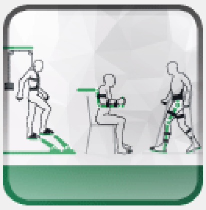

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Music supported therapy in neurorehabilitation

Chapter: Music supported therapy in neurorehabilitation

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Introduction and definitions

The healing powers of music have been recognized for thousands of years. In early shamanistic societies, illness was viewed as originating from magico-religious forces, or from the breaking of taboos (for a review, see [1]) and music was considered to be efficacious in exorcizing disease and healing wounds. Greek Philosophers such as Plato ascribed music powerful effects and it is notable that Apollo, the god of the healing powers and of science was also the patron of music and the arts, referring to the close relationships between these disciplines [2]. It was not until the second half of the nineteenth century—at a time when scientific medicine was becoming established—that research into the effects of music on mental disease began [3]. The term 'music therapy' was introduced a century later, when mechanisms underlying the healing effects of music began to be systematically studied [2]. While a consideration of music's efficacy for the treatment of psychiatric conditions such as anxiety and depression was an early consideration, the application of music to treat neurological conditions began in earnest in the 1980s. A key development in this regard was the establishment, by the German American music-therapist and researcher, Michael Thaut, of a subdiscipline of music therapy termed 'neurologic music therapy', comprising 'music supported therapy in neurorehabilitation' [4].

In the present paper, we define 'music supported therapy in neurorehabilitation' as clinical, evidence-based interventions using music to improve motor, sensory, cognitive, and emotional functions following central nervous injury and/or degeneration. The underlying scientific paradigm is music-induced functional brain plasticity, reinforced by motivational factors linked to music listening and music making. In contrast, 'music therapy' is defined as 'the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a qualified professional who has completed an approved music therapy program' [5]. In this definition, the emphasis is on the therapeutic relationship and the specific qualifications of music therapists, such as combining psychotherapeutic expertise with practical musical skills. These may be constituents of music supported therapy in neurorehabilitation, but also enable trained music therapists to apply music in many other clinical settings, such as psychiatric diseases, neurodevelopmental disorders, genetic disorders, and palliative care. Therefore, 'music therapy' has many more indications and its professional application would require a far more comprehensive treatment than the current chapter permits.

Neurobiological foundations of music interventions

Music is one of the richest human emotional, sensory-motor, and cognitive experiences. It involves listening, watching, feeling, moving and coordinating, remembering, and expecting musical elements. It is frequently accompanied by strong emotions resulting in joy, happiness, and bittersweet sadness or even in overwhelming bodily reactions like tears in the eyes or shivers down the spine. Correspondingly, a large number of cortical and subcortical brain regions are involved in music listening and music making activities (for reviews, see [6, 7]).

Primary and secondary regions in the cerebral cortex are critical for any conscious perception of sensory information, be it auditory, visual, or somatosensory. However, music also influences and changes activity in multisensory and motor integration regions in frontal, parietal, and temporo-occipital brain regions [8]. The frontal lobe is involved in the guidance of attention, in planning and motor preparation, in integrating auditory and motor information, and in specific human skills such as imitation and empathy [9]. Multisensory integration regions in the parietal lobe and temporo-occipital areas integrate different sensory inputs from the auditory, visual, and somatosensory system into a combined sensory impression; it is this multisensory brain representation which constitutes the typical musical experience [10]. The basal ganglia and the cerebellum also play a critical role in musical experience. Basal ganglia are crucial for motor learning, timing, and emotional integration, whereas the cerebellum is important for motor coordination, but it also plays an important role in various cognitive tasks especially when they include demands on timing [11]. Typically, basal ganglia and cerebellum are activated in rhythm processing, or tapping in synchrony with an external pacemaker such as a metronome [12]. Finally, the emotional network, subserved by the limbic system, is crucial for the emotional perception of music and therefore for an individual’s motivation to listen to or to engage in any musical activity ([13]; for a review on this topic, see [14]).

Musical training induces brain plasticity

During the past two decades, brain imaging has provided important insights into the enormous capacity of the human brain to adapt, via neural plasticity, to complex demands in healthy individuals of all ages. Plasticity can include morphological change, as in the generation of new synapses and new neurons as well as functional change, where the strength of synaptic connections can be altered (for a review, see [15]). Long-term training and the accompanying development of expertise through plasticity is seen in numerous domains (sports, music, chess to name a few) [16]. Since the present chapter focuses on the potential for rehabilitation to draw on aspects of music making, this section emphasizes the changes in brain architecture that have been found to accompany the development of expertise in high level musicians.

Briefly summarizing (but see [17] and [18] for reviews): 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 [19]. Furthermore, Gaser and Schlaug [20] could demonstrate enhancement of grey matter density in cortical sensory-motor regions, auditory regions, the left dorsolateral prefrontal cortex, and in the cerebellum in professional instrumentalists as compared to non-musicians and amateurs. These adaptations of brain structures are accompanied by behaviourally relevant improvements of fine finger coordination and two-point discrimination abilities [21], enhanced auditory working memory [22] and precision of timing [23]. Interestingly, musicians who start early, before the age of seven, do not display these structural adaptations of the brain at least in the sensory-motor cortices and the callosal fibres, however, they seem to have an ‘early optimized network’, which allows superior performance of motor tasks without enlarged anatomical structures [24, 25]. In contrast, later starters, after age seven do show the above-mentioned structural changes observed in many morphological brain imaging studies [e.g. 26, 27].

In addition to focusing on measures such as grey matter density, several studies have investigated measures that might reflect structural connectivity between brain regions. Using diffusion tensor imaging (DTI)—a technique which allows for the reconstruction of white matter tracts and the characterization of their microstructural status using diffusivity measures, such as fractional anisotropy (FA)—Bengtsson and her colleagues [28] and more recently Rueber et al. [29] found structural differences in the corticospinal tract, particularly in the posterior limb of the internal capsule, between musicians and non-musicians as well as within musicians' groups (keyboard players compared to string players). Halwani and colleagues [30]—also using DTI—reported differences in macrostructure and microstructure of the arcuate fasciculus (AF) (a prominent white matter tract connecting temporal and frontal brain regions) between singers, instrumentalists, and non-musicians. Thus, structural changes to white matter tracts are not only altered by musical training *per se*, but by the precise sensorimotor demands of the type of musical training (according to instrument), and as has been shown in behavioural tests, these morphological adaptations are often accompanied by faster reaction times and improved coordination [31].

These findings serve to illustrate the potential for musical training to result in structural and functional adaptations across a number of different brain areas and their connections. It is relevant to note that such changes are not only restricted to individuals who have undergone musical training over a period of years but have also been observed through longitudinal studies incorporating relatively short periods of training [e.g. 32, 33]. Given that active music-based rehabilitation involves multiple components analogous to training and music learning (i.e. iterated practice of movements coupled with auditory feedback and extensive cognitive processing) it is reasonable to suggest that some of the principles of music-training induced plasticity can be usefully exploited through the use of music supported therapy in neurorehabilitation.

It should be noted that patients who are receiving music supported therapy are not only *producing* aspects of music through their movement, they are also *perceiving* the music they produce (in addition to any live or recorded accompaniment that may be part of the protocol). The perception of music can elicit powerful feelings of pleasure, and studies have shown that such experiences (most dramatically seen during musical 'shivers' down the spine) strongly activate the dopaminergic mesolimbic system (for a review, see [34]). Dopamine release has been shown to have demonstrable effects on the strength of synaptic connections [35]. In a similar vein, music's anxiolytic properties are well known (see [36] for a review) and responses to music can produce measurable cardiovascular and endocrine responses, indicated by reduced serum cortisol levels and inhibition of cardiovascular stress reactions [37, 38]. In animal models, prolonged stress can have maladaptive effects on neuroplasticity, such as dendritic atrophy, synapse loss, and decreased hippocampal neurogenesis [39] while elevated cortisol levels in patients with acute stroke correlates with increased infarct volume, and increases the risk of depression, poor prognosis, and fatal outcome [40]. Hence, bearing in mind that that music is perceived as well as produced in music-support therapy, it may be that the potential of music to evoke both pleasure and reduce anxiety may confer particular benefits for sensorimotor learning and plasticity, though this remains to be empirically tested.

Music supported motor therapy in upper limb dysfunction in stroke patients

In a recent review, we identified seven controlled studies that evaluated the efficacy of music as an add-on therapy in stroke rehabilitation [41]. In these studies, training of finger dexterity of the paretic hand was done using either a piano-keyboard, or, for wrist movements, drum pads tuned to a C-major scale. Furthermore, in one study sonification of proximal arm movements was applied (see next for details). These patients had never played a musical instrument before. The main outcome measures were standard motor tests (e.g. Fugl-Meyer assessment (FMA), Box and Block test (BBT), Nine-hole Pegboard test (NHPT), Action Research Arm Test (ARAT), Arm-Paresis Score (APS); for review see [42]). Furthermore, mood, cognitive performance, quality of life, and speech abilities were often also assessed. In upper extremity paresis, music supported therapy (MST) aiming at rehabilitation of fine motor hand skills was first systematically investigated by Schneider et al. [43]. The setting included initially eight drum pads digitally set up to produce piano sounds and the drums forming a major scale. Patients had to tap with the paretic hands on the drum pads. As the patients progressed from tapping single sounds to well-known simple melodies, such as children songs or the ‘Ode to Joy’, they were transferred to a digital keyboard and had to perform individuated finger movements on the keyboard, again stepwise including technically more demanding melodies (i.e. more complicated sequences of finger flexions and extensions). Thus, behavioural shaping was achieved.

Superiority of the music group (MG) over fine motor training without music (TG) and over conventional physiotherapy (PT) was evident after intervention containing five 30-minute sessions per week for three weeks. Scoring of the BBT improved by 14 in the MG (2 TG, 1.8 PT) NHPT by 1.2 (TG = 0.2, PT, 0.15), ARAT by 9 (TG 1.2, PT 2.3), and APS by 2.4 (TG 1, PT 0.8). In order to obtain a measure of statistical significance, the effect sizes were determined using Cohen’s *d*. In the literature, effect sizes of 0.2 are considered small, effect sizes of 0.4 to 0.6 moderate, and effect sizes above 0.8 large. In the music group, effect sizes concerning improvements of behavioural tests varied between 0.66 and 0.34. In both control groups effect sizes were very small, with values between 0.01 and 0.14. The beneficial effect seen in the music group can be specifically attributed to the musical component of the training rather than the motor training *per se*, since patients practising with mute instruments remained inferior to the music group. Here, FMA was applied before and after 20 sessions of either MST on a keyboard or equivalent therapy without sound. FMA scores of the motor functions of the upper limb improved by 16 in the music group and by 5 in the control group, both improvements being statistically significant although to a lesser degree in the control group ($p = 0.02$ vs. $p = 0.04$) [44].

Regarding the neurophysiological basis of behavioural improvement, it was demonstrated that patients undergoing MST not only regained their motor abilities at a faster rate but also improved in timing, precision and smoothness of fine motor skills as well as showing increases in neuronal connectivity between sensory-motor and auditory cortex assessed by means of EEG-coherence measures [45, 46]. The establishment of an auditory-sensory-motor co-representation can therefore be suggested to be an important prerequisite to these improvements (see Fig. **31.1**).

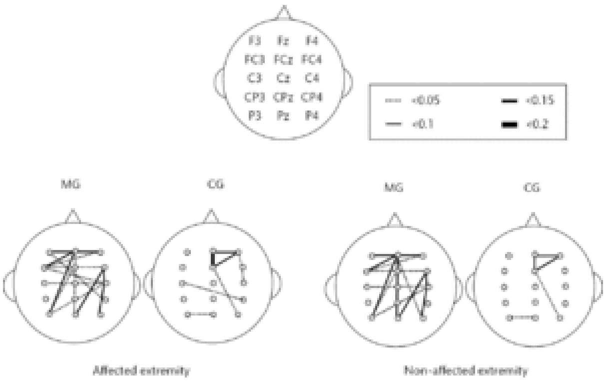

Fig. 31.1
Topographic task-related coherence maps for the music group (MG) compared to the control group (CG) during self-paced arm movements for the drum pad condition in the β-band (18–22 Hz). Statistically significant increases in task-related coherence during the motor performance after 3 weeks and 15 sessions of music supported therapy on sonified drum pads are displayed.

The importance of establishing an audio-sensory-motor co-representation in rehabilitation is corroborated by findings from a patient who underwent music supported training 20 months after suffering a stroke. Along with clinical improvement, fMRI follow-up demonstrated activation of motor and premotor areas, when listening to simple piano tunes, thus providing additional evidence for the establishment of an auditory-sensory-motor co-representation due to the training procedure [47]. In a larger group of 20 chronic stroke patients, increase in motor cortex excitability following a 4-week intervention with the same methods were demonstrated using transcranial magnetic stimulation (TMS). These changes were accompanied with marked improvements of fine motor skills [48]. The authors argue that the increased excitability demonstrated by the enlargement of motor evoked potential (MEP) amplitudes might be explained by an increase of the strength of synaptic transmission rather than a reduction in the threshold of the membrane potential. These results are coherent with previous studies demonstrating the effects on the modulation of the strength of synaptic plasticity within the motor cortex during the learning of new skill [49].

However, the situation in chronic stroke patients seems to be more complex. Fujioka and colleagues [50] could demonstrate, in a 10-week-long randomized controlled trial (RCT), including 14 patients with MST (MG) and 14 patients with conventional physiotherapy (CG), that both groups only showed minor improvements. As behavioural measures, the Chedoke McMaster Stroke Assessment (CMSA) and the ARAT were applied. The former improved by 0.2 in both, the MG and CG group and the ARAT score (for a single task, 0–3) improved by 0.2 in the MG, and by 0.05 in the CG. As to be expected, effect sizes according to Cohen's *d* were very small, between 0.15 and 0.25, and the music group showed merely a tendency towards better performance in the ARAT-test ($p = 0.08$) as compared to the control group. However, the music group performed significantly better in the trail-making test indicating an improvement in cognitive flexibility and furthermore showed enhanced social and communal participation in the Stroke Impairment Scale and in the PANAS (Positive and Negative Affect Schedule, [51]), again lending support to the prosocial effects of music. In another, shorter RCT with an intervention of only 4 weeks, Grau-Sanchez and colleagues [52] demonstrated no superiority on fine motor skills in the music group as compared to a control group, but also an increase in general quality of life as assessed by the Profile of Mood states (POMS, MG: 7–4, CG: unchanged) [53] and the stroke specific quality of life questionnaire, MG: 180–185, unchanged in the CG [54].

In a further development, the first author of this paper, E.A., developed movement sonification therapy [55]. Gross movements of the arm were transformed into discrete sounds, providing a continuous feedback in a melodic way, tuned to a major scale (i.e. patients could use movements of their paretic arms as a musical instrument, see Fig. **31.2**). Here sound perception could substitute for defective proprioception. Sonification therapy reduced joint pain in the Fugl-Meyer pain subscale (MG difference to CG by –10; $d = 1.96$) and improved smoothness of movement ($d = 1.16$) more than movement therapy without sound [56].

Fig. 31.2
Sonification of arm movements. The device contains a movement sensor applied to the forearm and upper arm (Xsense (R)) and allows to transform movements into music coding the vertical axis into pitch, the horizontal axis into timbre, and the z-axis into loudness. This way, the paretic arm is transformed into a simple musical instrument, allowing us to ‘move’ tunes.

Summarizing effects for the rehabilitation of the upper limb after stroke, music supported training is undoubtedly efficient and seems to be more helpful than functional motor training using no auditory feedback, but otherwise similar fine motor training. With respect to the underlying mechanisms, a number of open questions still remain. 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, regardless of the form of auditory stimulation, be it piano tones, or sonification of movement with other timbres. Thus, as already explored in the first part of this article, motivational and emotional factors might have contributed to the success of the training programme [57].

Another issue is related to the auditory feedback mechanisms. Up to now it has not been clarified 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 and time structure are prerequisites for the success of the training. This has to be addressed in a 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 [58], simple rhythmic cueing with a metronome significantly improves the spatiotemporal precision of reaching movements in stroke patients.

Furthermore, it is not clear whether timing regularity and predictability is crucial for the beneficial effect of MST using tapping on drum pads or playing on a keyboard. 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 were studied [59]. They 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, standard clinical tests such as the nine-hole-pegboard test and index finger tapping speed and regularity were used. Surprisingly, patients in the delay group improved in the nine-hole-pegboard test (time to complete difference—5.63; Cohen's d = 0.64), whereas patients in the normal group did not (time to complete—2.11). In finger tapping rate and regularity both groups showed improvements (reduction of inter-tap-interval in the music group from 396 to 333 ms, albeit to a lesser degree than in the normal group (from 398 to 292, Cohen's d between 0.32 and 0.29). The normal group showed reduced depression whereas the delay group did not. Thus, MST even with a randomly delayed keyboard can improve motor recovery after stroke, possibly because patients in the delayed feedback group implicitly learn to be independent of the auditory feedback and therefore outperform those in the normal condition when auditory feedback is not available.

Future research should address the long-term sustainability of improvements and strive to optimize the length and number of training sessions, according to patients' needs and preferences. Most probably, a client-tailored treatment algorithm considering severity of impairment, psychological status, and motivational drive will be most efficient.

Music supported motor therapy in rehabilitation of gait in stroke patients

With respect to *gait and lower limb malfunction*, simple rhythmic cueing with either a metronome or another sound-producing device has been applied. Since this is related to musical timing, we subsume this method under music supported motor therapy, although pitches and timbres are not varied and therefore important musical parameters are not included in this form of rehabilitation strategy. Furthermore, it is hypothesized that the mechanisms of action are more related to temporal organization of motor output, and less to emotional and motivational aspects of motor rehabilitation. Thus, rhythmic auditory cuing (RAC) may act on cerebellar and basal ganglia networks involved in timing of movement organization. In a study by Thaut et al. [60], a 3-week training programme for hemiparetic stroke patients reported an increase in gait speed for the rhythmic cueing group by 129%, while conventional physiotherapy resulted in 88% increase. Stride length increased by 66% (vs. 46%), cadence by 54% (vs. 22%), and walking symmetry by 39% (vs. 20%). Another group reported that rhythmic cueing increased stride length by 18% (vs. 0%), reduced asymmetry by 58% (vs. 20%), increased gait speed by 27% (vs. 4%) and increased length of foot contact to surface by 28% (vs. 11%) [61]. In a recent meta-analysis, the positive effects of music on gait velocity and stride length have been confirmed [62]. Analysing a total of 10 randomized or clinical controlled trials with 356 individuals included, large effect sizes were reported concerning walking velocity (increase in RAC vs. control by 0.3 m/s; Hedges's g = 0.98), cadence (increase in steps per minute by 9 steps in RAC vs. control; Hedges's g = 0.84) and stride length (increase in RAC vs. control by 5 cm 0.76). Additional subgroup analysis demonstrated that although the type of rhythmic cueing and stage of stroke did not lead to statistically substantial group differences, the effect sizes and heterogeneity values in each subgroup implied differences in treatment effect, depending on loudness, timbre, and sound structure of the rhythmic cueing.

Music in the rehabilitation of aphasia: melodic intonation therapy

While the close links between music and movement make motor rehabilitation an obvious avenue for music supported rehabilitation, recovery of language can also benefit from a music supported approach. 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% and 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 [63].

Based on clinical observations that patients with severe non-fluent aphasia can sing lyrics better than they can speak the same words, an intonation-based therapy called melodic intonation therapy (MIT) was first developed by Albert and colleagues in the 1970s [64, 65] and recently further elaborated by the Gottfried Schlaug and colleagues [66, 67]. The two unique components of MIT are first the intonation of words and simple phrases using a melodic contour that follows the prosody of speech, and second the rhythmic tapping of the left hand that accompanies the production of each syllable and serves as a catalyst for fluency. Thus, MIT emphasizes melody and contour and engages a sensorimotor network of articulation on the unaffected (usually right) hemisphere through rhythmic tapping.

To date, studies using MIT have produced positive outcomes in patients with non-fluent aphasia. These outcomes range from improvements on the Boston Diagnostic Aphasia Examination (BDAE [68]), to improvements in articulation and phrase production (increase in syllable production/minute) after 40 sessions in the MIT group by 200% group vs.

120% in the CG [69, 70] 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. [71] 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. These positive effects were also confirmed by Raglio et al. [72] as well as in an enlarged treatment programme, including breathing and awareness exercises [73].

The therapeutic effect of MIT is also 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 [74], as well as increased fibre number and volume of the arcuate fasciculus in the right hemisphere [75, 76] suggesting an increased audiomotor connectivity of the right hemisphere: these findings demonstrate that intensive 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 [75].

The mechanisms underlying the recovery-enhancing effects of MIT are not completely clear. Four possible mechanisms by which MIT's therapeutic effect is achieved have been discussed (for details, see [14, 76]): (1) *reduction of speed* to approximately one syllable/sec. which may specifically engage right hemisphere perceptual and perception-action coupling, since the right hemisphere has been shown to integrate sensory information over a larger time window than the left hemisphere [77, 78]; (2) *syllable lengthening* that isolates/emphasizes individual phonemes even as they remain part of the continuously-voiced words/phrases; and (3) *'chunking'* that not only combines prosodic information with meaningful content to facilitate production of longer, more fluent phrases, but has also been shown to lead to more right- than left-hemisphere activation in healthy subjects [79,80,81]. Given that patients with right hemisphere lesions have greater difficulty with global processing tasks (e.g. melody and contour processing) than those with left hemisphere lesions [82, 83]. it is possible that the melodic element of MIT does indeed engage the right hemisphere, particularly the right temporal lobe, more than therapies that do not make use of tonal information or melodic contour, and again intervention that would integrate information over a larger timescale favouring right over left hemispheric processing [77]. The fourth mechanism—*Left hand-tapping (one tap/syllable, one syllable/sec.)*—is likely to play an important role in engaging a right-hemispheric, sensorimotor network capable of providing an impulse for verbal production in much the same way that a metronome has been shown to serve as a 'pacemaker' when rhythmic motor activities prime and/or entrain sensorimotor networks [84, 85]. In addition, research suggesting that hand movements and articulatory movements may share neural correlates [86,87,88,89] further supports the notion that hand-tapping is critically important for facilitating the coupling of sounds to orofacial and articulatory actions [90]. Since concurrent speech and hand use occurs in daily life, and gestures are frequently used to emphasize/accompany important and/or elusive concepts in speech, rhythmic hand movements, in synchrony with articulatory movements, may have similarly beneficial effects on speech production and in particular in relearning of speech-motor functions after a stroke.

Music supported therapy in rehabilitation of other neurological disorders

Parkinson's disease

Rhythmic auditory cueing as a means to improve gait in Parkinson's disease (PD) has been scientifically investigated for the last 20 years [91], while the positive effects of dancing on locomotion and balance in PD patients were recognized more recently [92]. Generally, the majority of the studies on MST in PD have used music to improve mobility and gait parameters. In a recent review, effect sizes (Cohen's *d*) of the peer-reviewed published interventions were calculated [41]: the most coherent and clinically significant beneficial effect on motor symptoms in PD was produced by dancing. Compared to the control group, both tango and waltz/foxtrot intervention groups improved in balance (Berg Balance Scale between +2 and +5; Cohen's $d = 2.98$, $d = 3.17$, respectively), 6-minute walk test (+98 m vs. +24 m; $d = 2.50$, $d = 2.24$), and backward stride length (+14 cm vs. + 6 cm; $d = 2.19$, $d = 1.96$). Furthermore, dancing also improved overall mobility ($d = 2.50$) [93]. In a smaller study, tango improved balance ($d = 2.18$) [92]. These positive effects have been confirmed by a meta-analysis [94]. Bearing a close analogy to dancing, music therapy with rhythmic movements improved mobility, and gait training synchronized to music resulted in improved velocity (by 0.2 m/s; $d = 2.64$), stride time (by 0.21 s; $d = 1.76$), and cadence (by 0.17 m; $d = 2.16$) compared to the control group [94]. Other studies equally reported reduction in PD specific motor symptoms ($d = 0.50$) [95, 96], but while the effect was statistically significant, a meta-analysis found the effects of music-based movement therapy on the unified Parkinson's disease rating scale (UPDRS) motor score too heterogeneous for definitive conclusions [94].

Although the sample sizes were small, the reviewed evidence suggests that dancing and music-based interventions that synchronize movement to music can be beneficial in maintenance of motor performance in this slowly progressing disease, at least in a significant percentage of patients. In all of studies reviewed, the follow-up period was too short to allow conclusions on the long-term effects of music interventions. The effects of music on the autonomic disturbances in PD have not been addressed in controlled studies. Rhythmical use of musical stimulus most probably compensates for the failing control by the extrapyramidal system and enhances audio perception and movement synchronization [e.g. 97]. The perceived rhythm in music activates the neural circuits involved in motor actions and act as an external cue for movement thus replacing the impaired internal timing function in PD [97]. The use of music as stimulus may be more effective than auditory stimulation without music (e.g. metronome beat) in gait rehabilitation, as shown in stroke [98]. This might also explain the positive effects of dancing in PD. Furthermore, the improvement in motor control and decrease in disease specific symptoms could in turn improve the quality of life (QoL). However, according to a new study, it seems that there are 'responders' and non-responders with respect to both response to musical cueing and to improvement of QoL [99, 100]. One of the sources of this variability could be individual musical preferences and listening habits, however this has not been addressed in the above-mentioned studies. In this regard, Simone dalla Bella and colleagues [101] convincingly argue in a recent review that rhythmic auditory cueing needs to be individualized according to the patient's preferences, the stage of motor impairment, and the perceptual capabilities of the individual.

Multiple sclerosis

Multiple sclerosis is the most common severe neurological disease of the young adult population and manifests as a wide range of neurological deficiencies, including severe motor impairments and sensory deficits. Treatments aim to ameliorate the function after flare-up of an MS-episode or preventing new episodes, mostly acting via modulation of the autoimmune responses and anti-inflammatory effects. Two randomized controlled studies have addressed the effect of musical interventions in alleviating the manifestations of MS. In one study, the effect of keyboard playing (audible vs. mute) in hand functionality was investigated [102]. The audible keyboard playing improved the subjective functional use of the hand significantly in the audible keyboard group (ABILHAND assessment 2.3 to 3.5 vs. 2.2 to 2.3; $d = 0.60$ vs. $d = 0.32$), however, fine motor abilities assessed objectively with the NHPT improved in both groups (MG: 57–30 vs. CG 37–28). A feasibility study on MS patients with gait problems found rhythmic auditory cueing to be effective in decreasing double-support time, the effect size being large (from 54 s to 112 s; $d = 0.72$) [103]. While decreased double-support time may reflect improved dynamic balance, none of the other gait parameters differed from controls.

Epilepsy

Epilepsy was treated with music in only one RCT (N = 73) [104]. Patients were exposed to Mozart's music periodically every night for a year and a significant 17% reduction in seizure frequency was detected during the study period. In addition, a 16% reduction in seizure frequency persisted for 1 year. While no other RCTs on adult population have been published, a recent meta-analysis of 12 studies including both paediatric and adult patients indicated that 85% of the patients responded favourably to music, the average reduction in interictal epileptic activity being 31% and 24% during and after the listening period, respectively [105]. Definitive conclusions cannot be drawn, since all but two studies lacked a separate control group. In terms of underlying mechanism, it is hypothesized that exposure to patterned auditory stimuli provides an excitatory stimulation of the cortex, which may reduce epileptiform activity.

Music supported therapy in dementia

Since ancient times, music in connection with lyrics has been used as support for memory formation, be it in religious rites, memorization of heroic saga, or songs important for group identity. Indeed, biographical memories can be enriched and consolidated with music, probably due to tight linkages of biographical events and music to the limbic emotional system [106]. With respect to neurophysiological mechanisms, it could be demonstrated that musical training can induce functional plasticity in the human hippocampus [107] which provides a possible motivation for considering the effects of MST in memory loss due to dementia.

In a recent review, Sihvonen et al. [41] identified altogether 16 RCTs on persons with dementia (n = 1048). Mostly neuropsychiatric and behavioural symptoms, such as anxiety and agitation, depression, and cognitive status, as well as QoL measures were assessed and improved. Those studies specifically addressing cognitive elements (reminiscence, attention training) or physical exercise improved overall cognitive performance (measured by Mini-Mental State Examination (MMSE)) of patients with dementia compared to standard care in four studies published by three separate groups (d = 0.47–0.76) [108,109,110,111]. In addition, improved performance in these music interventions was reported for tests measuring attention and executive functions, orientation, and verbal or episodic memory [110, 111]. In one RCT, caregiver-implemented singing was also found to enhance working memory, especially in mild dementia and also to reduce caregiver burden [110]. On the contrary, no significant changes in cognitive performance were observed for group-based music. In this trial a cooking intervention in persons with moderate-severe dementia was included as a control for musical activities and similarly did not yield any effects on cognitive performance [112].

The cognitive benefits of musical activities such as singing or playing an instrument in the early stages of dementia may be related to enhanced cognitive reserve, the utilization of alternative networks and cognitive strategies to cope with advancing pathology [113]. Overall, the effects of musical interventions in dementia may be driven by the comfort and emotional safety induced by familiar music, which can temporarily overcome the confusion and disorientation by anchoring attention on a positive familiar stimulus in an otherwise confusing environment. As mentioned just now, familiar music is also imbued with personal emotions, which can trigger autobiographical memories and help to restore a sense of identity for a while [114].

Music supported therapy in rehabilitation of disorders of consciousness

Disorders of consciousness (DOC) may frequently be observed among early neurological rehabilitation patients [115]. It has been reported that 83% of hypoxic encephalopathy patients suffer from DOC on admission and less than one out of five comatose subjects regain consciousness during rehabilitation [115]. Alarmingly, there is only little evidence for the effectiveness of DOC rehabilitation interventions [116].

DOCs are subdivided into coma, unresponsive wakefulness syndrome (UWS)—previously known as vegetative state (VS)—and minimally conscious state (MCS). Coma is characterized by a state of deep, unarousable unconsciousness and may be graded based on the absence or presence of reflexive responses to stimuli, such as present or absent eye opening to strong painful stimuli [117]. In UWS, despite open eyes and existing reflex behaviour, patients are completely unresponsive (e.g. absence of command following) [118]. Patients in MCS exhibit some signs of consciousness, such as command following (even if inconsistent), visual pursuit, localization to noxious stimulation, and appropriate responses to emotional stimuli without being able to functionally communicate.

It has been hypothesized that comatose patients might suffer from a condition of 'environmental deprivation' [119]. Viewed in this context, patients might benefit from stimulation of all five sensory pathways and thus enhancing the rate and degree of recovery from coma. The concept of 'enriched environment' inspires therapeutic approaches using sensory stimulation in neurological early rehabilitation [120]. Preferred music as therapeutic auditory intervention has recently been used in a few studies in patients with UWS or MCS [121,122,123]. A neurophysiological and behavioural study compared electroencephalogram (EEG), heart rate variability, respiratory and behavioural responses of 20 healthy subjects with 21 individuals with UWS or MCS [121]. Healthy subjects and patients were presented with live music chosen according to their musical preferences. Furthermore, improvised music entrained to respiration (procedures typically used in music therapy) was applied, and recordings of disliked music, white noise, and silence. The ANOVA results indicated a range of significant responses across healthy subjects corresponding to arousal and attention in response to preferred music including concurrent increases in respiratory rate with globally enhanced EEG power spectra responses across frequency bandwidths. While physiological responses were heterogeneous across patient cohorts, significant post hoc EEG amplitude increases for stimuli associated with preferred music were found for frontal midline theta in six UWS and four MCS patients and frontal alpha in three UWS and four MCS subjects. Furthermore, behavioural data showed a significantly increased blink rate for preferred music within the UWS cohort. Two UWS patients exhibited concurrent changes across measures indicative of discriminatory responses to both music therapy procedures.

In another recent study, 13 DOC patients were examined using bedside EEG while listening to preferred music [122]. Event-related potentials to the patient's first name were recorded after either preferred music (music condition) or a continuous sound (control condition). The cerebral response to the patient's first name was more frequently observed in the music than in the control condition. Furthermore, the presence or absence of a discriminative response in the music condition seemed to be associated with a favourable or unfavourable outcome after 6 months. The authors suggested that preferred music might boost cognition in DOC. To the best of our knowledge, psychophysiological reactions like heart rate, blood pressure, or respiration frequency changes have not been examined as of yet. Taken together, the rehabilitative potential of music therapy in patients with coma, UWS, or MCS in neurological early rehabilitation merits further investigation. In a recent Cochrane review, the authors conclude that music interventions may be beneficial, and first results are encouraging. Controlled trials are strongly encouraged to improve the evidence-base of music as a therapeutic tool in neurological early rehabilitation patients with DOC [123].

Conclusion and outlook

The research of the last two decades reviewed in this chapter demonstrates that music exposure and active musical training can be a strong stimulant for neuroplastic adaptations and behavioural improvements following brain injury or degenerative processes. 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 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 neurotransmitters such as serotonin and dopamine—is experienced as joyous and rewarding 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 non-damaged brain regions.

As with other interventions, MST in neurorehabilitation needs to be grounded within a neurobiological understanding of how and why particular brain systems could be affected. The efficacy of these still experimental interventions should be assessed quantitatively and in an unbiased way. Here, researchers have started the journey towards a sound neuroscientific basis for music-based interventions, which, not unexpectedly, yielded in some instances controversial results. The studies reviewed here, mostly randomized clinical trials, are important steps in establishing neurologic music therapy that might have the power to enhance brain recovery processes by exploiting neuroplasticity.

What is urgently needed are larger RCTs demonstrating the assumed specific value of musical interventions based on the afore-mentioned neurobiological mechanisms. In order to transcend the effects of novelty or motivation, randomized controlled music therapy trials will need to include non-music related control activities with similar motivational power and novelty. Furthermore, in these trials, well-defined patient groups, stratified with respect to musical expertise, music listening behaviours, premorbid health, and cognitive status and timepoint of onset of therapies after the lesion have to be recruited. In order to gain more information on the sustainability of interventions, long-term follow-up studies are necessary. Finally, novel biomarkers may help to recruit patients based on their initial potential for reactive neurobiological recovery, for example, by assessing neurophysiological parameters, such as resting state connectivity of brain regions [124]. Collecting this information may allow clinicians to better predict which patients will benefit from which aspects of neurologic-based music therapy and provide a more personalized rehabilitation strategy.

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