European Journal of Neuroscience. 2021;**54**(11):7886-7898

[61] Särkämö T, Tervaniemi M, Laitinen S, Forsblom A, Soinila S, Mikkonen M, et al. Music listening enhances cognitive recovery and mood

after middle cerebral artery stroke. Brain. 2008;**131**:866-876

[62] Särkämö T, Ripollés P, Vepsäläinen H, Autti T, Silvennoinen HM, Salli E, et al. Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: A voxel-based morphometry study. Frontiers in Human Neuroscience. 2014;**8**:245

[63] Alyahya RSW, Halai AD, Conroy P, Lambon MA. A unified model of post-stroke language deficits including discourse production and their neural correlates. Brain. 2020;**143**:1541-1554

[64] Shaffer J. Neuroplasticity and clinical practice: Building brain power for health. Frontiers in Psychology. 2016;**7**(Jul):1-12

[65] Moreno-Morales C, Calero R, Moreno-Morales P, Pintado C. Music therapy in the treatment of dementia: A systematic review and meta-analysis. Frontiers in Medicine. 2020;**7**(May):1-11

[66] Matziorinis AM, Koelsch S. The promise of music therapy for Alzheimer's disease: A review. Annals of the New York Academy of Sciences. 2022;**1516**(1):11-17

[67] Belfi AM, Karlan B, Tranel D. Music evokes vivid autobiographical memories. Memory. 2016;**24**(7):979-989

[68] Janata P, Tomic ST, Rakowski SK. Characterisation of music-evoked autobiographical memories. Memory. 2007;**15**:845-860

[69] El Haj M, Antoine P, Nandrino JL, Gély-Nargeot M-C, Raffard S. Self-defining memories during exposure to music in Alzheimer's disease. International Psychogeriatrics. 2015;**27**:1719-1730

[70] Peretz I, Coltheart M. Modularity of music processing. Nature Neuroscience. 2003;**6**:688-691

[71] Groussard M, Chan TG, Coppalle R, Platel H. Preservation of musical memory throughout the progression of Alzheimer's disease? Toward a reconciliation of theoretical, clinical, and neuroimaging evidence. Journal of Alzheimer's Disease. 2019;**68**(3):857-883

[72] Thaut MH, Fischer CE, Leggieri MM, Vuong V, Churchill NW, Fornazzari LR, et al. Neural basis of long-term musical memory in cognitively impaired older persons. Alzheimer Disease & Associated Disorders. 2020;**34**(3):267-271

[73] King JB, Jones KG, Goldberg E, et al. Increased functional connectivity after listening to favored music in adults with Alzheimer dementia. The Journal of Prevention of Alzheimer's Disease. 2019;**6**:56-62

[74] Laske C, Stransky E, Leyhe T, Eschweiler GW, Wittorf A, et al. Stage-dependent BDNF serum concentrations in Alzheimer's disease. Journal of Neural Transmission. 2006;**113**:1217-1224

[75] Li WJ, Yu H, Yang JM, Gao J, Jiang H, et al. Anxiolytic effect of music exposure on BDNFMet/met transgenic mice. Brain Research. 2010;**1347**:71-79

[76] Matrone C, Brattico E. The power of music on Alzheimer's disease and the need to understand the underlying molecular mechanisms. Journal of Alzheimers Disease & Parkinsonism. 2015;**5**:196

[77] Särkämö T, Laitinen S, Numminen A, Kurki M, Johnson JK, Rantanen P. Pattern of emotional benefits induced by regular singing and music listening in dementia. Journal of the American Geriatrics Society. 2016;**64**(2):439-440

[78] Raglio A, Bellandi D, Baiardi P, et al. Effect of active music therapy and individualized listening to music on

dementia: A multicenter randomized controlled trial. Journal of the American Geriatrics Society. 2015;**63**(8):1534-1539

[79] Nicoll RA, Kauer JA, Malenka RC. The current excitement in longterm potentiation. Neuron. 1988;**1**(2):97-103

[80] Mulkey RM, Malenka RC. Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron. 1992;**9**(5):967-975

[81] Rocchi F, Oya H, Balezeau F, Billig AJ, Kocsis Z, Jenison RL, et al. Common fronto-temporal effective connectivity in humans and monkeys. Neuron. 2021;**109**(5):852-868

[82] Dietz B, Manahan-Vaughan D. Hippocampal long-term depression is facilitated by the acquisition and updating of memory of spatial auditory content and requires mGlu5 activation. Neuropharmacology. 2017;**115**:30-41

[83] Stegemoller EL. Exploring a neuroplasticity model of music therapy. Journal of Music Therapy. 2014;**51**(3):211-227

[84] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimulation. 2013;**6**(3):424-432

[85] Hsu W-Y, Zanto TP, Anguera JA, Lin Y-Y, Gazzaley A. Delayed enhancement of multitasking performance: Effects of anodal transcranial direct current stimulation on the prefrontal cortex. Cortex. 2015;**69**:175-185

[86] Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: Activity dependence and dendritic effects. Brain Stimulation. 2017;**10**(1):51-58

[87] Satow T, Kawase T, Kitamura A, Kajitani Y, Yamaguchi T, Tanabe N, et al. Combination of transcranial direct current stimulation and neuromuscular electrical stimulation improves gait ability in a patient in chronic stage of stroke. Case Reports in Neurology. 2016;**8**(1):39-46

[88] Inagawa T, Narita Z, Sugawara N, Maruo K, Stickley A, Yokoi Y, et al. A meta-analysis of the effect of multisession transcranial direct current stimulation on cognition in dementia and mild cognitive impairment. Clinical EEG and Neuroscience. 2019;**50**(4):273-282

[89] Ferrucci R, Mrakic-Sposta S, Gardini S, Ruggiero F, Vergari M, Mameli F, et al. Behavioral and neurophysiological effects of transcranial direct current stimulation (tDCS) in fronto-temporal dementia. Frontiers in Behavioral Neuroscience. 2018;**12**:235

[90] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimulation. 2008;**1**(3):206-223

[91] Impey D, Knott V. Effect of transcranial direct current stimulation (tDCS) on MMN-indexed auditory discrimination: A pilot study. Journal of Neural Transmission. 2015;**122**(8):1175-1185

[92] Assecondi S, Shapiro K. The benefits of combined brain stimulation and cognitive training: A pilot study. Journal of Vision. 2018;**18**:119-119

[93] Teismann H, Wollbrink A, Okamoto H, Schlaug G, Rudack C, Pantev C. Combining transcranial direct current stimulation and tailor-made

notched music training to decrease tinnitus-related distress–a pilot study. PLoS One. 2014;**9**(2):e89904

[94] Shekhawat GS, Searchfield GD, Stinear CM. Randomized trial of transcranial direct current stimulation and hearing aids for tinnitus management. Neurorehabilitation and Neural Repair. 2014;**28**(5):410-419

[95] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clinical Neurophysiology. 2017;**128**(1):56-92

[96] Forogh B, Mirshaki Z, Raissi GR, Shirazi A, Mansoori K, Ahadi T. Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: A pilot randomized controlled trial. Neurological Sciences. 2016;**37**(2):253-259

[97] Hyvärinen P, Mäkitie A, Aarnisalo AA. Self-administered domiciliary tDCS treatment for tinnitus: A double-blind sham-controlled study. PLoS One. 2016;**11**(4):e0154286

[98] Vanneste S, De Ridder D. Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity. European Journal of Neuroscience. 2011;**34**(4):605-614

[99] Joos K, Vanneste S, De Ridder D. Disentangling depression and distress networks in the tinnitus brain. PLoS One. 2012;**7**(7):e40544

[100] Langguth B, Landgrebe M, Kleinjung T, Sand GP, Hajak G. Tinnitus and depression. The World Journal of Biological Psychiatry. 2011;**12**(7):489-500

[101] Moossavi A, Mehrkian S, Najafi S, Bakhshi E. The effectiveness of the combined transcranial direct current stimulation (tDCS) and tailor-made notched music training (TMNMT) on psychoacoustic, psychometric, and cognitive indices of tinnitus patients. American Journal of Otolaryngology. 2022;**43**(1):103274

[102] Pantev C, Okamoto H, Teismann H. Music-induced cortical plasticity and lateral inhibition in the human auditory cortex as foundations for tonal tinnitus treatment. Frontiers in Systems Neuroscience. 2012;**6**:50

[103] Pantev C, Rudack C, Stein A, Wunderlich R, Engell A, Lau P, et al. Study protocol: münster tinnitus randomized controlled clinical trial-2013 based on tailor-made notched music training (TMNMT). BMC Neurology. 2014;**14**(1):1-8

[104] Aravantinou-Fatorou A, Georgakopoulou VE, Spandidos DA, Papalexis P, Tarantinos K, Mathioudakis N, et al. Effects of music therapy accompanied by transcranial direct current stimulation on the recovery from aphasia following stroke: A single-center retrospective cohort study. World Academy of Sciences Journal. 2022;**4**(6):1-9

[105] Vines BW, Norton AC, Schlaug G. Non-invasive brain stimulation enhances the effects of melodic intonation therapy. Frontiers in Psychology. 2011;**2**:230

[106] Magee WL, Burland K. An exploratory study of the use of electronic music technologies in clinical music therapy. Nordic Journal of Music Therapy. 2008;**17**(2):124-141

[107] Kirk P, Grierson M, Bodak R, Ward N, Brander F, Kelly K, et al. Motivating stroke rehabilitation through music: A feasibility study using digital musical instruments in the home [Conference paper]. In: Proceedings of

the 2016 CHI Conference on Human Factors in Computing Systems. New York, NY, United States: Association for Computing Machinery, San Jose, CA; 2016. pp. 1781-1785

[108] Agres KR, Schaefer RS, Volk A, van Hooren S, Holzapfel A, Dalla Bella S, et al. Music, computing, and health: A roadmap for the current and future roles of music technology for health care and well-being. Music & Science. 2021;**4**:2059204321997709

[109] Unbehaun D, Taugerbeck S, Aal K, Vaziri DD, Lehmann J, Tolmie P, et al. Notes of memories: Fostering social interaction, activity and reminiscence through an interactive music exergame developed for people with dementia and their caregivers. Human–Computer Interaction. NY, United States: Association for Computing Machinery, New York. 2021;**36**(5-6):439-472

[110] Huang K. Exergaming executive functions: An immersive virtual reality-based cognitive training for adults aged 50 and older. Cyberpsychology, Behavior and Social Networking. 2020;**23**(3):143-149

[111] Parsons TD, Rizzo AA. Affective outcomes of virtual reality exposure therapy for anxiety and specific pho-bias: A meta-analysis. Journal of Behavior Therapy and Experimental Psychiatry. 2008;**39**(3):250-261

[112] Brungardt A, Wibben A, Tompkins AF, Shanbhag P, Coats H, LaGasse B, et al. Virtual reality-based music therapy in palliative care: A pilot implementation trial. Journal of Palliative Medicine. 2021;**24**(5):736-742

[113] Cabezas CA, Arcos AR, Carrillo-Medina JL, Arias-Almeida GI. Effects of virtual reality and music therapy on academic stress reduction using a Mobile application. In: Botto-Tobar M, Gómez S, Rosero O, Miranda R, Díaz Cadena A, Montes León S, Luna-Encalada W, editors. Trends in Artificial Intelligence and Computer Engineering. ICAETT 2021. Lecture Notes in Networks and Systems. Vol. 407. Cham: Springer; 2022

[114] Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, et al. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. Journal of Cellular Physiology. 2020;**235**(6):5353-5362

[115] Raglio A, Bellelli G, Mazzola P, Bellandi D, Giovagnoli AR, Farina E, et al. Music, music therapy and dementia: A review of literature and the recommendations of the Italian psychogeriatric association. Maturitas. 2012;**72**(4):305-310

[116] Byrns A, Abdessalem HB, Cuesta M, Bruneau MA, Belleville S, Frasson C. Adaptive music Ther-apy for Alzheimer's disease using virtual reality. In: International Conference on Intelligent Tutoring Systems. Cham: Springer; 2020. pp. 214-219

[117] Carlomagno F, Brattico E. Relieve Social Isolation and its Consequent Neurological Damage in Pathological Aging through Electrical and Musical Stimulation in a Virtual and Augmented Reality Environment (VR+AR). [Unpublished manuscript]. Bari, BA, IT: University of Bari Aldo Moro; 2023

[118] Coulton S, Clift S, Skingley A, Rodriguez J. Effectiveness and cost-effectiveness of community singing on mental health-related quality of life of older people: Randomised controlled trial. British Journal of Psychiatry. 2015;**207**:250-255

[119] Johnson JK, Louhivuori J, Stewart AL, Tolvanen A, Ross L, Era P. Quality of life (QOL) of older adult community choral singers in Finland. International Psychogeriatrics. 2013;**25**:1055-1064

[120] Bugos JA, Perlstein WM, McCrae CS, Brophy TS, Bedenbaugh PH. Individualized piano instruction enhances executive functioning and working memory in older adults. Aging & Mental Health. 2007;**11**:464-471

[121] Pentikäinen E, Pitkäniemi A, Siponkoski S-T, Jansson M, Louhivuori J, Johnson JK, et al. Beneficial effects of choir singing on cognition and well-being of older adults: Evidence from a cross-sectional study. PLoS ONE. 2021;**16**(2):e0245666

[122] James CE, Altenmüller E, Kliegel M, et al. Train the brain with music (TBM): Brain plasticity and cognitive benefits induced by musical training in elderly people in Germany and Switzerland, a study protocol for an RCT comparing musical instrumental practice to sensitization to music. BMC Geriatr. 2020;**20**:418

[123] de Witte M, Spruit A, van Hooren S, Moonen X, Stams GJ. Effects of music interventions on stress-related outcomes: A systematic review and two meta-analyses. Health Psychology Review. 2020;**14**(2):294-324