# Music-based interventions in neurological rehabilitation

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## Summary

During the last ten years, an increasing number of controlled studies have addressed the rehabilitative effects of music-based interventions in several neurological diseases. While the amount of the studies and the level of evidence is highest in stroke and dementia, increasing evidence is accumulating for the effects of music-based interventions in Parkinson´s disease, epilepsy, and multiple sclerosis. Studies have confirmed that interventions, such as music listening, singing, or playing an instrument, are beneficial for cognition, motor function, or emotional well-being in these patients. Although music-based interventions may target divergent functions, such as motor performance, speech, or cognition, the psychological effects and neurobiological mechanisms underlying the impact

of music are likely to share common neural systems for reward, arousal, affect regulation, learning, and activity-driven plasticity. Although further controlled studies are still needed to establish the clinical efficacy of music in neurological recovery, music-based interventions are emerging as promising rehabilitation strategies.

## Introduction

The population is ageing rapidly and the number of persons suffering from severe age-related brain diseases is rising[1]. Less than 20% of the heavy economic burden of chronic brain diseases is due to acute treatment and care[2,3]. This has raised the need to pursue new cost-effective, light-input rehabilitation strategies, both independent of and complementary to traditional methods, such as physiotherapy, occupational therapy, or speech therapy.

Since neurogenesis in the adult brain has no clinically meaningful impact, brain recovery relies upon the spared neurons' ability to compensate for lost function by growing neurites and forming novel synapses to rebuild and remodel the injured networks[4–8]. This is thought to be achieved in traditional rehabilitation strategies by targeted training of the weakened function[9–12]. An alternative strategy would be to increase the overall level of brain activity through sensory and cognitive stimulation[13].

Music listening improves neuronal connectivity in numerous specific brain regions of the healthy participants[14–17], and musical activities, such as playing an instrument, promote neural plasticity, and induce changes in the grey matter and white matter[18–20]. Music has been shown to be efficacious in the recovery of postoperative patients by several outcome measures such as pain, anxiety, use of analgesics, and patient satisfaction,[21] suggesting that music might enhance neurological rehabilitation as well.

Formal music-based intervention, music therapy, can comprise of active interventions (e.g. music creating, instrument playing, singing, musical improvisation) and receptive interventions (e.g. music listening) administrated by a credentialed music therapist. Although a Cochrane review evaluating the effect of music interventions in acquired brain injury has been recently published[22], a comprehensive overview on music-related interventions in the rehabilitation of the major neurological diseases, including degenerative diseases and other neurological entities in which the rehabilitative effect of music has been studied, is needed. Here, we appraise the randomized controlled trials

(RCTs) investigating the effects of music-based interventions in the rehabilitation of stroke, dementia, PD, epilepsy, and MS.

## Search strategy and selection criteria

We searched PubMed up till April 11, 2017 using Medical Subject Headings (MeSH) for diseases “stroke”, “brain injuries”, “dementia”, “parkinsonian disorders", “epilepsy”, and “multiple sclerosis”, combined with MeSH for "music" or "music therapy” and keywords “melodic intonation therapy”, “rhythmic auditory stimulation”, “rhythmic auditory cueing”, and “music supported therapy”. Additional references were gathered from reference lists and relevant articles. We included only the RCTs applying a minimum of one-week intervention, published in English over the past 10 years, except for two older landmark studies.

## Music-based interventions for stroke

Stroke is the one of the leading causes of long-term disability in the world[23]. Of the major neurological entities, the strongest evidence for effectiveness of music-based interventions has been presented for stroke. We identified 16 RCTs utilizing music during recovery from stroke-related neurological and neuropsychiatric disturbances (Table 1)[24–39]. The parameters assessed included motor functions, such as gait and upper extremity function[24,25,27,30,33–39], language functions[26,28,29], cognitive functions, such as memory and attention[28,32], mood[28,32,34], or quality of life (QoL)[30,34]. The measurements were carried out with various standard motor tests (e.g., Fugl–Meyer assessment, the Box and Block Test, Berg Balance Scale, and Nine-Hole Pegboard Test), clinical neuropsychological assessments (e.g., CogniSpeed, Wechsler Memory Scale), standard language function assessments (e.g., Boston Diagnostic Aphasia Examination), and questionnaires (e.g., Stroke Impact Scale, Profile of Mood States, and Stroke and Aphasia QoL Scale-39). In addition, computer-based movement analyses[30,35,37,38], MRI analysis[28,32,39], magnetoencephalography[31], or electroencephalography[33] were utilized to assess motor performance and neuroplasticity. Metronome-like rhythmic stimulus was used in five studies on stroke-related motor paresis[30,34,36,37,39]. Favorite music selected through interview was used in three studies[28,31,32]. The genres of favorite music were not reported. Three studies used children’s songs and folk songs[24,33,35]. Five studies involved a trained music therapist[26–28,31,32].

## Effects on motor symptoms

Hemiparesis is the most common consequence of stroke, affecting over 70% of the patients[40]. In total, eight studies reported enhanced motor recovery when stroke patients were rehabilitated with music[25,27,30,33–37]. Four of these studies investigated the use of rhythmic auditory stimulation (RAS) in gait training and all found it to improve gait parameters more than gait training without any musical support[30,36–38]. In RAS, external auditory cues guide movement through anticipated temporal sequence, the frequency of which is adjustable and gradually entrains the movement. Across studies, significant improvements with small (Cohen's d ≥ 0·2), medium (d ≥ 0·5), or large (d ≥ 0·8) effect sizes (Table 1) were observed in gait velocity, stride length, length of foot contact to surface, cadence, and asymmetry after 3-6 weeks of RAS compared to conventional training without RAS[36–38]. Similar findings were reported when intensive gait training with RAS was investigated with respect to postural control and gait performance in chronic stroke patients[30]. In 6 weeks, RAS group improved in balance, gait velocity, cadence, stride length, and double support period on the affected side[30]. When RAS was utilized in the form of combining rhythmic music with movement therapy, stroke patients showed improved ankle and arm movement after 8 weeks of intervention, with medium and large effect sizes, respectively[34]. One study compared bilateral arm training with RAS to dose-matched therapeutic exercises, but found no significant differences between the groups[39]. Interestingly, RAS intervention conducted by a music therapist resulted in greater improvement compared to studies conducted by a non-music therapist[22].

Music-supported therapy (MST), in which musical instruments (electric drum pads and keyboards) are used to train gross and fine movements of the hemiparetic upper extremity by playing simple melodies, was found to be effective in rehabilitating the arm paresis after stroke in five RCTs[24,25,27,33,35]. Three weeks of MST improved motor skills of the paretic arm significantly more than conventional physiotherapy, an effect shown by several validated clinical tests with small to medium effect sizes[33,35]. The effects were accompanied by improved cortical connectivity and increased activation of the motor cortex[33]. These effects seem to be specifically caused by music rather than motor training per se, since patients practicing with mute instruments remained inferior to the music group[27].

One study utilized movement sonification therapy, a recent development in MST[25]. Gross movement was transformed into sound, providing continuous feedback, substituting for defective proprioception. Sonification therapy reduced joint pain and improved smoothness of movement more than movement therapy without sound with large effect sizes. Delayed auditory feedback in MST has been proposed to be as effective as the traditional immediate auditory feedback[24]. While both RAS and MST involve auditory-motor coupling, incorporating full music stimulus might result in additional enhancement due to the personal motivational value of music. Internal synchronization, based on musical memory, generates expectation of consecutive sounds of a familiar song and provides precise mental timing feedback for movement, thus supporting the patient's impaired proprioception.

### Effects on aphasia

Aphasia affects around 30% of stroke patients[40]. In two RCTs, active music therapy improved the speech of chronic aphasics[26,29]. In one of them, Melodic Intonation Therapy (MIT)[41], a singing-based speech therapy designed for non-fluent aphasics, was applied on subacute aphasics[29]. MIT is a formalized treatment to transform the prosody of speech into low and high pitches – which the patient then learns to use to intone the stressed and non-stressed syllables, respectively – accompanied by rhythmic tapping with the left, non-paretic hand on each syllable. Training starts with two-syllable words and proceeds gradually to phrases. MIT improved the daily life communication and object naming significantly more than the control group receiving other types of language rehabilitation with medium and large effect sizes, respectively[29]. Music-related speech therapy, MIT in particular, is conceptually elegant and music therapy interventions may be more effective in aphasia than speech training without music[22].

### Effects on cognitive and emotional deficits

Deficits in cognitive functions (e.g., memory, attention, executive function) and mood (e.g. depression) affect around 30-50% of stroke survivors[42,43]. In one RCT, one-hour daily listening to favorite music selected with the help of a music therapist and continued during the first two post-stroke months enhanced cognitive recovery[32]. In a 6-month follow-up, the music group still showed significant improvements with large effect sizes in performance of tasks measuring verbal memory and focused attention compared to a control intervention (audio book listening) or standard care[32] (see Figure 1A). Compared to standard care, music listening was also associated with less depression and confusion with medium effects[32] (see Figure 1A). The cognitive gains induced by music listening were associated with enhanced auditory memory-related function in temporal brain areas[31] and increased gray matter volume in spared prefrontal regions[28] (Figure 1B-C). Music-induced reduction in negative mood was linked to increased grey matter volume in limbic areas[28]. In addition to music listening, RAS therapy improved patients' mood but with non-significant effect size[34]. Although the long-lasting positive effects were shown by several outcome measures, these effects need to be replicated.

## Music-based interventions for dementia

The most common etiologies of dementia are Alzheimer's disease, cerebrovascular diseases, and their combination. In these entities, neural degeneration progresses over several years leading sequentially to memory problems and other behavioral disturbances. Altogether 17 RCTs on persons with dementia (PWDs; Table 1) have assessed the effects of music intervention on neuropsychiatric and behavioral symptoms, such as anxiety, and agitation (14 studies)[44–57], depression (six studies)[47,49,55,58–60], cognitive status (five studies)[47,49,51,58,59] as well as on QoL (four studies)[46,47,59,60]. Neuropsychiatric and behavioral symptoms were assessed with tests, rating scales, or questionnaires measuring overall symptom severity (e.g., Neuropsychiatric Inventory (NPI), Cohen-Mansfield Agitation Inventory, Behavior Pathology in Alzheimer's Disease Rating Scale), depression (e.g., Cornell Scale for Depression in Dementia, Geriatric Depression Scale), cognitive status [e.g. Mini-Mental State Examination (MMSE), Severe Impairment Battery), and QoL or well-being (Cornell-Brown Scale for QoL in Dementia, Dementia Care Mapping). Most interventions used vocal or instrumental music presumably familiar to the PWDs, such as personal favorites, all-around popular music or common children's songs. All studies except for one involved a music therapist.

### Effects on cognitive deficits

Music listening coupled with cognitive elements (reminiscence, attention training) or physical exercise improved overall cognitive performance (measured by MMSE) of patients with dementia compared to standard care in four studies published by three separate groups[47,51,58,59]. The effect sizes varied from small to medium. In addition, improved performance in these music interventions was reported for tests measuring attention and executive functions (small to medium effect size)[51,59], orientation (medium effect size)[59], and verbal or episodic memory (medium effect size)[51,59]. In one RCT, also caregiver-implemented singing was found to enhance working memory with medium effect size, especially in mild dementia and also to reduce caregiver burden as shown by a large effect size[59]. On the contrary, no significant changes in cognitive performance were observed for group-based music and cooking interventions in persons with moderate-severe dementia[49]. The cognitive benefits of music 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[61].

### Effects on neuropsychiatric symptoms, mood, and quality of life

Six studies found music therapy to be effective in improving the neuropsychiatric symptoms of dementia with medium to large effect sizes[44,46–48,54,56]. Three studies assessed the carry-over effect[44,55,58], which varied from less than four weeks to two months. In contrast, two studies failed to show any significant effect of music therapy or music listening on neuropsychiatric symptoms[45,49]. The music intervention program resulted also in improved PWD-caregiver interaction and well-being of the PWDs (large effect size)[46]. Regarding specific neuropsychiatric symptoms, two studies showed music to reduce anxiety and agitation in PWDs[52,55], but their effect sizes diverged. In contrast, four RCTs found music to be ineffective in reducing anxiety or agitation[50,51,53,57].

QoL was assessed in three studies[47,59,60]. While Cooke et al. (2010) did not find any significant differences between the effects of music and control (reading) interventions[60], Särkämö et al. (2014) reported that music listening compared to standard care increased QoL significantly and with large effect size[59]. Music listening was found especially beneficial in moderate dementia with etiology other than Alzheimer's disease[47]. Improvement of mood in PWDs has been reported in four studies, effect sizes varying between small and large[47,55,58,59]. Two other RCTs failed to show such an effect[49,60]. 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. This anchoring effect may be enhanced by using headphones. Familiar music is also imbued with personal emotions, which can trigger autobiographical memories and help to restore a sense of identity for a while.

## Music-based interventions for Parkinson’s disease

Parkinson’s disease (PD) is primarily a movement disorder due to degeneration of dopaminergic nigro-striatal tract. In addition, the early phase of PD includes autonomic nervous system and other non-motor deficits, and 30% of the patients develop dementia-level cognitive decline in the late phase[62]. Effects of music on several symptoms and signs of PD have been studied in five RCTs (Table 1)[63–67]. Four studies examined the effects of music-assisted motor training using motor parameters as outcome measures[63–66]. Two studies[63,67] evaluated non-motor parameters, QoL, cognition, or social parameters. In all trials, medication remained unchanged during the interventions.

General motor performance was assessed by motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III), and specific motor functions by e.g. Berg Balance Scale and 6-minute walk test. Specific gait parameters were analyzed using video recordings and computer-assisted motion analysis programs. QoL was evaluated using validated questionnaires. Music used in the intervention varied from rhythmic auditory cueing to self-selected favorite music. The genres of the patient’s favorite music were not reported. Only one study involved a music therapist[63].

Based on effect sizes calculated from the reviewed data, the most coherent and clinically significant beneficial effect on motor symptoms was produced by dancing. Compared to the standard care, both tango and waltz or foxtrot intervention groups improved in balance, 6-minute walk test, and backward stride length with large effect sizes[65]. In a smaller study, tango improved balance with large effect[66]. Dancing also improved overall mobility with large effect size[67]. Bearing a close analogy to dancing, music therapy with rhythmic movements[63] improved overall mobility in patients with PD. Gait training synchronized to music resulted in improved velocity, stride time, and cadence with large effect sizes compared to the control group[64]. Both studies reported reduction in PD specific motor symptoms (medium effect size)[63,64].

Two studies found music-based intervention to improve QoL with large effect size[63,67]. Dancing tango appeared to be significantly more effective than waltz, Tai Chi or regular treatment[67]. In addition, patients reported better social support after the intervention. Improvements in cognition have been reported in one study[63].

Although the sample sizes were relatively small, the reviewed evidence suggest that dancing and music-based interventions that synchronize movement to music can be beneficial in maintenance of motor performance in this slowly progressing disease. Rhythmical use of musical stimulus compensates for the failing control by the extrapyramidal system and enhances audio perception and movement synchronization[30,36,37]. 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[68]. 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[22]. This might also explain the positive effects of dancing in PD. Furthermore, the improvement in motor control and possible decrease in disease specific symptoms could in turn improve the QoL. 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.

## Music-based interventions for multiple sclerosis

Multiple sclerosis (MS) is one of the most common severe neurological disease in the young adult population. Despite relatively low prevalence, it bears need for expensive medication and long-lasting rehabilitation[3]. MS treatments aim to ameliorate function after flare-up of an MS-episode or to prevent new episodes. Only two RCTs[69,70] (Table 1) have studied the effect of musical interventions in alleviating the manifestations of MS. Between the studies, outcomes were different, and only one study involved a music therapist.

The RCT without music therapist included 19 patients and studied the effect of keyboard playing (audible vs. mute) in hand functionality[69]. Audible keyboard playing improved the functional use of the hand significantly with medium effect size, indicated by a questionnaire. Using a computerized gait analysis, a feasibility study on ten MS patients with gait problems found RAS to be effective in decreasing double-support time with large effect size[70]. While decreased double-support time may reflect improved dynamic balance[71], none of the several other gait parameters differed from controls receiving standard care. The results of music-based interventions in MS are scanty and allow no definite conclusions on the rehabilitative effect of music. Although designing studies may be challenging due to diversity of MS deficits, motor functions, spasticity, fatigue, cognitive deficits, and mood might be feasible outcome measures in the future studies.

## Music-based interventions for epilepsy

Epileptic seizures arise from abnormal synchronization of electrical activity in the brain, and the most of them cease spontaneously by largely unknown mechanisms. Exposure to patterned auditory stimuli provides a noninvasive excitatory stimulation of the cortex, which has been suggested to reduce epileptiform activity[72]. In this vein, one RCT (N=73; Table 1) has examined the effectiveness of music in epilepsy[73]. 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 carry-over effect of 16% reduced seizure frequency persisted for one year. While no other RCTs on adult population have been published, a recent meta-analysis of 12 studies including both pediatric and adult patients with epilepsy of any kind indicated that 130 out of 153 patients respond favorably to music, the average reduction in interictal epileptic activity being 31% and 24% during and after the listening period, respectively[74]. Further studies are definitely needed, since all but two studies lacked a separate control group.

## Mechanisms underlying the rehabilitative effect of music

Specific pathologies of the diseases evaluated here may affect, sometimes critically, the way the patient's brain processes music, and diverse manifestations of the diseases influence the selection of feasible music intervention. Considering the widely varying nature of the diseases in which music has led to improved recovery, enhanced rehabilitation, or alleviation of symptoms, several distinct explanatory mechanisms can be postulated.

### Neural activation and neuroplasticity

Functional neuroimaging studies have shown that music induces widespread activation of the brain[14–17] (Figure 2), and correspondingly increases blood flow through the medial cerebral artery due to autoregulation[75] (Figure 3). This should provide favorable circumstances for recovery processes in general regardless of their nature, as for example after stroke, neuroplastic changes associated with functional recovery are activity-dependent[76]. Musical activities bear similarity to the concept of enriched environment which facilitates recovery at behavioral and neurobiological levels in animal models of many neurological illnesses[13].

Given that active music-based rehabilitation involves multiple components analogous to musical training and music learning (i.e. iterated practice of movements coupled with auditory feedback and extensive cognitive processing), it is plausible that music-based neurological rehabilitation induces similar structural and functional neuroplastic changes as musical training[18,19]. Indeed, individual studies have reported memory-related plastic effects after mere music listening in recovering stroke patients[28,31] as well as neural reorganization after MST[33]. Supporting literature has provided further evidence of neuroplasticity after MST[77–79] and MIT[80] in stroke patients.

In general, the specific cellular mechanisms of neuroplasticity remain unknown. While significant neurogenesis in elderly individuals seems unlikely, other putative mechanisms include neuronal hypertrophy, increased volume of neuropil, and changes in the vascular or glial compartments. An intriguing question would be to investigate, whether previous music exposure during a specific period of lifetime affects the plasticity of recovering brain. The possibility of negative plastic changes due to overly intense and/or premature intervention should be considered.

## Activation of reward, arousal, and emotion networks

Music activates the dopaminergic mesolimbic system which regulates memory, attention, executive functions, mood, and motivation[81] (Figure 3). A key part of this reward system is the nucleus accumbens, which regulates mood and experienced pleasure. Its activation by intense emotional response (“chills”) to music leads in healthy subjects to increased dopamine secretion directly proportional to the intensity of the experience[81]. This may partly explain the cognitive-emotional gains induced by music also in neurological patients. It is feasible to postulate that music-induced improvement of mood, arousal, and relief of confusion may enhance recovery of cognitive functions in neurological patients. Music-induced activation of the parasympathetic and inhibition of the sympathetic nervous system in PWDs, and corresponding changes in catecholamine and cytokine secretion has been considered as a soothing effect of music[82]. This is also a possible mechanism behind the effect of music ameliorating neuropsychiatric symptoms in dementia.

Music also produces measurable cardiovascular and endocrine responses indicated by lowered serum cortisol levels and inhibition of cardiovascular stress reactions[82,83] (Figure 3). In animal models, prolonged stress can have maladaptive effects on neuroplasticity, such as dendritic atrophy, synapse loss, and decreased hippocampal neurogenesis[84]. In patients, elevated cortisol level in acute stroke correlates with increased infarct volume, and increases the risk of depression, poor prognosis, and fatal outcome[85]. We speculate that listening to music lowers stress hormone secretion in acute stroke, as it does in postoperative patients[86,87].

Overall, neurological diseases and mood disorders have a high comorbidity, ranging from 20% to 50%[88,89]. Common clinical experience is that depression diminishes adherence to rehabilitation, and published studies indicate that depression impairs functional outcome, QoL, and increases mortality[90]. According to the data reviewed here, music improved mood or diminished anxiety in PWDs[52,59] and stroke patients[32,34]. We conclude that music interventions are viable in improving the mood of neurologic patients. Yet, the causal relationship between music-induced mood improvement and neurological outcome still remains to be proved.

### Activation of alternative or spared neural networks

Some music interventions allow access to an impaired function by engaging specific regions associated with musical rhythm, movement, singing, or memory[68]. Rhythmic entrainment, our inherent tendency to time movements to the regular beat of music, which forms the basis of RAS and playing-based music interventions, is based on the strong connectivity between the auditory system and motor system[14]. In diseases in which the internal sequencing and monitoring of actions is not working due to the dysfunction of the motor system, rhythmic entrainment can act as an external timer, cueing the execution of movements[68]. For instance, a stroke patient with impaired muscle coordination or a Parkinson patient with stiffness and bradykinesia may find it easier to execute motor tasks with rhythmic support provided by music listening or dancing[30,36–38,63–66].

Singing, which is the key component of MIT, engages frontotemporal language and vocal-motor regions more extensively and bilaterally compared to speaking[91,92]. This enables training of speech in aphasia via both spared left hemisphere regions and homologous right hemisphere regions. The preserved ability to sing in aphasia has been reported as early as 1745, when a stroke patient with severe aphasia was reported to be only able to verbalize “yes”, but was able to correctly sing familiar hymns producing both the melody and the text of the songs[93].

Familiar music specifically activates the anterior cingulate and medial prefrontal cortex in the healthy brain, suggesting that they are important in musical memory[94]. In persons with Alzheimer’s disease, the medial prefrontal cortex degenerates more slowly than other cortical regions and the regions that encode musical memory also show only minimal atrophy or decrease in glucose metabolism despite visible amyloid-beta accumulation[94].

These observations provide a potential explanation why Alzheimer patients are able to recognize and respond emotionally to familiar songs even at late stages of the disease[94].

## Conclusions and future directions

Acute care and treatment accounts for a substantial proportion of costs associated with neurological diseases, and therefore, study of novel rehabilitation strategies to replace or complement traditional methods is warranted. With this aim, the effects of music-based rehabilitation in major neurological disorders have been studied in 41 RCTs. Music interventions seem to be beneficial particularly in motor rehabilitation in PD and stroke. Additionally, music interventions can have favorable effects on cognition, mood, and QoL in stroke and dementia.

Although the majority of the reviewed studies have reported positive effects, the possibility of publication bias should be considered. In addition, only few of the primary outcomes have been studied repeatedly. Limitations involved in most studies arise from small sample sizes and methodological heterogeneity in study design and in the interventions and outcome measures used across studies. In most studies, the duration of the music-induced rehabilitation effect was not systematically evaluated and is still largely unknown. Thus far, music-based interventions have been observed to have long-term effects in stroke (3 months)[32], dementia (max. 2 months)[44,55,58], and epilepsy (12 months)[73].

In some studies, the difference between active and receptive intervention as well as the role of the music therapist (if participating) remained unclear. The therapeutic relationship inherent in formal music therapy is likely to have an additional impact on the outcome. While this aspect is difficult to delineate from the music intervention used, the outcome of an intervention given by a music therapist may in some cases be superior to that given by another health-care professional, as has been observed for RAS in gait rehabilitation[22]. However, the studies reviewed here showed that both music therapy and other music-based interventions have beneficial effects. Most of the studies lacked adequate description of the music type used. As music types can greatly vary (e.g. stimulating vs. soothing), the expected effects on physiological parameters, arousal, and affect regulation differ. Furthermore, most of the reviewed studies did not use patient-selected or favorite music. Concerning the strong emotional components of musical experience, using patient-selected music would be beneficial as it is meaningful and rewarding to the patient.

More high-quality intervention studies, particularly large-scale trials, such as cluster-randomized multicenter RCTs, where the established music interventions are embedded into the clinical rehabilitation practice, would be needed to establish their efficacy and the real-life applicability. For better comparability of the studies, it would also be important to use common outcome measures, clearly document the type of the intervention (active vs. receptive), and music used (patient-selected vs. experimenter-selected) as well as define the optimal timing and length of the music interventions and determine the long-term duration of their rehabilitation effects. In addition, multimodal studies combining behavioral outcome measures with neuroimaging and neuroendocrinological markers are needed to determine specific neurophysiological mechanisms and effects of various music-based interventions in neurological patients.

Analysis of the amount of core therapeutic activities received, such as physiotherapy and occupational therapy, suggests that stroke patients receive only approximately 60% out of the recommended rehabilitation[95]. Scarceness of rehabilitation resources is likely to exist in most neurological wards. Thus, there is room for music interventions that are widely available and could easily be realized with minimal investments. These include self- or caregiver-implemented musical activities, such as music listening, and group-based musical interventions, such as group singing or dancing.

In future, mobile music applications (e.g., music streaming, games) as well as novel music-based rehabilitation technology utilizing virtual reality or adaptive music stimulation systems tailored for motor rehabilitation, will play an increasing role in bringing music to neurological patients, in both hospital, community, and home environments.

## Contributors

A.J.S, V.L., and S.S. searched and reviewed the literature, A.J.S. created figures and tables, A.J.S. and S.S. wrote the primary manuscript, which was circulated among the other authors T.S., E.A., M.T. and V.L. All made significant additions based on their special areas of interest, which were incorporated into the final manuscript.

## Declaration of interests

The authors have no conflict of interest to declare.

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## Figures and tables

Figure 1 Cognitive, emotional and neural effects of daily music listening (Music group), audio book listening (Audio book group), and standard care (Control group) 1 week (baseline, BL), 3 months (3 m) and 6 months (6 m) after stroke. **(A)** Neuropsychological results (mean ± SEM) showing improved recovery of verbal memory and focused attention (baseline score subtracted from the values) and less depression and confusion in the Music group compared to the Audio book and Control groups. **P < 0.01, *P < 0.05 by mixed-model ANOVA. ##P < 0.05, #P < 0.1 by one-way ANOVA. Adapted from Särkämö et al. 2008. **(B)** Magnetoencephalography (MEG) group results (mean ± SEM) showing increased right hemisphere mismatch negativity (MMN) responses to pitch changes in the Music and Audio book groups compared to the Control group. Adapted from Särkämö et al. 2010. **(C)** Voxel-based morphometry (VBM) results of MRI data from left hemisphere-damaged patients (lesion areas in blue-green) showing larger grey matter volume (GMV) increases (mean ± SEM) in prefrontal and limbic areas in the Music group compared to the Audio book and Control groups. Results are shown at $p < 0.01$ (uncorrected) with ≥50 voxels of spatial extent. L = left hemisphere. Adapted from Särkämö et al. 2014.

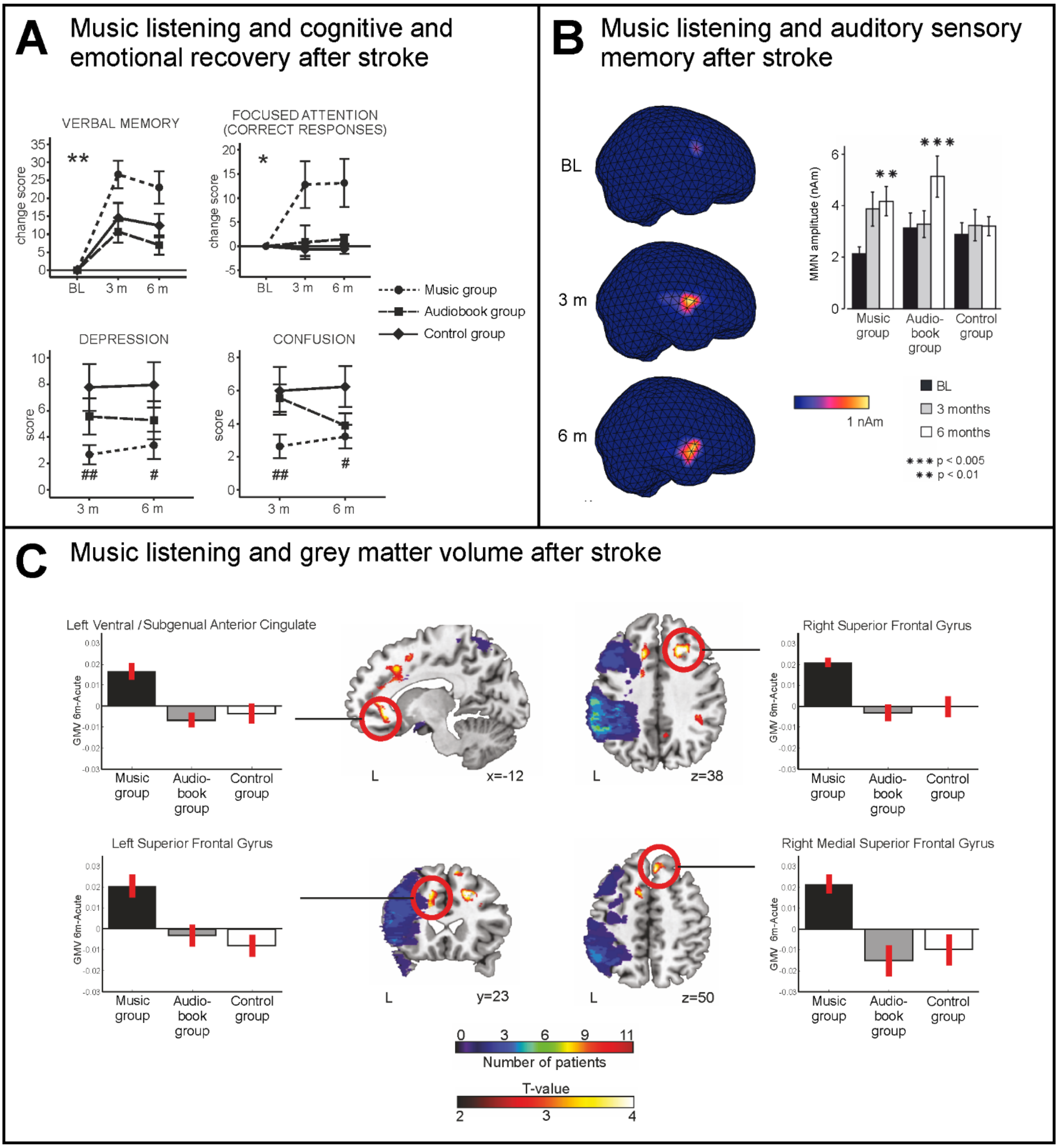

Figure 2 Schematic illustration of key brain areas associated with music processing-based neuroimaging studies of healthy subjects. Note that although the image displays the lateral and medial parts of the right hemisphere, many musical subfunctions are actually largely bilateral (with the exception of pitch and melody processing, which are lateralized, the activity in the right hemisphere being dominant). Adapted from Särkämö et al. 2013.

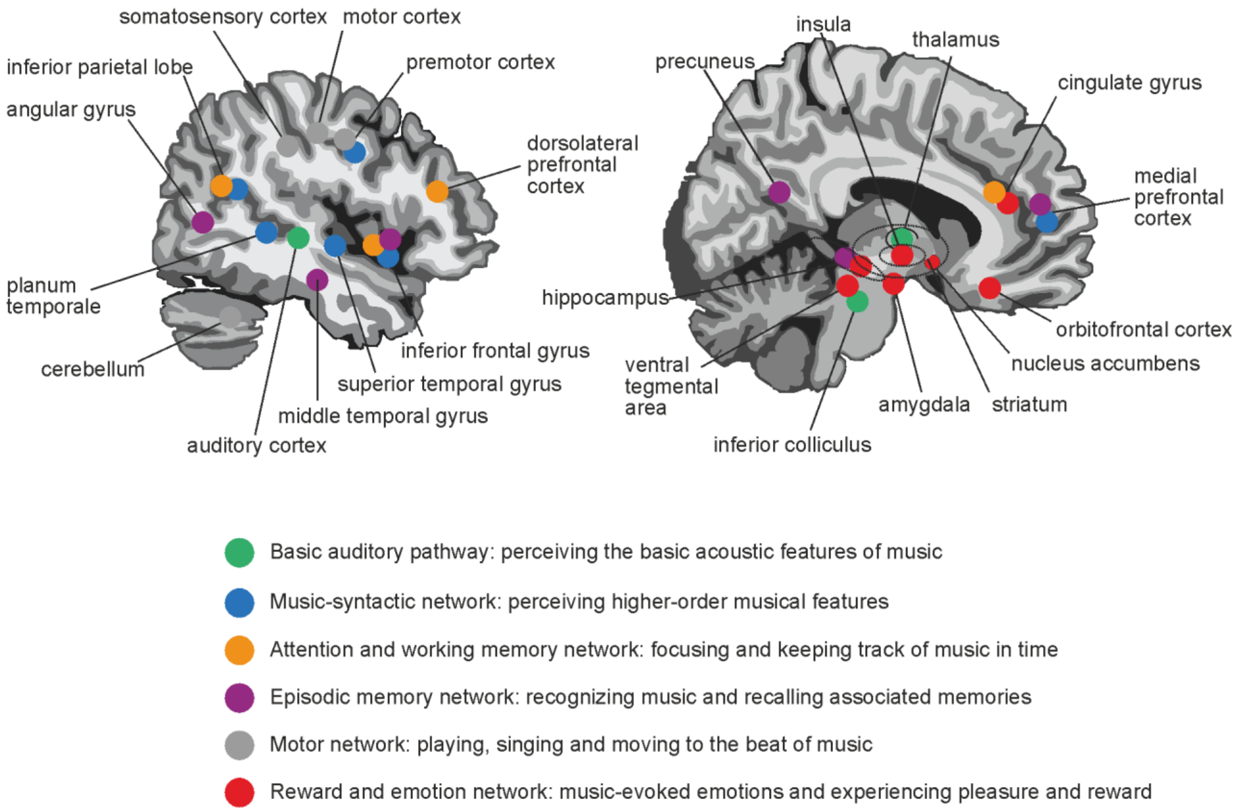

Figure 3 Schematic illustration of possible neurobiological mechanisms for underlying the rehabilitative effect of music. Orange circles and yellow arrows represent the mesolimbic system, and the green circles represent the hypothalamic–pituitary–adrenal axis (HPA-axis). ACTH = Adrenocorticotropic hormone, CORT = Cortisol, CRH = Corticotropin-releasing hormone.

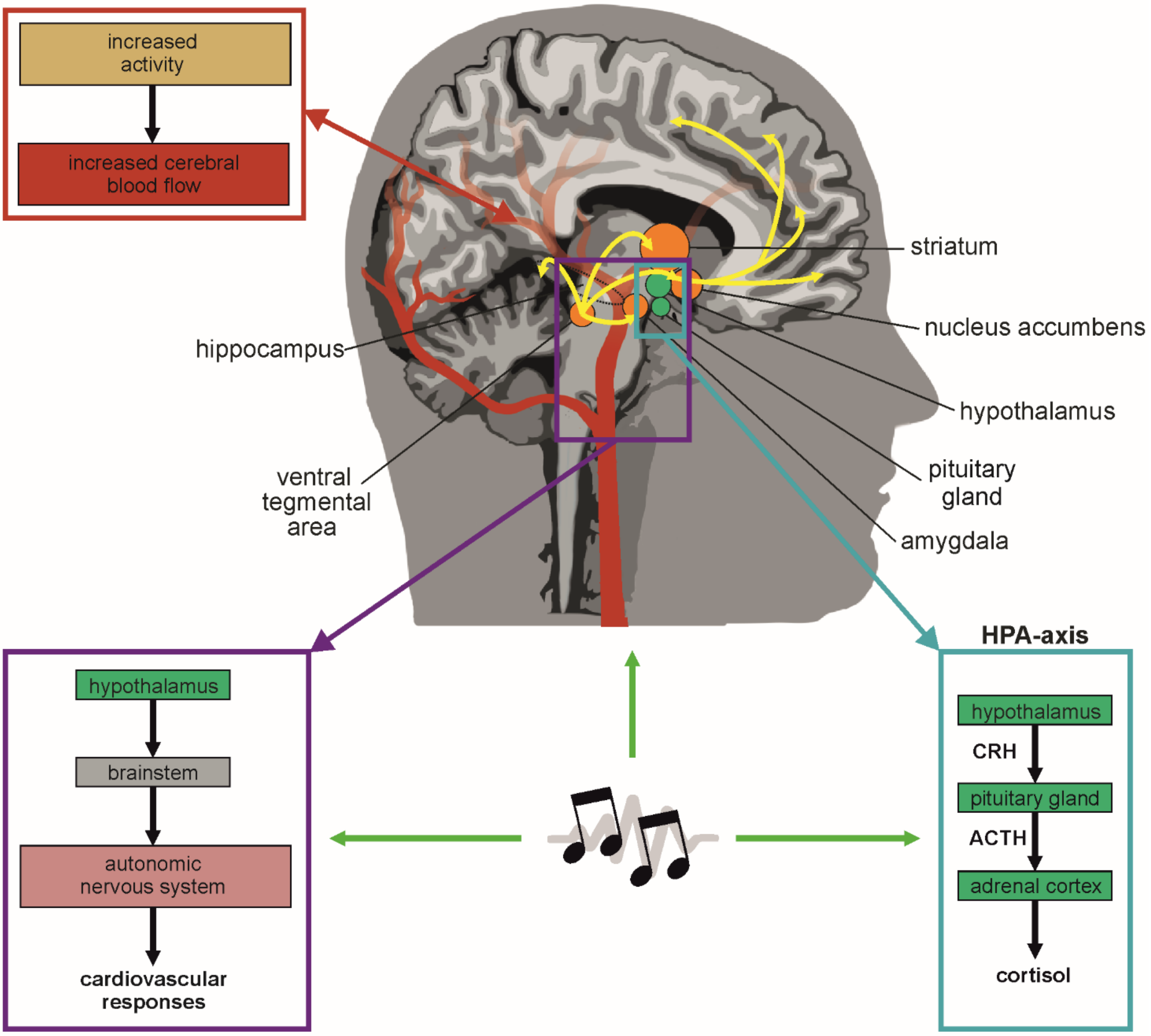
increased activity
increased cerebral blood flow
striatum
nucleus accumbens
hippocampus
hypothalamus
pituitary gland
ventral tegmental area
amygdala
HPA-axis
hypothalamus
brainstem
autonomic nervous system
cardiovascular responses
hypothalamus
CRH
pituitary gland
ACTH
adrenal cortex
cortisol

Table 1 Study characteristics.

| | Number of participants | MT involved | Blinding | Study design / Primary outcome | Overall intervention time | Main results |
|---|---|---|---|---|---|---|
| **STROKE** | | | | | | |
| van Vugt et al. (2016)[24] | 34 | No | Single | MST vs. MST with delayed sound / Hand movement. | 5 hours in 4 weeks | There were no significant differences between the groups. |
| Scholz et al. (2016)[25] | 25 | No | No | Sonificated movement vs. movement without sound / Gross motor function. | 10 days | Sonification therapy reduced joint pain (p < 0·05, d = 1·96) and improved movement smoothness (p = 0·04, d = 1·16). |
| Raglio et al. (2016)[26] | 20 | Yes | No | Singing, playing instruments, improvisation vs. speech therapy / Speech parameters in chronic aphasics. | 22·5-37·5 hours in 15 weeks | Music therapy improved spontaneous speech (p = 0·020, d = 0·35). |
| Tong et al. (2015)[27] | 33 | Yes | No | MST vs. playing mute instruments / Upper-limb motor function. | 20 sessions in 4 weeks | MST improved motor functions (p = 0·039). |
| Särkämö et al. (2014)[28] | 49 | Yes | Single | Favourite music vs. standard care / Grey matter changes associated with cognitive improvement. | 60 hours in 8 weeks | Music listening increased gray matter volume in frontal areas, limbic areas, and right ventral striatum. Reorganization in the frontal areas correlated with enhanced recovery of verbal memory, focused attention, and language skills, whereas the limbic area reorganization correlated with reduced negative mood. |
| van der Meulen et al. (2014)[29] | 27 | No | Single | MIT vs. other language intervention / Speech parameters in nonfluent aphasics. | 30 hours in 6 weeks | MIT improved the daily life communication (d = 0·76) and object naming (d = 1·73). |
| Cha et al. (2014)[30] | 20 | | No | RAS vs. intensive gait training / Postural control and gait performance. | 15 hours in 6 weeks | RAS improved balance, gait velocity, cadence, stride length and double support period on the affected side, and in stroke-specific quality of life scale. |
| Whitall et al. (2011)[39] | 92 | No | Single | BATRAC vs. normal exercise / Functional reorganization and outcome. | 18 hours in 6 weeks | There were no significant differences between the groups. |
| Särkämö et al. (2010)[31] | 54 | Yes | Single | Favourite music and audiobook listening vs. standard care / Auditory sensory memory. | 60 hours in 8 weeks | Listening to music and speech after neural damage can induce long-term plastic changes in early sensory processing. |
| Altenmüller et al. (2009)[33] | 62 | No | No | Children's music, folk songs, and tunes vs. conventional therapy / Neuroplasticity and motor recovery. | 7·5 hours in 3 weeks | MST improved motor skills showed by ARAT score (p < 0·001, d = 0·32), Arm paresis score (p < 0·05, d = 0·46), Box and Block Test (p < 0·001, d = 0·43), and Nine Hole Pegboard Test (p < 0·05, d = 0·32). |
| Särkämö et al. (2008)[32] | 54 | Yes | Single | Favourite music and audiobook listening vs. standard care / Cognitive functions and mood. | 60 hours in 8 weeks | Music listening improved verbal memory (p = 0·002, d = 0·88) and focused attention (p = 0·012, d = 0·92) compared to the audiobook and control groups. Music group also experienced less depression (p = 0·031, d = 0·77) and confusion (p = 0·045, d = 0·72) than the control group. |
| Jeong et al. (2007)[34] | 33 | No | No | RAS vs. referral information / Upper and lower limb mobility, mood, interpersonal relationships, and quality of life. | 16 hours in 8 weeks | RAS improved range of ankle extension (p = 0·018, d = 0·61) and arm flexibility up (p = 0·001, d = 0·99) and down (p = 0·008, d = 0·62), mood (p = 0·017, d = 0·03), and increased frequency and quality of interpersonal relationships (p = 0·003, d = 0·96). |
| Schneider et al. (2007)[35] | 40 | No | No | Children's music, folk songs, and tunes vs. conventional therapy / Motor recovery. | 7·5 hours in 3 weeks | Music group improved in speed, precision and smoothness of movements as well as motor control in everyday activities evaluated by ARAT (p < 0·001, d = 0·36), Arm paresis score (p < 0·05, d = 0·42), Box and Block Test (p < 0·001, d = 0·69), and Nine Hole Pegboard Test (p < 0·05, d = 0·24). |
| Thaut et al. (2007)[36] | 78 | No | Single | RAS vs. Neurodevelopmental therapy / Gait parameters. | 7·5 hours in 3 weeks | RAS improved velocity (p = 0·006, d = 2·13), stride length (p < 0·001, d = 1·50), cadence (p < 0·001, d = 1·82), and symmetry (p = 0·049, d = 0·83). |
| Schauer et al. (2003)[37] | 23 | No | No | RAS vs. gait training without musical feedback / Gait parameters. | 5 hours in 3 weeks | RAS improved gait velocity (p = 0·008, d = 0·46), stride length (p = 0·009, d = 0·49), cadence (p = 0·045, d = 0·02), symmetry (p = 0·008, d = 0·55), heel-toe distance (p = 0·006, d = 0·40). |
| Thaut et al. (1997)[38] | 20 | No | Single | RAS vs. physical therapy / Gait parameters. | 30 hours in 6 weeks | RAS improved gait velocity (d = 1·45), stride length (d = 0·93), symmetry (d = 0·52), and cadence (d = 0·44). |
| 16 studies | 664 | | | | | |

|  | Number of participants | MT involved | Blinding | Study design / Primary outcome | Overall intervention time | Main results |
|---|---|---|---|---|---|---|
| **DEMENTIA** |  |  |  |  |  |  |
| Sánchez et al. (2016)[57] | 18 | No | No | Multisensory stimulation vs. music listening / Neuropsychiatric symptoms and cognition. | 16 hours in 16 weeks | Multisensory stimulation showed positive effects on anxiety symptoms and dementia severity that were not observed in the music group. |
| Särkämö et al. (2016)[44] | 83 | Yes | Single | Music listening and/or singing vs. standard care / Emotional parameters. | 15 hours in 10 weeks | Both music listening and singing groups improved in behavioral disturbances (p = 0·04, d = 0·42) and physical signs (p = 0·008, d = 0·52) more than the control group· 6 months after the intervention, found effects were not present anymore. |
| Raglio et al. (2015)[45] | 98 | Yes | Single | Music therapy and music listening vs. standard care / Behavioral and psychological symptoms of dementia. | 10 hours in 10 weeks | There were no significant differences between the groups. |
| Hsu et al. (2015)[46] | 13 | Yes | No | Music listening, singing, improvising and talking vs. standard care / Neuropsychiatric symptoms, well-being, and carer-resident interaction. | 11 hours in 22 weeks | Music group showed improvement in symptoms (p = 0·002, d = 2·32) and in levels of wellbeing (p < 0·001, d = 3·85). Staff in the intervention group reported enhanced caregiving techniques as a result of the programme. |
| Särkämö et al. (2015)[47] | 83 | Yes | Single | Singing or music listening vs. standard care / Clinical, demographic, and musical background factors influencing the cognitive and emotional efficacy of caregiver-implemented musical activities. | 15 hours in 10 weeks | Singing was beneficial especially in improving working memory in mild dementia and in maintaining executive function and orientation in younger PWDs. Music listening was beneficial in supporting general cognition, working memory, and quality of life especially in moderate dementia not caused by Alzheimer's disease (AD) who were in institutional care. Both music interventions alleviated depression especially in mild dementia and AD. The musical background of the PWD did not influence the efficacy of the music interventions. |
| Chu et al. (2014)[58] | 100 | Yes | Single | Group music therapy vs. standard care / Mood and cognition. | 6 hours in 6 weeks | Group music therapy decreased depression (p = 0·001, d = 0·21) and delayed the deterioration of cognitive functions, especially recall (p = 0·004, d = 0·72). The effects were present 1 month after cessation of the intervention. |
| Vink et al. (2014)[48] | 76 | Yes | Single | Music therapy (listening and singing) vs. other activities / Neuropsychiatric symptoms. | 21 hours in 16 weeks | Neuropsychiatric symptoms decreased significantly in the music therapy group (p = 0·01). |
| Narme et al. (2014)[49] | 37 | - | Single | Music therapy (listening, playing and singing) vs. cooking / Patients' mood, cognition, behavioral disturbances, and on the and stress experienced by nurses. | 8 hours in 4 weeks | There were no significant differences between the groups. |
| Särkämö et al. (2014)[59] | 83 | Yes | Single | Singing or music listening vs. standard care / Quality of life, mood and cognition. | 15 hours in 10 weeks | Music listening improved the patients' mood (p = 0·001, d = 0·80), orientation (p = 0·005, d = 0·71), episodic memory (p = 0·036, d = 0·54) attention and executive functions (p = 0·039, d = 0·48), overall cognitive performance (p = 0·041, d = 0·47), and the quality of life (p < 0·001, d = 0·99). Singing resulted in additional improvement in short-term memory and working memory (p = 0·006, d = 0·75), and improved the caregiver wellbeing (p = 0·026, d = 0·85). |
| Vink et al. (2013)[50] | 77 | Yes | Single | Music listening and singing vs. other activites / Agitation. | 21 hours in 16 weeks | There were no significant differences between the groups. |
| Ceccato et al. (2012)[51] | 50 | Yes | Single | Music therapy vs. standard care / Cognition and anxiety. | 18 hours in 12 weeks | The music group improved performance in attention (p = 0·001, d = 0·76) and verbal episodic memory tasks (immediate p = 0·001 d = 0·76, delayed p = 0·001 d = 0·73), but not in anxiety. |
| Sung et al. (2012)[52] | 52 | No | No | Favourite music vs. standard care / Anxiety. | 6 hours in 6 weeks | Anxiety decreased in the music group (p = 0·004, d = 0·06). |
| Lin et al. (2011)[53] | 100 | Yes | No | Music therapy (playing and listening) vs. standard care / Agitation. | 6 hours in 6 weeks | There were no significant differences between the groups. |
| Cooke et al. (2010)[60] | 47 | Yes | Single | Music therapy (listening and playing) vs. reading / Mood and quality of life. | 32 hours in 16 weeks | There were no significant differences between the groups. |
| Raglio et al. (2010)[54] | 60 | Yes | Single | Music therapy vs. standard care / Behavioral disturbances. | 6 hours in 4 weeks | Music reduced the behavioral disturbances showed by significant group difference (p < 0·05, d = 0·63). |
| Guétin et al. (2009)[55] | 30 | Yes | Single | Music therapy vs. resting and reading / Anxiety and mood. | 5 hours in 16 weeks | Music therapy decreased anxiety (p < 0·001, d = 2·42) and depression (p = 0·002, d = 1·05). These effects persisted up to 2 months after stopping the intervention. |

|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| Raglio et al. (2008)[56] | 59 | Yes | Single | Music therapy vs. other activites / Behavioral and psychologic symptoms. | 15 hours in 16 weeks | Music therapy improved behavioral symptoms (p < 0·0001, d = 1·04), functional ability (p < 0·0001, d = 0·79), and empathetic behavior (p < 0·0001, d= 0·61) compared to the control treatment. |
| 17 studies | 1066 |  |  |  |  |  |

|  | Number of participants | MT involved | Blinding | Study design / Primary outcome | Overall intervention time | Main results |
|---|---|---|---|---|---|---|
| **PARKINSON'S DISEASE (PD)** |  |  |  |  |  |  |
| Pohl et al. (2013)[63] | 18 | Yes | Single | Music listening, rhythmic clapping or stomping vs. standard care / Motor performance, cognition, quality of life | 12 hours in 6 weeks | Music therapy improved mobility (p = 0·006), UPDRS (p = 0·003), Text re-call (p = 0·036), Item naming (p = 0·033), performance in Stroop test (p = 0·007), and Quality of life (p = 0·031). |
| de Bruin et al. (2010)[64] | 22 | No | Single | Favorite music synchronized to gait vs. regular activities / Walking parameters | 19·5 hours in 13 weeks | Walking to music improved velocity (p = 0·002, d = 2·64), stride time (p = 0·019, d = 1·76), cadence (p = 0·007, d = 2·16), UPDRS (p = 0·002, d = 0·50). |
| Hackney et al. (2009)[65] | 48 | No | Single | Tango or waltz/foxtrot vs. standard care / Functional motor control. | 20 hours in 13 weeks | Tango group improved in balance (p = 0·001, d = 2·98), 6-minute walking (p = 0·001, d = 2·50) and backward stride length (p = 0·001, d = 2·19) and Waltz/Foxtrot group in balance (p = 0·001, d = 3·17), 6-minute walking (p = 0·001, d = 2·24) and backward stride length (p = 0·018, d = 1·96). |
| Hackney et al. (2009)[67] | 61 | No | No | Tango and waltz/foxtrot vs. Tai Chi or standard care / Health-related quality of life. | 20 hours in 13 weeks | Tango improved mobility (p = 0·03, d = 2·50), social support (p = 0·05, d = 2·97), and Quality of life (p < 0·01, d = 2·09). |
| Hackney et al. (2007)[66] | 19 | No | Single | Tango vs. physical exercise / Functional mobility. | 20 hours in 13 weeks | Tango group improved in balance (p = 0·01, d = 2·18). |
| 5 studies | 168 |  |  |  |  |  |

|  | Number of participants | MT involved | Blinding | Study design / Primary outcome | Overall intervention time | Main results |
|---|---|---|---|---|---|---|
| **MULTIPLE SCLEROSIS (MS)** |  |  |  |  |  |  |
| Gatti et al. (2015)[69] | 19 | No | No | Keyboard playing vs. mute keyboard playing / Hand function. | 7·5 hours in 2 weeks | The music group improved in the functional use of the hand significantly more showed by Time x Group interaction (p = 0·003, d = 0·60). |
| Conklyn et al. (2010)[70] | 10 | Yes | No | RAS vs. standard care / Gait parameters. | 2 weeks | RAS significantly decreased double-support time (left: p = 0·018, d = 1·61; right: p = 0·025, d = 1·46). |
| 2 studies | 29 |  |  |  |  |  |

|  | Number of participants | MT involved | Blinding | Study design / Primary outcome | Overall intervention time | Main results |
|---|---|---|---|---|---|---|
| **EPILEPSY** |  |  |  |  |  |  |
| Bodner et al. (2012)[73] | 73 | No | Single | Nightly exposure of Mozart Sonata K. 448 vs. no intervention / Seizure occurrence. | Every night for 1 year | Music group significantly decreased in seizure frequency during the treatment phase (17%, p = 0·014) and even one year post-treatment (16%, p = 0·027). |
| 1 study | 73 |  |  |  |  |  |

Effect size = mean pre-post change in the treatment group minus the mean pre-post change in the control group, divided by the pooled pre-test standard deviation.[96]

Effect size was defined small when d = 0·2, medium when d = 0·5 and large when d = 0·8.

d = Effect size, BATRAC = Bilateral arm training with rhythmic auditory cueing, MIT = Melodic Intonation Therapy, MST = Music-supported Therapy, MT = Music therapist, RAS = Rhythmic auditory stimulation.

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