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Effectiveness of music-based interventions on motricity or cognitive functioning in neurological populations: A systematic review.

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ABSTRACT

INTRODUCTION: Motor and cognitive symptoms are frequent in persons with neurological disorders and often require extensive long-term rehabilitation. Recently, a variety of music-based interventions have been introduced into neurological rehabilitation as training tools.

AIM: This review aims to a) describe and define music-based intervention modalities and content which are applied in experimental studies, and b) describe the effects of these interventions on motor and/or cognitive symptoms in the neurological population.

EVIDENCE ACQUISITION: The databases PubMed and Web of Science were searched. Cited references of included articles where screened for potential inclusion. A systematic literature search up to 20th of June 2016 was conducted to include controlled trials and cohort studies that have used music-based interventions for ≥3 weeks in the neurological population (in- and outpatients) targeting motor and/or cognitive symptoms. No limitations to publication date was set.

EVIDENCE SYNTHESIS: Nineteen articles comprising thirteen randomised controlled trials (total participants N_{exp} = 241, N_{ctrl} = 269), four controlled trials (N_{exp} = 59, N_{ctrl} = 53) and two cohort studies (N = 27) were included. Fourteen studies were conducted in stroke, three in Parkinson's disease, and two in multiple sclerosis population. Modalities of music-based interventions were clustered into four groups: instrument-based, listening-based, rhythm-based, and multicomponent-based music interventions. Overall, studies consistently showed that music-based interventions had similar or larger effects than conventional rehabilitation on upper limb function (N=16; fine motricity, hand and arm capacity, finger and hand tapping velocity/variability), mobility (N=7; gait parameters), and cognition (N = 4; verbal memory and focused attention).

CONCLUSIONS: Variety of modalities using music-based interventions has been identified and grouped into four clusters. Effects of interventions demonstrate an improvement in the domains assessed. Evidence is most available for improving motricity in stroke. More studies are warranted to investigate cognition as well as motor and cognition dysfunctions in combination.

CLINICAL IMPLICATIONS: Instrument-based music interventions can improve fine motor dexterity and gross motor functions in stroke. Rhythm-based music interventions can improve gait parameters of velocity and cadence in stroke, Parkinson's disease and multiple sclerosis. Cognition in the domains of verbal memory and focused attention can improve after listening-based music interventions in stroke.

Key words: Music, music-based interventions, neurological disorders, cognitive dysfunction, motor dysfunction.

TEXT

Introduction

In recent years, music-based interventions have been increasingly investigated in the neurological rehabilitation context. The interest in music was motivated by findings of enhanced neuroplasticity induced by musical training in neuroimaging studies of healthy persons, specifically in musicians (1-5). Meanwhile, standardised music-based clinical therapeutic techniques have been described (6), such as rhythmic auditory stimulation

(RAS), therapeutic instrumental music performance, melodic intonation therapy, and musical mnemonic training. These techniques form the core of a Neurologic Music Therapy (NMT). For details we refer to the Handbook of Neurologic Music Therapy (6).

The effect of RAS has been investigated in studies that involve a single training session (immediate effects) with Parkinson subjects (7, 8), Huntington subjects (9), and Alzheimer subjects (10). As well as in studies that involve several training sessions (intervention effect) with Parkinson subjects (11-13), stroke subjects (14-19), and subjects with cerebral palsy (19). The effects of RAS, including rhythmic auditory cueing, on spatio-temporal parameters of gait (20, 21) and upper extremity function (21) have been reviewed in the neurological population, and a meta-analysis has been conducted in the stroke population (21). Overall, the reviews supported the evidence-based use of rhythmic cueing. Large effect sizes for the improvement in gait (velocity, cadence, and stride length) and upper-limb function (Fugl Meyer motor assessment of upper extremity) have been documented.

Different music-based interventions have been reported with a variety of goals and in a variety of neurological populations. So far, reviews on music-based interventions have focused on mechanisms of action and brain plasticity (22, 23), their effects on psychological symptoms in neurological populations (24), or specifically targeting interventions on mechanically ventilated patients (25, 26), cardiovascular disorders (27), dementia (28-32), dementia and palliative support for pain and anxiety (33), traumatic brain injury (34), and end of life care (35). Additionally, studies investigating music-based interventions have been conducted on coma patients (36), patients in vegetative or minimally conscious state (37), and in adolescence with brain damage (38).

The effectiveness of interventions in the context of music-based interventions has been explained in terms of auditory-motor entrainment (39), sensorimotor coupling to temporally structured auditory input, as well as the recruitment of a striato-thalamo-cortico-system, involving the basal ganglia, thalamus, premotor, supplementary motor and dorsolateral prefrontal cortex (40). The effects were found to be relevant for connecting upper and lower body segments in co-ordinated movements, symmetrically or asymmetrically (uni- or bi-manually) (23).

Besides motricity, music-based interventions have also been investigated for effects on cognitive functions. Some examples are symptoms of spatial (41), unilateral (42-44) and visual neglect (45, 46), memory in Alzheimer subjects (47), verbal memory and learning in Alzheimer subjects (48, 49) and MS subjects (50, 51). These studies showed improvements in the cognitive outcomes measured. Cognitive clinical effects have been observed in the domains of attention, memory, concentration, and learning (52, 53), where affective vocalisations have been shown to modulate attention via activation of prefrontal-limbic networks (54). These effects are seen after training with both passive (listening) and active (producing) music activities as these tasks require cognitive effort (55). In short, recent work shows that music-based clinical therapeutic techniques provide a promising evidence-based approach to the rehabilitation of a range of neurological diseases.

Yet, the content of music-based interventions and the effect on either motor or cognitive clinical or patient reported outcome measures or in combination in the neurological population has not yet been systematically reviewed.

The present review focuses on the outcome measures of motricity and cognition or in combination in neurological rehabilitation, as these symptoms are frequently present in neurological pathologies. We aim to provide an insight on the applied modalities and contents of music-based interventions in neurological conditions systematically, and to investigate its effects on motor and/or cognitive functions in comparison to control interventions.

Evidence Acquisition

In the present systematic review we investigate the effect of music-based rehabilitative interventions on either motor or cognitive dysfunctions or in combination in adult neurological patients. For the remainder of the manuscript, for grammatical accuracy, the term *'or'* is used when refering to motor '*and/or'* cognitive functions.

We included cohort studies, controlled trials (CTs) and randomised control trials (RCTs) with intervention periods of ≥ 3 weeks, as effects on motor function are mostly found with a minimum training volume of multiple weeks. Case studies were excluded, and therefore studies with < 3 participants were excluded. We also excluded studies with dementia patients, as we primarily focused on neurological rehabilitation of motor or cognitive function. Given their coverage in recent review studies (20, 21), music-labelled intervention studies based on RAS were excluded. Lastly, only studies published in English were included.

The studies considered in the present review were identified by searching electronic databases (PubMed and Wed of Science) up to the 20th of June 2016 and scanning reference lists of selected articles. The following search term was used: ((music AND (training OR intervention OR therapy)) AND (multiple sclerosis OR stroke OR Parkinson's OR traumatic brain injury OR epilepsy OR amyotrophic lateral sclerosis OR chronic quadriplegia OR motor neuron disorders)) AND (cognition OR cognitive function OR motor function OR motricity)). The search strategy is found in appendix 1.

Figure 1 shows the PRISMA flow diagram summarising the selection process of the studies. The following data were extracted for the selected studies: aims of the study, study design, participant characteristics (age, number of subjects, neurological condition, other descriptive data provided), participants' baseline motor or cognitive functions, description of interventions (name of music intervention used, description of the intervention, therapy dosage, occupation of the intervention administrator, the descriptive procedure, instruments and technologies used, detailed duration of trial period and sessions, training progression), experimental motor or cognitive outcome measures, and intervention effects.

The risk of bias in individual studies was assessed by the PEDro scale (56, 57). To minimise publication and selective-reporting biases, the key words from the titles and last author of the included studies were checked for presence on the EU clinical trials register. Similarly, a search for the study protocols alongside the published articles was conducted in Medline. Additionally, the outcome measures reported in the methodology and results sections of the publications were checked to note inconsistencies when reporting results. Lastly, authors of the included studies were contacted for the full data set where data was not reported or published in full detail.

The summary measures used to investigate intervention effects were the raw pre and post values inclusive of their SDs, statistical significance of intervention, and group by time interactions.

Evidence Synthesis

Results

Descriptive analysis

As shown in Figure 1 the literature search identified a total of 19 studies that met the inclusion criteria. Out of the 19 studies included, 14 were from stroke patients, three from Parkinson's disease patients, and two from multiple sclerosis patients. All study designs excluded patients with hearing deficits and musical expertise.

A quality assessment of the included studies using the PEDro checklist is found in the Supplementary Table a in the appendix. Overall, the included studies scored high on the PEDro scale. The items in the PEDro allocated for eligibility criteria and the random allocation of subjects was high across studies. Subject allocation concealment and blinding of assessors were often scored low, as mostly this information was missing. Two studies did not have a control group (within-subject studies) (58) and one study had a case-control design (59). Most articles provided between-group statistical comparisons, point measures, and measures of variability across the studies. Selective reporting bias was minimised as data requested was provided from three out of nine contacted authors of the included studies. Additionally, no inconsistencies were found in the included studies when comparing the outcome measures described in the methodology to those reported in the results. However, publication bias could not be verified fully, as study protocols or clinical trial registration were not available to compare the full original research protocol to the methodology reported in the publications.

Below, we present the results in three parts. In part one, the contents of the interventions are described; in part two, an overview of the applied experimental designs and outcome measures is provided. In part three, the effects of the music-based interventions on motor or cognitive functions are presented.

{Insert Figure 1.}

Figure 1. PRISMA flow diagram to summarise the study selection process.

Part 1. Content of interventions

We grouped the studies according to the actual content of the applied music-based interventions into four clusters: a) instrument-based music interventions; b) listening-based music interventions; c) rhythm-based music interventions; and d) multicomponent-based music interventions. Descriptive characteristics of subjects, type of music-based intervention, outcome measures used, and dosage parameters are presented in Table I.

A) Instrument-based music interventions. This type of intervention was applied only in stroke patients. Within this group, three types of interventions were found: music-supported therapy, an adapted form of music-supported therapy, and training using a piano.

Six studies applied "music-supported therapy" (59-64). They involved a training using two musical instruments; a piano and drum set, both equipped with a musical instrument digital interface that allowed the recording of data. This type of training targeted fine and gross motor functions in patients suffering from mild to moderate upper limb paresis after stroke. For the piano, all keys except for eight white notes of G, A, B, C, D, E, F, and G were covered. For the drums, there were eight pads of 20 cm in diameter, which were programmed to emit piano sounds of the eight notes used.

One study applied an adapted form of music-supported therapy (65), using two musical instruments, a xylophone and a wooden percussion instrument, in two conditions being muted (made of sponge material), and usual instruments. Subjects played music using sticks, and if they could not hold them independency, the sticks where fixed to the affected hand with bandages.

Three studies applied different protocols of training, using a piano. The first study used a touch sensitive Yamaha 155 piano keyboard (58), where a visual display cued the sequences of key presses required to produce each melody by showing blue dots falling from the upper part of the screen down to the correct key on a virtual keyboard. After each cue, the program paused until the correct key was pressed by the participant before moving on. Moreover a home-based training was also included, using the Hand Roll Piano, 61K (a roll-up flexible piano). Subjects were asked to reproduce short sequences of the practiced pieces at home. The second study used a light touch M-key V2 musical instrument digital interface controller keyboard (66). The subjects played a simple set of children's songs, and the main emphasis of the songs was set to use a large variation of finger movement exercises. The study further investigated if there were differences in playing the pieces together in a group, or each individual in turn. The third study used a keyboard, which had numbered coloured adhesive labels applied on the keys. Subjects had to produce music by performing a sequence of finger movements. The sequences were also available in front of each participant. In total, 46 exercises were used. This study made use of the keyboard, but investigated producing music with the keyboard sound turned on and off (67).

The average training dosage of the interventions in this cluster was 16{range 9-20} sessions each 39 {30-90} minutes, for 3 {3-4} weeks, and a total of 8.4 {5-10} hours. Progression was used in both trainings in the form of increasing the difficulty of musical pieces, by increasing the variety of finger or hand movements (to play the piece), the tempo and the velocity. Moreover, the cognitive load during training was further increased by the request to learn and play new pieces of music.

B) Listening-based music interventions. Only one study used music listening as an intervention and it was conducted on a population of stroke patients (68). The intervention focused on subjects listening to musical pieces using portable music players, in comparison to listening to storytelling via audio books and standard care. The training protocol used was 60 minutes daily sessions, for 8 weeks, totalling 60 hours. No form of progression was present.

C) *Rhythm-based music interventions.* This cluster contains all studies in which the subject's motor actions were reactive to music that served as an auditory stimulus. Three studies were found to use this form of intervention in Parkinson's disease patients (69) and stroke patients (70).

Two studies provided the subjects with a portable music player, where the tempo of individualised pieces of music was adjusted to approximately ±10% of the subject's spontaneous cadence during gait. The subjects were then asked to walk while listening to the pieces.

One study focused on upper extremity rehabilitation (71), which entailed using a custom designed bilateral arm trainer apparatus, consisting of two independent T-bar handles that move in the transverse plane. The apparatus was located perpendicular to the participant who used it by sitting in front of the trainer in the following position: neutral ankle position, knees and hips placed at 90, neutral shoulder position, elbows in 60° flexion, and neutral wrist position. The subjects then pushed the handles away and then pulled them towards the body, in synchrony with an auditory metronome.

The average training protocol for these interventions were 23 {range 20-30} minutes per session for 8 {3-13} weeks, with a total amount of 10 {5-19.5} hours. In the first two studies, progression was present in the form of adjusting the musical pieces' tempo to the subject's changed spontaneous cadence. In the literature, the terminology to describe the interventions were walking to music and musical motor feedback, respectively.

D) Multicomponent-based music interventions. In this cluster, we identified five studies (72-76) that applied interventions including different music components: The Ronnie Gardiner Rhythm and Music Method© in Parkinson's disease patients (72), Nordoff Robbins approach in multiple sclerosis patients (73), active music therapy in Parkinson's disease patients (74), and both music movement therapy (75) and theory-driven music and movement program (76) in a population with stroke patients. Progression was not present within this cluster except in the Ronnie Gardiner Rhythm and Music Method©. This method focused on exercises that challenge cognition and sensorimotor control to improve mobility and co-ordination in patients with neurological deficits, using rhythm and music.

One study (72) comprised of three phases. The first and last phases were five minutes of breathing and stretching exercises while listening to relaxing music. The second phase lasted 50 minutes, and commenced with simple rhythmic exercises like handclapping to music, in order to feel the beat. Hand-claps and foot-stomps to the selected music with the left and right hand or foot were then performed. While doing this, the subjects followed specific notes in the form of symbols that were projected against the wall. These symbols were (a) of different shapes (hand or feet) (b) coloured red (left side of body) or blue (right side of body) (c) accompanied by specific sound expressions. These were termed choreoscores. Specific choreoscores of notes were then projected against the wall with rhythmical cues, and subjects were asked to follow these scores by producing movements. The progression was set by the complexity of the choreoscores.

The remaining four studies (73-76) used a combination of different facets of music to produce creative forms of therapy. These studies consisted of listening to music, singing, playing percussion instruments (such as the tambourines and maracas), and producing rhythmic movements with the upper and lower extremities. In all interventions, the music material was popular music familiar to the subjects. The average training protocol of the interventions in this cluster were 15 {range 6-39} weeks, 84 {60-120} minutes per session for a total of 17 {10-24} hours.

For an overview of descriptive characteristics of the experiemntal and control groups, type, frequency, duration and volume of the intervention, please refer to the Supplementary Table b in the appendix .

Part 2. Experimental designs and outcome measures

Experimental designs

Of the 19 studies, two were cohort studies (58, 71), four were controlled trials (60, 61, 73, 75), and thirteen were randomised controlled trials (59, 62-70, 72, 74, 76). Five randomised controlled trials differed in design: one used two experimental groups, where the first underwent the music-based intervention in a group setting and the other in an individual setting (66). Two studies used a three-arm randomised controlled trial design (63, 68), comparing the music intervention to another control intervention as well as to standard care. Two studies used a muted and a non-muted (usual) instrument design (65, 67). Furthermore, in one study the music-based intervention was investigated on single motor and dual cognitive-motor tasks for both the experimental and control groups (69).

All interventions targeted either the motor component, cognitive component, or both. The outcome measure selection in the studies was based on the parameters that were expected to improve, following specific trainings. One study used exclusively cognitive outcome measures (68), while three studies used both motor and cognitive outcomes (59, 72, 73). The remaining thirteen studies used only motor outcome measures (58, 60-64, 66, 69, 70, 74-76).

Outcome measures

In total, 14 studies (one with Parkinson's disease patients, one with MS patients, and the rest with stroke patients) used exclusively motor outcome measures. For the upper limb, these were the Box and Block Test (58, 59, 61-64), Nine Hole Peg Test (58, 59, 61-64, 66, 67), Action Reach Arm Test (59, 61-64), Finger to Nose Test (58), Jebsen Hand Function Test (58) and Arm Paresis Score (59, 61-64), Jamar grip and pinch dynamometer (67). In addition, computerised movement analysis was used to quantify finger and hand tapping frequency and velocity, supination-, pronation- reaching frequencies, velocities and distances (60, 62-64, 66). These measures were mainly used in the studies that applied instrument-based music interventions (Cluster A).

For mobility, the outcome measures used were timed up and go test (72) and spatio-temporal gait parameters, specifically velocity, stride length and time, double support, cadence, and symmetry deviation (69, 70). These measures were used in the studies that applied rhythm-based music interventions (Cluster C). Lastly, the studies that applied multicomponent-based music interventions (Cluster D) made use of other outcome measures, such as the posture-locomotion-manual test (72), goniometric measurement of range of motion of shoulder (71, 75, 76) and elbow flexion (71, 75), hip flexion (75) and ankle flexion and extension (76), as well as muscle strength (71, 75) and upward and downward reach as a measure of flexibility (76). Disease-specific outcomes used were the Expanded Disability Severity Scale for MS patients (73) the motor score of the unified Parkinson's disease rating scale part III for Parkinson's disease patients (69, 74), the Fugl-Meyer motor assessment scale (65, 71) and the Wolf motor function test (65, 71) for stroke patients. Additionally, the ABILHAND was used in one study (67).

Four studies used exclusively cognitive outcome measures using neuropsychological batteries to test for verbal memory, short-term and long term working memory, language, music cognition, visuospatial cognition, executive function, and focused and sustained attention. These measures were mainly used in the studies clustered in instrument-based (59), listening-based (68), and multicomponent-based music interventions (72, 73).

Table I.- Descriptive characteristics of subjects, type of music-based intervention, outcome measures used and dosage parameters.

{Insert Table I}

Part 3. Effects of music-based interventions on motricity or cognition

The effects of the different music-based interventions on motor or cognitive outcomes are shown in detail in Tables II and III. In Cluster A, the experimental groups who underwent music-supported therapy (60-64) for stroke resulted in significant differences in the finger and hand tapping frequency and velocity tests, action research arm test, nine hole peg test, box and block test and arm paresis score compared to those who received conventional therapy (59, 62-64). In this cluster, one study which also used cognitive outcomes showed improvements on the trail making test A, Stroop test C and the Rey auditory verbal learning test (A1-A5) in the experimental group compared to controls who did not receive any music therapy (59). Moreover, the experimental groups in the remaining studies in this cluster showed significant improvements on upper extremity measures compared to control groups not receiving a music-based intervention (58, 59, 61).

In Cluster B, the music listening group showed significant improvements over the controls (both audiobook and no intervention groups) in the domains of verbal memory and focused attention (68). Verbal memory was assessed by the story recall subtest of the Rivermead Behavioural Memory Test and a word list learning task. Focused attention was assessed by summed correct responses and summed reaction times of the CogniSpeed mental subtraction and Stroop subtests (68).

Within Cluster C, significant differences were found in gait velocity, stride time and cadence in the experimental groups, while no significant changes were found in the control groups (those who did not receive a music based intervention) (69, 70).

In cluster D, the study using Ronnie Gardiner Rhythm and Music Method© showed significant improvements in the music-based experimental group on posture-locomotion manual movement time, unified Parkinson’s disease rating scale part III, naming 30 items and Stroop test (72), while no changes were observed in the control group. In the remaining studies in this cluster, the experimental groups also showed significant improvements in degrees of range of motion of shoulder, elbow, and hip flexion (75) as well as ankle extension and increased flexibility of arms (76). Moreover, the unified Parkinson's disease rating scale part III score, bradykinesia factor, and rigidity factor improved in the music-based experimental group, while no changes were observed in controls not receiving an intervention (74).

The study that used two instrumental groups, one playing music in turn and the other together in a group, revealed a significant improvement for the nine hole peg test for both groups. However no significance group x time interaction was found, indicating no superiority of simultaneous or individual music playing (66). For the studies using conditions of mute and non-mute instrument playing found a significant group x time interaction in the ABILHAND (67), nine hole peg test (67) and Fugl-Meyer motor assessment of the upper extremity (65).

To summarise, the vast majority of the studies demonstrated significant effects of the interventions on the motor or cognitive outcomes measures within the experimental (music-based intervention) groups compared to the control groups (not receiving music as an intervention). Moreover, evidence is most available for improving motricity in stroke studies.

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

{Insert Table II.}

Table III**.-** Effect of the interventions in the three armed randomised control trials.

{Insert Table III}

Discussion

Our analysis of the selected studies reveal that music-based interventions have a strong clinical potential for the rehabilitation of motor or cognitive functions in the neurological population. Specific interventions have a tendency to be applied to a specific pathology group. Of all such groups, it appears that most evidence is available for improving motricity in stroke patients. One needs to be cautious for over-interpreting the beneficial effects of the interventions given the potential impact of spontaneous recovery. This is however taken into account by the experimental designs of the selected studies (inclusion of a control group) or the phase of the stroke. Additionally, one may hypothesize an under-estimation of the effect for the degenerative diseases MS and Parkinson's given its progressive nature. However, since the intervention period reported was relatively short and the presence of control groups, it would be very unlikely that disease progression would have importantly hampered a correct interpretation of our results.

A lot of variability was found in the type of music-based interventions applied as well as in the outcome measures. Therefore, to facilitate interpretation of intervention of effects, and for simplicity of explanation, we have grouped all selected studies into four clusters according to the content of music-based intervention: instrument-based (Cluster A), listening-based (Cluster B), rhythm-based (Cluster C) and finally multicomponent-based (Cluster D) music interventions.

The different types of interventions and contents throughout the included studies prevented us from comparing the effects of the music-based interventions between these studies. However, we found that each study yielded positive promising results in the motor or cognitive outcome measures assessed, and mostly the music interventions even showed superiority over conventional therapy or no intervention. As such, this review is providing support for implementing elements of music-supported rehabilitation in the neurological field. However, it should be noted that the outcome measures selected were specific to the symptom and/or to the pathology that was targeted. Therefore, the results are not generalizable for all studied motor or cognitive functioning or for all studied neurological conditions. For example in stroke, instrument-based interventions (Cluster A) were used in order to train fine and gross motor hand co-ordination (62, 63), with only one study measuring cognitive function as well (59), while listening (Cluster B) was used to improve cognitive dysfunction (68). In Parkinson's disease, the main interventions focused on motor functions specific to gait by using rhythmic based interventions (Cluster C) (69), whilst in multiple sclerosis, both interventions were used (73, 77).

The multicomponent-based interventions (Cluster D) made use of different aspects of music such as singing, moving to music, and playing to a rhythm on percussion instruments such as tambourines. These interventions are very difficult to standardize or compare with other interventions, due to their unstructured and improvisation-based content (73-76). Yet, when the music group was compared to their respective control group in each study within this cluster, positive effects of the intervention favoured the music group on motor or cognitive outcomes that were assessed. It is even conceivable that the applied music-based interventions could have had even more effects on motor or cognitive functioning than what were reported with the targeted outcome measures used in the studies. For example, studies applying bimanual training on the piano, or walking to the auditory stimuli of music also did not respectively use outcome measures for bimanual coordination and dexterity, or sophisticated methods for balance.

Our review's results correspond with the discussions of previous non-systematic reviews (22, 23), that is of using music supported therapy, rhythmic auditory stimulation, and listening to music as standardised therapies to improve motor deficits and psychological status. Our review differed from these by the use of systematic methodology with a defined inclusion criteria and key words. We aimed at providing a comprehensive review, not only on the effects of clinical motor or cognitive outcome measures in the neurological population, but also of detailed contents of music-based interventions (type, method, frequency, duration, etc.). This was in order to facilitate future planning of the study design (specifically of the music components), as well as determining the outcome measures that could be used.

A potential limitation of the present review, is that we did not calculate effect sizes or performe a meta-analysis in favour of music-based compared to non-music-based interventions. This was a deliberate decision because in the studies selected for this review, there was heterogeneity in the (a) modality of music intervention and (b) outcome measures used to determine effects of the intervention, (c) variation in number of participants included in studies, and because (d) some studies included multiple music groups (for both experimental and controls), or had more than one control group. Other limitations were related to the small sample size of studies (61, 72, 73). Dropout rates in the music-based groups were overall very small when the therapy was conducted for the duration of less than two months. An explanation could be due to the participants' increased motivation and confidence in the ability to play music (62). For example, in one study (67), an observation of the therapist providing the intervention was that the pleasure of playing a musical instrument pushed participants to confidently use their hands in everyday life activities. Moreover, the therapists noted that the enthusiasm of the participants in the first session did not decrease over other sessions. Finally, it is important to take into account potential biases, such as within-study, publication, or self-selection bias. In our review, we have taken measures to limit these biases as described in the methodology and results.

Music-based interventions can be integrated in a clinical program with a possibility of individualization and personalization of the therapy (the choice of the intervention), as well as modification to use progression in the therapy. Detailed recommendations cannot be inferred from our analysis, as the review showed (a) variations in intervention modalities and inconsistency of training frequency, duration, and dosage as well as (b) variations in the pathologies investigated. However, we believe that useful insights can be deduced for practical applications. For example, if one applies instrument-based music intervention, then the motor components trained through the process of producing the music would be: strength, co-ordination, and fine motricity, for both uni- and bimanual dexterity. The cognitive components involved in the process of acquiring this new skill would be in the domains of: memory, learning, attention, information processing speed, and executive functions.

Music-based interventions may also be relevant for training cognitive-motor interference, which is often prevalent in neurological diseases (78-80). This is important given the fact that parallel executive deficits often interfere with the effective rehabilitation of cognitive (81) or motor impairments (82). Music-based interventions can be used as a dual-task training, apart from providing simple training of motricity or cognition. To demonstrate components of the dual task, using the example above in the instrument based-music intervention, the action of physically producing music (use of the motor system to move, e.g., the fingers) is performed simultaneously with auditory stimuli processing or visual stimuli processing (use of the cognitive system for the acquisition of the new skill and processing of the new musical information, such as rhythm or pitch). This is relevant as large cognitive-motor interferences resulting from dual tasks were shown in many neurological conditions and were associated with risk of falls (83, 84).

Although the clinical effects of music-based interventions are promising, as shown in this review, further research is needed to better understand the principles of how music interacts with motricity or cognition. For that reason, it is important to work towards controlled study designs in which the effects of identical motor training program performance with and without music are compared. Moreover, in the field of systematic musicology, musical activity has been proposed to strengthen learning, as expressive interaction occurs with music, which in turn is motivating and rewarding (86). Therefore, it would be relevant to consider investigating the effect of different types of auditory stimuli (music and metronome) on motor or cognitive outcomes (or in combination) in neurological conditions which differ in pathophysiological mechanisms.

Conclusion

Based on our review, we conclude that music-based interventions applied to patients with neurological diseases lead to positive results in their motor or cognitive functions. There is growing evidence in that music may directly promote neuroplasticity (87-89) through increased activation of auditory-motor, cortico-spinal pathways (90, 91) and mesolimbic dopaminergic pathways (87, 92, 93). To further investigate this hypothesis, it is important to apply comparative experimental designs and to use neuroimaging techniques investigating the neurophysiological processes of music-based interventions, as is currently investigated in music supported therapy (59, 91) and music listening (94). Finally, it is likely that music therapy enhances psychological well-being and that it provides motivational assets (95) that influencing the motor training intensity during and perhaps even after the training sessions.

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Table I. - Descriptive characteristics of subjects, type of music-based intervention, outcome measures used and dosage parameters.

Table II. - Effect of intervention, comparison of experimental and control groups in included studies.

Table III. - Effect of the intervention in the three armed randomised controlled trials.

Supplementary Table a. - Quality assessment of the included studies using the PEDro checklist.

Supplementary Table b. - Descriptive characteristics of experimental and control groups, type, frequency, duration and volume of the intervention.

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Figure 1. - PRISMA flow diagram to summarise the study selection process.

Table I. - Descriptive characteristics of subjects, type of music-based intervention, outcome measures used and dosage parameters.

AUTHOR AND YEAR OF PUBLICATION	NEUROLOGICAL DISEASE	AGE	NUMBER OF PARTICIAPNTS	MUSIC-BASED INTERVENTION	MAIN OUTCOME MEASURE			TRAINING PROGRESSION	TRAINING FREQUENCY, INTENSITY AND VOLUME
					COGNITIVE	UPPER LIMB	LOWER LIMB		
CLUSTER A **INSTRUMENT-BASED MUSIC INTERVENTIONS**									
VILLENEUVE ET AL., 2014[58]	Stroke	60	13	Piano playing		●		Yes	3x/week for 3 weeks. 60’/session for 9 sessions. Total duration (h): 9h
VAN VUGT ET AL., 2014[66]	Stroke	65.6±10.5	14	Piano training		●		Yes	For 3-4 weeks, 60-120’/session for 10 sessions. Total duration (h): 5h
GATTI ET AL., 2015[67]	MS	43.3 ± 8.8	19	Piano playing		●		Yes	5x a week, for 3 weeks, 30' session for 15 sessions, total duration: 7.5h
GRAU-SANCHEZ ET AL., 2013[61]	Stroke	61.9±9.8	9	Music-supported therapy		●		Yes	For 4 weeks, 30’/session for 20 sessions. Total duration (h): 10
AMENGUAL ET AL., 2013[60]	Stroke	59.05±9.05	20	Music supported therapy		●		Yes	For 4 weeks, 30’/session for 20 sessions. Total duration (h): 10
ALTENMULLER ET AL., 2009[62]	Stroke	55.7±12.3	32	Music-supported therapy		●		Yes	For 3 weeks, 30’/session for 15 sessions. Total duration (h): 7.5
SCHNEIDER ET AL., 2007[64]	Stroke	58.1±9.9	20	Music-supported therapy		●		Yes	For 3 weeks, 30’/session for 15 sessions. Total duration (h): 7.5
SCHNEIDER ET AL., 2010[63]	Stroke	55.7±12.3	32	Music-supported therapy		●		Yes	For 3 weeks, 30’/session for 15 sessions. Total duration (h): 7.5
RIPOLLES ET AL., 2015[59]	Stroke	59.1 ± 9.04	20	Music-supported therapy	●	●		Yes	For 4 weeks, 30' session for 20 sessions, total duration: 10h
TONG ET AL., 2015[65]	Stroke	50.1 ± 14.8	30	Adapted music-supported therapy		●		Yes	for 3 weeks, 30' session for 20 sessions, total duration: 10h
CLUSTER B **LISTENING-BASED MUSIC INTERVENTIONS**									
SARKAMO ET AL., 2008[68]	Stroke	56.1±9.6	20	Music listening	●			No	Daily for 8 weeks. 60’/session. Total duration (h): 56

AUTHOR AND YEAR OF PUBLICATION	NEUROLOGICAL DISEASE	AGE	NUMBER OF PARTICIPANTS	MUSIC BASED INTERVENTION	OUTCOME MEASURE			TRAINING PROGRESSION	TRAINING FREQEUNCY, DURATION AND VOLUME
					Cognitive	Upper limb	Lower limb		
CLUSTER C **RHYTHM-BASED MUSIC INTERVENTIONS**									
SCHAUER & MAURITZ, 2003[70]	Stroke	59±12	18	Musical motor feedback			●	No	5x/week for 3 weeks. 20'/session for 15 sessions. Total duration (h): 5h
DE BRUIN ET AL., 2010[69]	Parkinson's Disease	64.1±4.2	16	Walking to music			●	No	3x/weekly for 13 weeks. 30'/session for 39 sessions. Total duration (h): 19.5.
WHITALL ETL AL., 2000[71]	Stroke	63.8 ± 12.8	14	Bilateral Arm Training with rhythmic cueing		●		No	For 6-9 weeks, 20' session for 18 sessions, total duration: 6h
CLUSTER D **MULTICOMPONENT-BASED MUSIC INTERVENTIONS**									
POHL ET AL, 2013[72]	Parkinson's Disease	68.2±5.1	12	The Ronnie Gardiner Rhythm and Music Method© (RGRM™)	●	●	●	Yes	2x/weekly for 6 weeks. 60'/session for 12 sessions. Total duration (h): 12h.
ALDRIDGE ET AL., 2005[73]	MS	29-47 (range)	10	Nordoff Robbins approach	●	●	●	No	Weekly, 60'/session for 8-10 sessions. Total duration (h): 10
PACCHETTI ET AL., 2000[74]	Parkinson's Disease	62.5±5	16	Active music therapy		●	●	No	1x/week for 12 weeks. 120'/session. Total duration (h): 24
JUN, ROH, & KIM, 2013[75]	Stroke	60.7±8.59	20	Music movement therapy		●	●	No	3x/week for 3 weeks. 60'/session for 8 weeks. Total duration (h): 24
JEONG & KIM, 2007[76]	Stroke	58.0±7.192	16	Theory-driven music and movement program		●	●	No	1x/week for 8 weeks. 120'/session. Total duration (h): 16

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDY	STUDY DESIGN	CLINICAL MEASURES	EXPERIMENTAL			OTHER INTERVENTION			P BETWEEN GROUP	P GROUP X TIME INTERACTIONS
			Pre	Post	p Group	Pre	Post	p Group		
VAN VUGT ET AL., (2014)[66]	RCT	NHPT(s)	72.4 ± 32.8	58.6 ± 31.3	<0.001	57.5 ± 36.8	51.8 ± 34.5	<0.001	0.065	ns
		IF TS(s)	500.1 ± 302.9	391.9 ± 186.5	ns	377.7 ± 116.1	377.7 ± 173.5	ns	ns	ns
		IF TV(%)	20.3 ± 19.8	19.2 ± 14.7	ns	33.7 ± 30.8	17.5 ± 12.8	ns	ns	ns
		MF TS(s)	598.5 ± 347.4	488.9 ± 281.3	ns	414.2 ± 112.8	398.9 ± 176.2	ns	ns	ns
		MF TV(%)	17.2 ± 9.9	20.2 ± 11.9	ns	30.2 ± 19	20.1 ± 13.5	ns	0.08	ns
GRAU-SANCHEZ ET AL., (2013)[61]	CT	ARAT(0-57)	37.7 ± 21.8	45.5 ± 5.35	<0.05	57 ± 0	57 ± 0	ns	NR	NR
		Arm paresis score(n)	5 ± 2.5	5.7 ± 1.8	<0.05	7 ± 0	7 ± 0	ns	NR	NR
		BBT(n)	28.4 ± 19.5	33.7 ± 23.09	<0.05	62.2 ± 10	68 ± 8.6	ns	NR	NR
		NHPT(s)	4.7 ± 4.1	4.7 ± 3.8	ns	9 ± 0	9 ± 0	ns	NR	NR
AMENGUAL ET AL., (2013)[60]	CT	ARAT(0-57)	42.19 ± 13.5	46.65 ± 10.2	<0.001	57 ± 0	57 ± 0	NR	<0.001	NR
		FREQ FT(cycle/s)	1.71± 0.58	2.16 ± 0.83	<0.05	3.81 ± 0.89	3.7 ± 0.96	ns	ns	ns
		Vmax FT (deg/s)	603 ± 392	737 ± 574	ns	748 ± 253	648 ± 121	ns	<0.05	ns
		NIV FT(n)	2.03 ± 2.1	2.1 ± 1.6	ns	1.3 ± 0.29	1.12 ± 0.71	ns	<0.001	ns
		FREQ HT (cycle/s)	1.86 ± 0.8	2.4 ± 0.9	ns	3.9 ± 1.3	3.94 ± 1.4	ns	<0.05	ns
		Vmax HT (deg/s)	690 ± 527	669 ± 283	ns	1223 ± 520	1421 ± 584	ns	<0.05	ns
		NIV HT(n)	2.87 ± 1.5	2.25 ± 1.9	0.01	1.32 ± 0.34	1.29 ± 0.39	ns	<0.05	<0.05
		FREQ PS (cycle/s)	1.47 ± 1.57	1.12 ± 0.46	ns	2.26 ± 0.82	2.56 ± 0.89	ns	<0.05	<0.05
		Vmax PS (deg/s)	640 ± 434	734 ± 508	ns	1121 ± 503	1180 ± 602	ns	<0.05	ns
		NIV PS(n)	2.46 ± 2.2	2.79 ± 2.07	ns	1.56 ± 0.91	1.41 ± 0.79	ns	<0.001	ns
ALTENMULLER ET AL., (2009)[62]	RCT	FREQ FT(Hz)	2 ± 1.4	2.8 ± 1.5	NR	1.6 ± 1.4	1.6 ± 1.5	NR	NR	<0.001
		Vmax FT (deg/s)	160.2 ± 105.5	216.9 ± 105.1	NR	126.8 ± 112.1	112.7 ± 114	NR	NR	<0.05
		NIV FT(n)	1.7 ± 0.3	1.3 ± 0.3	NR	2.1 ± 0.4	2.4 ± 0.4	NR	NR	<0.05
		FREQ HT (Hz)	1.8 ± 1.4	2.4 ± 1.6	NR	1.5 ± 1.4	1.4 ± 1.6	NR	NR	<0.05
		Vmax HT (deg/s)	102.5 ± 80.1	158.9 ± 152.8	NR	100.6 ± 110.8	67 ± 72.1	NR	NR	<0.05
		NIV HT(n)	1.9 ± 0.3	1.5 ± 0.3	NR	2.5 ± 0.4	2.9 ± 0.4	NR	NR	<0.05
		FREQ PS (cycle/s)	1.2 ± 0.8	1.6 ± 1	NR	1.2 ± 1.1	1.2 ± 1.1	NR	NR	ns

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDIES	STUDY DESIGN	CLINICAL MEASURES	EXPERIMENTAL			OTHER INTERVENTION			*P* BETWEEN GROUP	*P* GROUP X TIME INTERACTIONS
			Pre	Post	P Group	Pre	Post	P Group		
CONTINUED		Vmax PS(deg/s)	398.8 ± 354.7	420.8 ± 298.7	NR	423.1 ± 462.2	395.5 ± 380.5	NR	NR	ns
		NIV PS(n)	2 ± 0.3	1.5 ± 0.3	NR	2.3 ± 0.4	2.3 ± 0.4	NR	NR	<0.05
		V2 target movement 5cm (mm/s)	456.7 ± 232.1	614.1 ± 276.8	NR	479.4 ± 373.9	463.1 ± 373.6	NR	NR	<0.001
		V2 target movement 0.8cm (mm/s)	487.5 ± 243.4	596.9 ± 284	NR	464.4 ± 366.8	451.3 ± 363.3	NR	NR	<0.05
		ARAT(n)	33.3 ± 23.9	41.4 ± 17.6	NR	36.4 ± 23.3	36.9 ± 23.3	NR	NR	<0.001
		Arm paresis score(n)	4.5 ± 2.8	5.9 ± 1.8	NR	4.7 ± 2.8	4.8 ± 2.8	NR	NR	<0.05
		BBT(n)	25.12 ± 17.6	35.1 ± 18.3	NR	30.8 ± 21	32.5 ± 20.9	NR	NR	<0.001
		NHPT(s)	4.1 ± 4	5.4 ± 3.5	NR	4.9 ± 4.1	4.9 ± 4.1	NR	NR	<0.05
SCHNEIDER ET AL., (2007)[64]	RCT	Arm Paresis Score(n)	5.3 ± 2.3	6.5 ± 0.7	<0.05	4.4 ± 2.9	4.5 ± 2.9	ns	NR	<0.05
		BBT(n)	25 ± 15.7	39.3 ± 16.4	<0.001	27.6 ± 21.3	28.9 ± 21.5	ns	NR	<0.001
		NHPT(s)	4.9 ± 4.3	6.1 ± 3.7	<0.05	4.15 ± 4.4	4.3 ± 4.2	ns	NR	<0.05
		FREQ FT(cycle/s)	NR	NR	<0.001	NR	NR	ns	NR	<0.001
		NIV FT(n)	NR	NR	<0.05	NR	NR	ns	NR	<0.05
		Vmax FT(deg/s)	NR	NR	ns	NR	NR	ns	NR	<0.05
		FREQ HT(cycle/s)	NR	NR	<0.001	NR	NR	ns	NR	<0.001
		NIV HT(n)	NR	NR	<0.05	NR	NR	ns	NR	<0.05
		Vmax HT(deg/s)	NR	NR	ns	NR	NR	ns	NR	<0.05
		Vmax HT(deg/s)	NR	NR	ns	NR	NR	ns	NR	<0.05
SCHAUER ET AL., (2003)[70]	RCT	Gait velocity (m/s)	0.64 ± 0.30	0.81 ± 0.29	<0.05	0.77 ± 0.30	0.80 ± 0.29	ns	NR	NR
		Stride length (m)	0.84 ± 0.30	0.99 ± 0.33	<0.05	0.96 ± 0.30	0.96 ± 0.32	ns	NR	NR
		Gait cadence (stride/min)	45.5 ± 8.5	47.6 ± 8.7	ns	46.5 ± 7.6	48.5 ± 7.8	<0.05	NR	NR
		Symmetry deviation (%)	17.1 ± 16.6	7.1 ± 6.0	<0.05	10.5 ± 11.8	8.4 ± 9.7	ns	NR	NR
		Heel-on-toe-off distance (mm)	68.6 ± 26.2	87.6 ± 23.6	<0.05	80.5 ± 24.7	89.2 ± 19.0	ns	NR	NR

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDY	STUDY DESIGN	CLINICAL MEASURES	EXPERIMENTAL			OTHER INTERVENTION			*P* BETWEEN GROUP	*P* GROUP X TIME INTERACTIONS
			Pre	Post	*P* Group	Pre	Post	*P* Group		
GATTI ET AL., (2015)[67]	RCT	ABILHAND(logit)	2.33 ± 1.9	3.52 ±1.9	<0.05	2.62 ± 1.3	2.82 ± 1.4	0.072	ns	<0.05
		NHPT(s)	57.9 ± 33.4	50.1 ± 32.2	<0.05	37.5 ± 19.1	28.9 ± 13	<0.05	0.07	0.06
		Jamar grip dynamometer(kg)	20.4 ± 6.9	22 ± 7.4	ns	20.5 ± 9.9	20.8 ± 9.9	ns	ns	ns
		Jamar pinch dynamometer(kg)	4.7 ± 2.1	4.9 ± 2.1	ns	3.2 ± 1.9	4.2 ± 2.1	<0.05	ns	ns
RIPOLLES ET AL., (2015)[59]	RCT	BBT (n)	NR	NR	<0.05	NR	NR	ns	<0.001	NR
		ARAT (0-57)	NR	NR	<0.001	NR	NR	ns	<0.05	NR
		Arm paresis score (n)	NR	NR	ns	NR	NR	ns	ns	NR
		NHPT (s)	NR	NR	ns	NR	NR	ns	<0.001	NR
		Verbal digit span test, forward-backward (n)	2.5 ± 1.1	2.2 ± 1.6	ns	3.3 ± 2.3	2.4 ± 2.1	ns	ns	ns
		Verbal digit span forward (n)	7.4 ± 1.3	7.8 ± 1.6	ns	9.3 ± 2.2	8.8 ± 2.2	ns	<0.05	ns
		Verbal digit span backward (n)	4.9 ± 1.1	5.5 ± 1.7	ns	6 ± 2.7	6.4 ± 2	ns	ns	ns
		Stroop test, PC (n)	36.1 ± 11.7	40.2 ± 11.9	ns	41.2 ± 5.7	44.3 ± 10.9	ns	ns	ns
		Stroop test, C-PC (n)	18.4 ± 12.6	20.9 ± 9.4	ns	28.3 ± 7.8	28.1 ± 13.4	ns	<0.05	ns
		Trial making test, part B-A (s)	84.1 ± 46	95.9 ± 46	<0.05	55 ± 26.4	48.6 ± 22.5	ns	<0.001	ns
		Trial making test A (s)	76.1 ± 55.3	64.2 ± 44.3	ns	39.2 ± 15.1	36.1 ± 14.3	ns	<0.05	ns
		Trial making test B (s)	132.8 ± 52.8	136.5 ± 51.9	ns	94.4 ± 32.6	85 ± 29.2	ns	<0.001	ns
		Stroop test, P (n)	82.8 ± 21.2	86.8 ± 12.2	ns	112.6 ± 8.1	115.1 ± 10.2	ns	<0.001	ns
		Stroop test, C (n)	55.6 ± 13.7	61.2 ± 14.9	<0.05	70 ± 8.7	72.1 ± 9.4	ns	<0.001	ns
		Simple reaction time (ms)	501.8 ± 113	478.2 ± 155	ns	454 ± 60.5	423 ± 73.3	ns	ns	ns
		Complex reaction time (ms)	622.4 ± 117	594.1 ± 88	ns	565.3 ± 81.8	552.6 ± 105	ns	ns	ns
		Short-term auditory-verbal memory (RAVLT, A1) (n)	4.6 ± 1.3	4.9 ± 1.6	ns	5.3 ± 1.8	5.6 ± 1.5	ns	ns	ns
		Rate of learning (RAVLT, A1-A5)	37.7 ± 10.5	40 ± 11.1	<0.05	43.8 ± 10.3	41.5 ± 10	ns	ns	<0.05
		Delayed memory (RAVLT, A7)	6.8 ± 3.6	7.1 ± 4.2	ns	8.5 ± 3	7.9 ± 2.8	ns	ns	ns
TONG ET AL., (2015)[65]	RCT	Fugl Meyer motor assessment	35.4 ± 6.4	48.3 ± 7.9	ns	36.9 ± 9.1	45.6 ± 11.2	ns	<0.05	<0.05
		Wolf motor function test quality	40.7 ± 12.2	51.7 ± 14.5	<0.05	39.6 ± 12.3	45.2 ± 12.4	<0.01	>0.05	ns
		Wolf motor function test time	452.9 ± 346.7	287.2 ± 298.8	<0.05	587.9 ± 341.9	507.6 ± 323.9	<0.01	ns	ns

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDY	STUDY DESIGN	CLINICAL MEASURES	EXPERIMENTAL pre	EXPERIMENTAL Post	EXPERIMENTAL *p* Group	OTHER INTERVENTION Pre	OTHER INTERVENTION Post	OTHER INTERVENTION *p* Group	*P BETWEEN GROUP*	*P* GROUP X TIME INTERACTIONS
DE BRUIN ET AL., (2010)[69]	RCT	***Single task***							**Between Exp.**	
		Velocity (m/s)	1.28 ± 0.22	1.31 ± 0.22	<0.05	1.27 ± 0.16	1.25 ± 0.17	<0.05	<0.05	NR
		Stride time (s)	1.07 ± 0.07	1.06 ± 0.07	<0.05	1.06 ± 0.11	1.06 ± 0.13	ns	<0.05	NR
		Stride length(m)	1.36 ± 0.17	1.37 ± 0.18	ns	1.33 ± 0.13	1.30 ± 0.14	ns	Ns	NR
		Cadence (steps/min)	112 ± 7.86	114 ± 7.85	<0.05	114 ± 11.7	115 ± 13.1	ns	<0.05	NR
		Error rate (%)	NA	NA	NA	NA	NA	NA	Ns	NR
		UPDRS III score(n)	25.5 ± 9.28	19.9 ± 9.05	<0.05	20.4 ± 5.03	18.6 ± 7.38	ns	<0.05	NR
		Dual task							**Between Ctrl**	
		Velocity (m/s)	1.09 ± 0.26	1.16 ± 0.24	<0.05	1.03 ± 0.41	1.01 ± 0.42	ns	ns	NR
		Stride time (s)	1.20 ± 0.15	1.11 ± 0.08	<0.05	1.51 ± 0.88	1.53 ± 0.90	ns	ns	NR
		Stride length(m)	1.27 ± 0.20	1.28 ± 0.21	ns	1.25 ± 0.20	1.23 ± 0.20	ns	ns	NR
		Cadence (steps/min)	102 ± 12.0	108 ± 7.76	ns	96.3 ± 32.8	94.7 ± 35.5	ns	ns	NR
		Error rate (%)	13.2 ± 12.8	7.42 ± 9.50	ns	13.4 ± 19.4	16.2 ± 19.4	ns	ns	NR
		UPDRS III score(n)	NA	NA	NA	NA	NA	NA	NA	NA
PACCHETTI AT AL, (2000)[74]	RCT	UPDRS- motor score(n)	40.2 ± 7.7	24.3 ± 5.2	NR	40.7 ± 7	39.3 ± 5.4	NR	NR	<0.001
		UPDRS-MS Bradykinesia factor(n)	28.2 ± 7.4	15.5 ± 5.3	NR	28.6 ± 6.5	31.8 ± 6	NR	NR	<0.001
		UPDRS-MS Rigidity factor(n)	9 ± 1.9	8.8 ± 2	NR	9 ± 1.6	3.8 ± 0.5	NR	NR	<0.001
JUN ET AL., (2012)[75]	CT	Shoulder F(deg)	38.66 ± 42.74	48.00 ± 52.81	NR	68.00 ± 67.31	67.33 ± 62.61	NR	NR	<0.05
		Elbow F(deg)	50.00 ± 46.59	59.33 ± 49.20	NR	74.33 ± 58.15	75.33 ± 58.53	NR	NR	<0.05
		Hip F(deg)	92.66 ± 38.26	101.73 ± 43.68	NR	87.33 ± 54.57	84.00 ± 51.10	NR	NR	<0.05
		Upper arm muscle strength(n)	2.26 ± 0.96	2.53 ± 0.83	NR	2.60 ± 1.18	2.80 ± 1.01	NR	NR	Ns
		Lower leg muscle strength(n)	3.00 ± 0.75	3.20 ± 0.77	NR	3.06 ± 1.10	3.13 ± 0.99	NR	NR	ns

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDY	STUDY DESIGN	OUTCOME MEASURE	EXPERIMENTAL			OTHER INTERVENTION			*P* BETWEEN GROUP	*P* GROUP X TIME INTERACTIONS
			Pre	Post	*P* Group	Pre	Post	*P* Group		
JOENG ET AL., (2007)[76]	RCT	Shoulder F(deg)	123.12 ± 57.20	126.87 ± 56.29	ns	96.47 ± 44.57	96.17 ± 46.35	ns	ns	ns
		Ankle F(deg)	10.13 ± 6.44	11.25 ± 7.41	ns	5.58 ± 7.47	5.58 ± 7.88	ns	ns	ns
		Ankle E(deg)	27.50 ± 18.25	33.43 ± 17.67	ns	35.50 ± 27.03	27.05 ± 21.79	ns	ns	<0.05
		Upward flexibility of affected arm(cm)	45.12 ± 16.07	35.87 ± 15.21	ns	45.50 ± 16.07	52.56 ± 24.51	ns	ns	<0.001
		Downward flexibility of affected arm(cm)	39.93 ± 16.30	32.50 ± 14.56	ns	54.58 ± 21.53	59.23 ± 26.43	ns	0.003	<0.05
			Pre	**Δ**		**Pre**	**Δ**			
POHL ET AL., (2013)[72]	RCT	PLM movement time (s)	2.07 (1.78;2.81)	-0.20 (-0.34;-0.03)	<0.05	2.07 (1.78;2.81)	+0.03 (-0.24; +0.16)	ns	ns	NR
		TUG(s)	10.5 (8.3;13.8)	-0.5 (-2.0; +1.0)	ns	10.0 (8.3; 11.8)	+1.0 (-2.3; +2.0)	ns	ns	NR
		UPDRS (III) score(n)	19.0 (15.3;25.0)	-4.5 (-8.8; -3.3)	<0.05	17.5 (8.5;26.5)	-8.5 (-14.0; 0.0)	<0.05	ns	NR
		Recall test(n)	4.0 (3.0;6.8)	+3.5 (-1.5; +4.8)	<0.05	3.5 (0.8;6.3)	+2.3 (+1.3; 2.9)	0.068	ns	NR
		SDMT(s)	36.0 (29.0;41.5)	+1.5 (-40; +2.8)	ns	20.5 (15.0; 29.8)	+3.5 (+3.5; +12.3)	ns	ns	NR
		Clock and cube(n)	11.5 (9.3;12.0)	±0.0 (-0.8; +1.8)	ns	10.5 (9.3;11.8)	-0.5 (-1.0; 0.0)	ns	ns	NR
		Naming 30 items(n)	28.0 (27.0;28.8)	+0.5 (0.0; +2.0)	<0.05	26.0 (21.5;29.0)	+1.0 (0.0; +2.0)	ns	ns	NR
		Stroop(n)	28.0 (22.0;41.5)	-2.0 (-8.0; -0.3)	<0.05	30.5 (24.5; 54.5)	-0.5 (-16.5; +2.8)	ns	ns	NR
		PaSMO(n)	82.5 (65.5;87.0)	-6.5 (-17.0; +1.0)	<0.05	122.5 (75.3;277.8)	-22.0 (-24.0; -6.5)	0.066	ns	NR
ALDRIDGE ET AL., (2005)[73]	CT	EDSS(a.u.)	2.3 (1.4;3.5)	-0.303	NR	2.5 (1.5; 3.6)	ns	NR	NR	ns
		MSFC(z-score)	0.23 (-0.21;0.47)	-0.507	NR	0.14 (-0.45; 0.34)	ns	NR	NR	ns

Table II.- Effect of interventions, comparison of experimental and control groups in included studies.

STUDY	STUDY DESIGN	CLINICAL MEASURES	EXPERIMENTAL					
			Δ	% difference	*P* Group			
VILLENEUVE ET AL., (2014)[58]	Within subject study	BBT(n)	7.4 ± 4.1	38.6 ± 10.2	<0.001	N/A		
		NHPT(s)	-13.3 ± 10.2	-25.1 ± 9.7	<0.001			
		FTN(n)	4.7 ± 1.6	35.3 ± 25.2	<0.001			
		Index FTT(n)	5.6 ± 5.1	33.5 ± 34.2	<0.001			
		Jebsen(s)	-32.4 ± 24	-27.1 ± 12.7	<0.001			
			Pre	**Post**	***P* Group**	**Retention**	**Time (pre, post, retention)**	**Time (pretest vs retention)**
WHITALL ET AL., (2000)[71]	Within subject study	Fugl Meyer motor assessment	NR	NR	ns	NR	<0.05	ns
		Wolf motor function test	NR	NR	ns	NR	<0.05	ns
		University of Maryland Arm questionnaire for stroke	NR	NR	ns	NR	<0.05	ns
		Isometric strength Paretic hand						
		Wrist flexion(kg)	NR	NR	ns	NR	ns	ns
		Elbow flexion(kg)	7.93	9.28	<0.05	9.77	<0.05	ns
		Non-paretic hand						
		Wrist extension(kg)	9.40	10.45	ns	11.84	ns	<0.05
		Elbow flexion(kg)	12.95	14.17	ns	16.55	ns	<0.05
		Paretic hand						
		AROM shoulder extension (°)	39.55	48.45	<0.01	44.10	ns	ns
		AROM wrist flexion(°)	23.27	36.36	<0.05	27.91	ns	ns
		PROM wrist flexion(°)	NR	NR	<0.05	NR	ns	ns
		Thumb opposition	0.91	1.36	<0.0	1.45	ns	<0.05

Data is presented as X ± SD; data presented in brackets indicate (upper quartile; lower quartile)

Abbreviation: ns = not significant; NR = not reported; N/A = not applicable; RCT- randomised controlled trial; CT- controlled trial; n-number; s- seconds; m- meters; min- minutes; mm-millimetres; deg-degrees; F-flexion; E-extension; Δ- delta; NHPT- nine hole peg test; IF TS- index finger tapping speed; IF TV- index finger tapping variability; MF TS- middle finger tapping speed; MF TV- middle finger tapping variability; ARAT- action reach arm test; BBT- box and block test; FREQ FT- finger tapping frequency; VMAX FT- finger tapping average angular velocity; NIV FT- finger tapping number of inversions of velocity; FREQ HT- hand tapping frequency; VMAX HT- hand tapping average angular velocity; NIV HT- hand tapping number of inversions of velocity; FREQ PS- pronation and supination frequency; VMAX PS- pronation and supination average angular velocity; NIV PS- pronation and supination number of inversions of velocity; V2- maximum velocity of wrist; T25FW- time 25 foot walk; UPDRS- unified Parkinson's Disease rating scale; PLM- posture-locomotion-manual; TUG- time up and go; SDMT- single digit modality test; PaSMO- parallel serial mental operations; EDSS- expanded disability severity scale; MSFC- multiple sclerosis functional composite; FTN- finger to nose test

Table III.- Effect of the interventions In the three armed randomised control trials.

STUDY	CLINICAL MEASURES	EXPERIMENTAL			OTHER INTERVENTION 1			OTHER INTERVENTION 2			*P* BETWEEN GROUP	*P* GROUP X TIME INTERACTION
		Pre	Post	*p* Group	Pre	Post	*p* Group	Pre	Post	*P* Group		
SCHNEIDER ET AL, (2010)[63]	BBT(n)	25.1±17.6	35.1±18.3	<0.001	30.8±21.0	32.5±20.9	ns	30.5±16.2	33.7±16.3	NR	<0.001	<0.001
	NHPT(n)	4.1±4.0	5.4±3.5	<0.05	4.9±4.1	4.9±4.1	ns	4.9±3.8	5.1±3.8	NR	<0.05	<0.05
	ARAT(n)	33.3±23.9	41.4±17.6	<0.001	36.4±23.3	36.9±23.3	ns	42.7±19.6	45.4±18.6	NR	<0.001	<0.001
	Arm paresis score Wade(n)	4.5±2.8	5.9±1.8	<0.05	4.7±2.8	4.8±2.8	ns	5.2±2.5	5.5±2.4	NR	<0.05	<0.05
	FREQ FT(cycle/s)	2±1.4	2.8±1.5	<0.05	1.6±1.4	1.6±1.5	ns	2.0±1.4	1.9±1.2	NR	<0.05	<0.001
	Vmax FT(deg/s)	160.2±105.5	216.9±105.1	ns	126.8±112.1	112.7±114	ns	143.4±124.0	138.7±98.5	NR	ns	<0.05
	NIV FT(n)	1.7±0.3	1.3±0.3	ns	2.1±0.4	2.4±0.4	ns	1.7±2.9	1.8±2.9	NR	ns	<0.05
	FREQ HT(cycle/s)	1.8±1.4	2.4±1.6	<0.05	1.5±1.4	1.4±1.6	ns	1.8±1.2	1.9±1.3	NR	<0.05	<0.05
	Vmax HT(deg/s)	102.5±80.1	158.9±152.8	ns	100.6±110.8	67±72.1	ns	75.2±49.8	65.6±42.0	NR	ns	<0.05
	NIV HT(n)	1.9±0.3	1.5±0.3	ns	2.5±0.4	2.9±0.4	ns	2.1±3.3	2.0±3.2	NR	ns	<0.05
	FREQ PS(cycle/s)	1.2±0.8	1.6±1	<0.05	1.2±1.1	1.2±1.1	ns	1.2±0.7	1.4±0.9	NR	<0.05	ns
	Vmax PS(deg/s)	398.8±354.7	420.8±298.7	ns	423.1±462.2	395.5±380.5	ns	345.7±272.2	482.6±426.7	NR	ns	ns
	NIV PS(n)	2±0.3	1.5±0.3	<0.05	2.3±0.4	2.3±0.4	ns	2.0±2.8	2.0±2.7	NR	<0.05	<0.05
	V2 target movement											
	5cm(mm/s)	456.7±232.1	614.1±276.8	<0.05	479.4±373.9	63.1±373.6	ns	497.6±263.9	541.8±278.0	NR	<0.05	<0.05
	0.8cm(mm/s)	487.5±243.4	596.9±284	<0.05	464.4±366.8	451.3±363.3	ns	519.0±275.5	573.1±326.2	NR	<0.05	<0.05

Table III.- Effect of the interventions In the three armed randomised control trials.

STUDY	CLINICAL MEASURES	EXPERIMENTAL			OTHER INTERVENTION 1			OTHER INTERVENTION 2			*P* BETWEEN GROUP	*P* GROUP X TIME INTERACTION
		Pre	Post (3 months)	follow up (6 months)	Pre	Post (3 months)	Follow up (6 months)	Pre	Post (3 months)	Follow up (6 months)		
SARKAMO ET AL. (2008)[68]	verbal memory (n)	45.1±21.2	72.1±21.1	70.3±21.1	60.7±21.7	71.4±21.7	67.7±20.2	50.0±25.6	64.4±23.1	62.3±22.7	0.006	<0.05
	short-term and working (n)	19.7±9.4	22.7±6.7	24.3±7.3	23.3±7.2	24.8±8.7	24.5±7.1	17.7±9.5	19.9±7.0	21.2±7.7	NR	ns
	language (n)	109.2±36.8	130.7±13.4	133.9±16.2	122.1±28.3	128.2±27.5	130.4±27.7	110.7±31.7	122.2±15.4	125.8±14.3	NR	ns
	music cognition (n)	19.9±4.5	22.3±3.3	NR	19.2±5.2	20.8±4.9	NR	17.1±3.5	19.7±3.9	NR	NR	ns
	visuospatial cognition (n)	82.8±23.4	95.5±7.1	91.5±13.9	89.2±13.3	93.7±11.3	93.3±10.5	77.3±23.7	91.7±9.0	86.6±20.0	NR	ns
	executive functions (n)	12.6±3.7	15.3±2.1	14.8±2.8	13.9±3.5	15.8±2.4	15.5±3.0	12.6±3.6	14.9±2.7	14.6±3.7	NR	ns
	focused attention; correct responses (n)	74.8±19.5	86.2±4.2	86.3±4.5	84.3±8.5	83.9±13.6	85.3±7.9	87.3±3.2	85.9±5.1	86.0±4.8	NR	<0.05
	focused attention; reaction time (s)	3.0±1.1	3.0±0.1	3.0±1.5	3.4±1.5	2.9±1.6	2.7±1.3	3.7±2.0	3.3±1.5	3.2±1.4	NR	ns
	sustained attention; correct responses (n)	87.0±23.0	94.8±10.6	97.5±4.4	91.1±12.1	95.6±8.6	97.6±3.0	95.9±7.4	98.8±2.7	99.1±1.8	NR	ns
	sustained attention (RT,s)	1.0±0.3	0.9±0.3	NR0.9±0.2	1.2±0.5	0.9±0.2	0.9±0.2	1.0±0.2	1.0±0.3	0.9±0.1	NR	ns

Data is presented as X ± SD

Abbreviation: ns = not significant; NR = not reported; n-number, RT- reaction time; deg-degree; BBT- box and block test; NHPT- nine hole peg test; ARAT- action reach arm test; FREQ FT- finger tapping frequency; VMAX FT- finger tapping average angular velocity; NIV FT- finger tapping number of inversions of velocity; FREQ HT- hand tapping frequency; VMAX HT- hand tapping average angular velocity; NIV HT- hand tapping number of inversions of velocity; FREQ PS- pronation and supination frequency; VMAX PS- pronation and supination average angular velocity; NIV PS- pronation and supination number of inversions of velocity; V2- maximum velocity of wrist

Supplementary Table a. Quality assessment of the included studies using the PEDro checklist.

Quality assessment	Study design	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
Villeneuve at al., 2014[58]	Cohort	Y	U	U	U	U	U	U	N	U	Y	Y
Van Vugt et al., 2014[66]	RCT	Y	Y	N	Y	Y	N	N	N	Y	Y	Y
Grau- Sanchez et al., 2013[61]	MCT	Y	U	U	U	U	U	U	N	Y	N	Y
Amengual et al., 2013[60]	MCT	Y	U	U	U	U	U	U	Y	Y	Y	Y
Altenumuller et al., 2009[62]	RCT	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y
Schneider et al., 2007[64]	RCT	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y
Schneider et al., 2010[63]	RCT	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y
Sarkamo et al., 2008[68]	RCT	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Schauer et al., 2003[70]	RCT	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y
De Bruin et al., 2010[69]	RCT	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Pohl et al., 2013[72]	RCT	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Aldridge et al., 2005[73]	MCT	Y	N	N	Y	N	N	N	N	Y	Y	Y
Pacchetti et al., 2000[74]	RCT	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y
Jun at al., 2013[75]	MCT	Y	Y	U	Y	U	U	U	Y	Y	Y	Y
Joeng et al., 2007[76]	RCT	Y	U	U	U	U	U	U	N	Y	Y	Y
Tong et al., 2015[65]	RCT	Y	Y	N	Y	N	N	N	Y	Y	Y	Y
Gatti et al., 2015[67]	RCT	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y
Ripolles et al., 2015[59]	RCT	Y	Y	N	N	N	N	N	Y	Y	Y	Y
Whitall et al., 2000[71]	Cohort	Y	N	N	N	N	N	N	Y	Y	N	N

RCT= randomized controlled trial, MCT= matched controlled trial, C1=eligibility criteria, C2=random allocation, C3=concealment of allocation, C4=group similarity at baseline, C5=blinding of subjects, C6=blinding of therapists, C7=blinding of assessors, C8=variability of key outcome measures of more than 85% of the subjects, C9=intention-to treat analysis, C10=between-group statistical comparisons; C11=point measures and measures of variability, Y=Yes, N=No, U= Unclear.

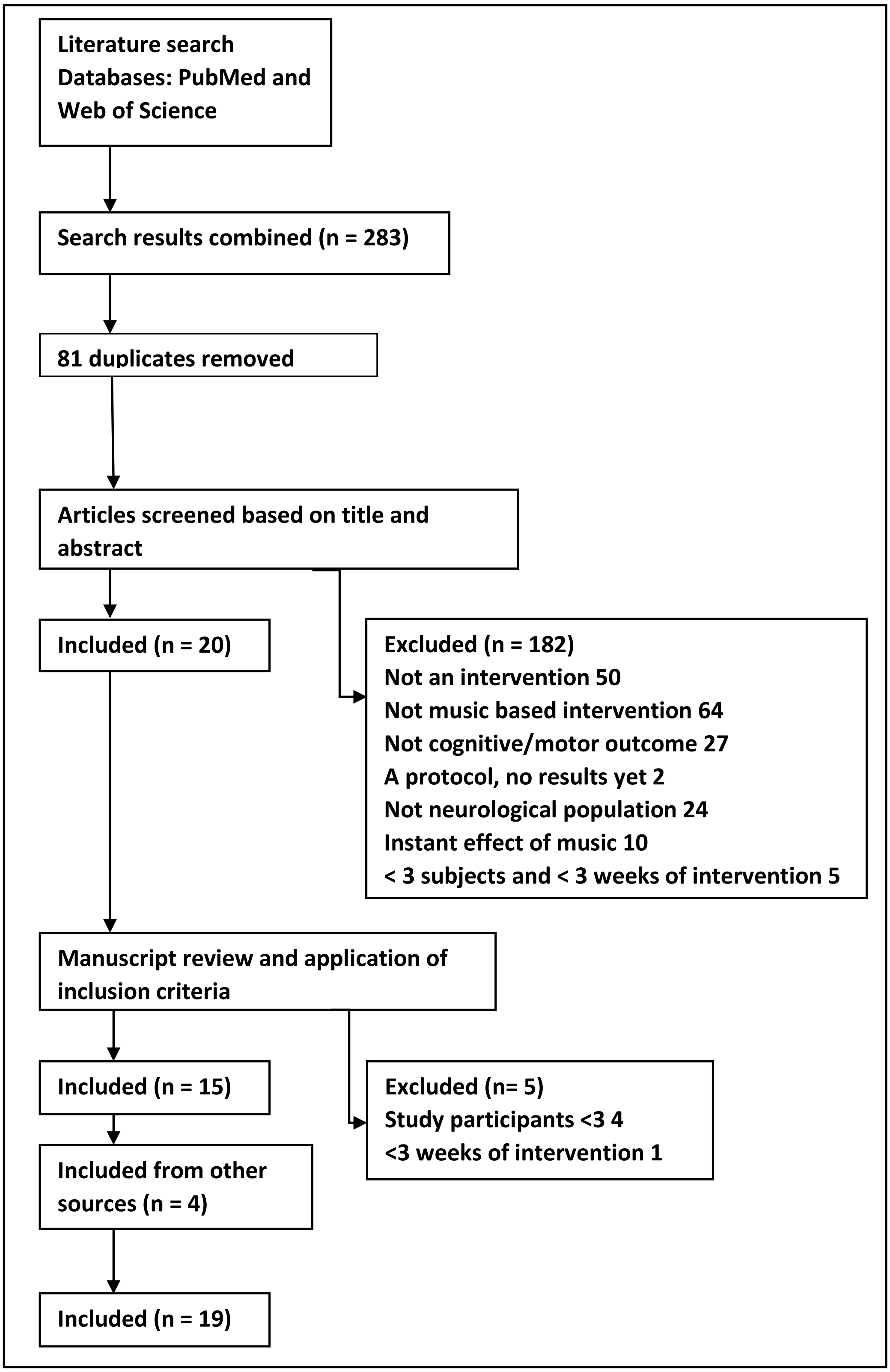
Supplementary Table b. Descriptive characteristics of experimental and control groups, type, frequency, duration and volume of the intervention.

Study		Type of training	Age	Number of participants	Dropouts	Reasons	Progression	Duration (week)	Days/week	Session (n)	Duration/ session (h)	Total time of training (h)
Villeneuve at al, 2014[58]	Exp	Instrument-based music interventions	60	13	NR	NR	Yes	3	3	9	1	9
	Ctrl											
Van Vugt et al., 2014[66]	Exp	Instrument-based music interventions; together group	65.6±10.5	14	NR	NR	Yes	3-4	NR	10	1-2	5
	Exp	Instrument-based music training; in-turn group	67.1±11.8	14	NR	NR	Yes	3-4	NR	10	1-2	5
Grau-Sanchez et al., 2013[61]	Exp	Instrument-based music interventions	61.9±9.8	9	NR	NR	Yes	4	NR	20	1/2	10
	Ctrl (healthy)	Instrument-based music training	59.3±9.5	9								
Amengual et al., 2013[60]	Exp	Instrument-based music interventions	59.05±9.05	20	NR	NR	Yes	4	NR	20	1/2	10
	Ctrl (healthy)	No intervention	56±9.6	14								
Altenmuller et al., 2009[62]	Exp	Instrument-based music interventions + conventional therapy	55.7±12.3	32	NR	NR	Yes	3	NR	15	1/2	7.5
	Ctrl	Conventional therapy	53±11.8	30	NR	NR	Yes	3	NR	15	1/2	7.5
Schneider et al., 2007[64]	Exp	Instrument-based music interventions + conventional therapy	58.1±9.9	20	NR	NR	Yes	3	NR	15	1/2	7.5
	Ctrl	Conventional therapy	54.5±10.2	20	NR	NR	Yes	3	NR	15	1/2	7.5
Gatti et al., 2015[67]	Exp	Instrument-based music interventions	4.3±8.8	9	0	NA	Yes	3	5	15	1/2	7.5
	Ctrl	Muted Instrument-based music interventions	48.4±10.0	10	0	NA	Yes	3	5	15	1/2	7.5

Study		Type of training	Age	Number of participants	Dropouts	Reasons	Progression	Duration (weeks)	Days/week	Session (n)	Duration/session (h)	Total time of training (h)
Schneider et al., 2010[63]	Exp	Instrument-based music training	55.7±12.3	32	NR	NR	Yes	3	NR	15	1/2	7.5
	Ctrl	Conventional therapy	53±11.8	30	NR	NR	Yes	3	NR	15	1/2	7.5
	Ctrl	Constraint-induced movement therapy	56.1±10.7	15	NR	NR	Yes	3	NR	15	1/2	7.5
Tong et al., 2015[65]	Exp	Instrument-based music interventions	50.1±14.8	15	0	NA	Yes	4	NR	20	1/2	10
	Ctrl	Instrument-based music interventions	48.6±14.6	15	3	Not motivating	Yes	4	NR	20	1/2	10
Ripolles et al., 2015[59]	Exp	Instrument-based music interventions	59.1±9.04	20	0	NA	Yes	4	NR	20	1/2	10
	Ctrl	No intervention	56±9.6	14								
Sarkamo et al., 2008[68]	Exp	Listening-based music interventions	56.1±9.6	21	1	False diagnosis	No	8	7	56	1	56
	Ctrl	Listening to audio-books	59.3±8.3	21	1	New stroke	No	8	7	56	1	56
	Ctrl	No intervention	61.5±8.0	23	3	Dementia + refusal						
Shauer et al., 2003[70]	Exp	Rhythm-based interventions	59±12	18	14 (in total)	Disapproval of tests/use of music	No	3	5	15	1/3	5
	Ctrl	Convention gait training; neurodevelopment therapy	61±12	19			No	3	5	15	1/3;3/4	5
Whitall et al., 2000[71]	Exp	Rhythm-based interventions	63.8±12.8	14	2	Transportation issues	No	6-9	3	18	1/3	6
De Bruin et al., 2010[69]	Exp	Rhythm-based interventions	64.1±4.2	16	5	Medication change	No	13	3	NR	1/2	19.5
	Ctrl	Regular activities	67.0±8.1	17	6	NR	No	13	3	NR	1/2	19.5
Pohl et al., 2013[72]	Exp	Multicomponent-based music interventions	68.2±5.1	12	NR	NR	Yes	6	2	12	1	12
	Ctrl	Waiting list control		8	2	Illness + altered medication						

Study		Type of training	Age	Number of participants	Dropouts	Reasons	Progression	Duration (weeks)	Days/week	Session (n)	Duration/session (h)	Total time of training (h)
Aldridge et al., 2005[73]	Exp	Multicomponent-based music interventions	29-47 range	10	NR	NR	No	39	8-10	NR	1	10
	Ctrl	No intervention	NR	10								
Pacchetti et al., 2000[74]	Exp	Multicomponent-based music interventions	62.5±5	16	NR	NR	No	12	1	NR	2	24
	Ctrl	Traditional physiotherapy	63.2±5	16	NR	NR	No	12	1	NR	2	24
Jun et al., 2012[75]	Exp	Multicomponent-based music interventions	60.7±8.59	20	5	Withdrawn/discharge	No	8	3	NR	1	24
	Ctrl	Waiting list control	55.10±17.23	20	5	Discharged						
Jeong et al., 2007[76]	Exp	Multicomponent-based music interventions	58.0±7.192	16	NR	NR	No	8	1	NR	2	16
	Ctrl	Referral information in surrounding community	62.2±8.158	17	NR	NR						

Abbreviations: Exp- experimental, Ctrl- control, n- number, h- hour, NR- not reported, NA- not applicable, age is presented as X ± SD


Literature search
Databases: PubMed and Web of Science
Search results combined (n = 283)
81 duplicates removed
Articles screened based on title and abstract
Included (n = 20)
Excluded (n = 182)
Not an intervention 50
Not music based intervention 64
Not cognitive/motor outcome 27
A protocol, no results yet 2
Not neurological population 24
Instant effect of music 10
< 3 subjects and < 3 weeks of intervention 5
Manuscript review and application of inclusion criteria
Included (n = 15)
Excluded (n= 5)
Study participants <3 4
<3 weeks of intervention 1
Included from other sources (n = 4)
Included (n = 19)