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Review article

Potential benefits of music playing in stroke upper limb motor rehabilitation

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ABSTRACT

Music-based interventions have emerged as a promising tool in stroke motor rehabilitation as they integrate most of the principles of motor training and multimodal stimulation. This paper aims to review the use of music in the rehabilitation of upper extremity motor function after stroke. First, we review the evidence supporting current music-based interventions including Music-supported Therapy, Music glove, group music therapy, Rhythm- and music-based intervention, and Musical sonification. Next, we describe the mechanisms that may be responsible for the effectiveness of these interventions, focusing on motor learning aspects, how multimodal stimulation may boost motor performance, and emotional and motivational aspects related to music. Then, we discuss methodological concerns in music therapy research related to modifications of therapy protocols, evaluation of patients and study designs. Finally, we highlight clinical considerations for the implementation of music-based interventions in clinical settings.

1. Introduction

Stroke is one of the most prevalent non-communicable diseases and a leading cause of mortality and acquired disability worldwide. In 2016 there were 79.5 million people affected by stroke globally, and among them, 13.6 million were new strokes (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Although stroke mortality has been reduced in developed countries in recent decades due to improvements in acute management (Feigin et al., 2015), one-third of stroke survivors are left with some form of disability (GBD 2016 DALYs and HALE Collaborators, 2017). Motor deficits of the upper extremity are common sequelae of stroke (Rathore et al., 2002) including paresis, spasticity and poor spatiotemporal coordination. This results in impaired reaching, grasping and manipulation abilities (Jones, 2017). The inability to perform movements with the upper extremity leads to limitations in activities of daily living and restrictions on participation, affecting the individual's autonomy and quality of life (Algurén et al., 2012; Carod-Artal et al., 2000; Daniel et al., 2009; Mayo et al., 2002; Mutai et al., 2016). In the absence of pharmacological treatments to save or even regenerate neural tissue, the recovery of motor deficits relies almost exclusively on rehabilitation techniques (Langhorne et al., 2011).

Stroke rehabilitation aims to improve and maintain functioning through restitution, substitution and compensation of functions using therapeutic interventions that promote adaptive learning (Langhorne et al., 2011; Selzer et al., 2006). Critically, recovery at the behavioural level depends on the ability of the nervous system to reorganize its structure, connections and functions in response to intrinsic and extrinsic stimuli (Cramer et al., 2011). While immediately after the stroke, changes in blood flow, inflammation, and diaschisis impair functioning of morphologically intact brain regions, these processes are reduced over time, which explains the spontaneous recovery observed in the initial days and weeks after stroke (Kwakkel et al., 2004). Importantly, there is a period of increased plasticity that is extended up to three

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months where the expression of growth-promoting genes induces the remodelling of dendritic spine architecture, axonal sprouting and synaptogenesis (Carmichael, 2006; Carmichael et al., 2001; Dancause and Nudo, 2011; Krakauer et al., 2012; Stroemer et al., 1995). This period of increased endogenous plasticity is of particular clinical relevance because therapeutic interventions can take advantage of this favourable cellular environment for the establishment of new connections to promote learning-dependent plasticity through experience (Buma et al., 2013; Dancause and Nudo, 2011; Zeiler and Krakauer, 2013). Stroke motor rehabilitation aims to enhance motor functions and induce and modulate plasticity through two main approaches: training and enriched environment.

Training refers to therapeutic interventions requiring the patient to actively engage in motor skill re-learning. Several principles derived from basic research on motor learning have been shown to boost skill acquisition and might provide insights about the optimal conditions to facilitate effective learning and better motor performance in stroke patients (Kitago and Krakauer, 2013; Wulf and Lewthwaite, 2016). Accordingly, training should be task-specific, relevant for the individual, and involve mass practice of movements (Arya et al., 2012; Fu et al., 2012; Langhorne et al., 2009; Wressle et al., 2002). Instructions and guidance by the therapist as well as the type of feedback and reinforcements influence learning and rehabilitation success (Galea et al., 2015; Hooyman et al., 2014; Hosp and Luft, 2013; Wulf and Lewthwaite, 2016; Wulf et al., 2001). Motor training after stroke may promote reorganization of cortical maps in primary motor areas and the somatosensory cortex of the lesioned hemisphere (Dancause and Nudo, 2011). However, reorganization in the unaffected hemisphere can also take place if there is not sufficient *structural reserve* to support functioning in the damaged hemisphere (Carey et al., 2002; Cramer et al., 1997; Di Pino et al., 2014; Johansen-Berg et al., 2002; Liepert et al., 1998).

The second approach, enriched environment, refers to providing an interactive context that stimulates physical, cognitive and social activities, as well as multimodal sensory processing (Johansson, 1996; Johansson and Ohlsson, 1996). This approach has been first used in animals whose cage conditions were modified to enhance sensory stimulation and hence activity (Johansson, 1996; Markham and Greenough, 2004). Enriched environment has been shown to boost the recovery of sensorimotor function and promote plasticity after stroke, increasing neurogenesis, dendrite spine growth, synaptogenesis, and the production of neurotrophic factors (Biernaskie, 2004; Biernaskie and Corbett, 2001; Hicks et al., 2007; Komitova et al., 2005; Livingston-Thomas et al., 2016). The human equivalent to environmentally enriched cages is multimodal stimulation, which requires modifying the rehabilitation and home environment to make them stimulating and challenging. Although this approach is difficult to test in humans using experimental designs (Janssen et al., 2014), the strong evidence behind enriched environment in animal models suggests that rich and varied stimulation and the promotion of exercise and participation in different activities could benefit the rehabilitation process (Janssen et al., 2014; Sommer and Schäbitz, 2017; White et al., 2015). Conversely, it has been estimated that more than 70 % of the time in rehabilitation centres, stroke patients are inactive and alone in their rooms (De Wit et al., 2005). Enriched environments in rehabilitation could engage patients in activities, having a positive influence on motivation and well-being, and could be easily combined with other treatments to boost motor recovery (Sommer and Schäbitz, 2017; White et al., 2015).

Evidence-based therapies to restore motor function after stroke include repetitive task-specific training, constraint-induced movement therapy, robotic therapy, bilateral training, electrical stimulation, mental practice and virtual reality based interventions (Winstein et al., 2016). Lately, music-based interventions have emerged as a promising tool in stroke motor rehabilitation capable of integrating most of the principles of motor training and multimodal stimulation (François et al., 2015). This review focuses on music-based interventions to enhance upper extremity motor function after stroke.

2. Music in stroke rehabilitation

Musical activities such as listening, playing, singing or dancing are common in our daily lives. The therapeutic use of music has traditionally been based on music's ability to induce emotions and to regulate mood. Music-based interventions can be broadly divided into passive and active interventions. On the one hand, passive interventions usually refer to listening to music, which has been shown to be effective in different neurological conditions to enhance cognition and mood (Särkämö et al., 2008, 2014). On the other hand, active music-based interventions require the production of music (Sihvonen et al., 2017). In this context, the main active music-based approach to treat paresis of the upper extremity after stroke is playing musical instruments. This activity aims to enhance motor function by providing a context for motor skill learning where the patient actively trains movements to generate music. Playing musical instruments requires highly skilled movements and the perception and integration of information from different modalities (Altenmöller and Schlaug, 2015). Therefore, playing music in the context of stroke motor rehabilitation constitutes both, a training to overcome different motor and cognitive deficits and a form of multimodal stimulation to enhance cognition, engage patients, and increase their motivation and well-being.

A literature search was done to identify therapies for stroke motor rehabilitation with a musical component (Box 1), which resulted in a total of 23 articles included in this review. There are several active music-based interventions for the rehabilitation of upper extremity motor function in stroke (Table 1). These include Music-supported Therapy (Schneider et al., 2007), Music glove (Friedman et al., 2014), Therapeutic instrumental music performance (Street et al., 2018), Music upper limb therapy-integrated (Raghavan et al., 2016), Active music therapy (Raglio et al., 2017), Rhythm- and music-based therapy (Bunketorp-Käll et al., 2017b) and Musical sonification therapy (Scholz et al., 2016). In the following sections, we present the evidence that supports these interventions. Table 2 provides a summary of the studies included in this review, presenting their main results and highlighting type of design, control intervention, number of participants and their stroke recovery phase, primary outcomes and duration of intervention.

Box 1
Search strategy and selection criteria.

A search was conducted in Pubmed for articles published in English before December 2019. The search was based on the question: what is the effectiveness of music-based interventions for treating motor deficits of the upper extremity in stroke patients? Thus, the population of interest was stroke patients and we considered any type of intervention with a musical component. The primary outcome of this search was the motor function of the paretic upper extremity. Search strategies included the Medical Subject Headings (MeSH) "*stroke*" combined with "*music*" or "*music therapy*" and keyword "*music-supported therapy*". We also used the MeSH "*motor skills*", "*motor activity*" and "*paresis*" to narrow down searches. For the review, we included articles testing music-based interventions regardless of their type of design. We did not include experiments based on a single training session or proof-of-concept studies. Additional references were gathered from references lists.

Table 1
Description of different music-based interventions.

Intervention	Description
Music-supported Therapy Schneider et al., 2007	Music playing training to enhance fine and gross movements of the paretic extremity. The therapy is based on the principles of mass repetition of finger and arm movements; audio-motor coupling and integration; shaping; and emotion-motivation effects. Training sessions consist of playing an electronic keyboard and drum pads and exercises are based on a program that allows individualization. Patients play simple sequences that increase in complexity until they learn to play folk songs. Sessions are usually individual and provided by a therapist at the rehabilitation center or hospital. The therapy has also been adapted to be done at the patient's home as a form of telerehabilitation.
Music glove Friedman et al., 2014	Training to regain hand function using a device that consists of a glove that produces different sounds when moving. Patients wear the music glove and perform grip and pinch movements using an interactive computer game to play along with songs. In this computer game, scrolling notes appear on the screen and indicate the type of movement. When notes reach the bottom of the screen patients have to perform the movement in the correct timing. Feedback is provided for correct and incorrect trials. A therapist supervises training sessions, which can be done at the clinic or the patient's home.
Music upper limb therapy-integrated Raghavan et al., 2016	Group music making intervention based on the Nordoff-Robbins approach to music therapy. The training combines music therapy with occupational therapy and aims to reduce motor and sensory impairment of the upper extremity as well as increase well-being and participation. Sessions consist of interactive live music making and focus groups discussions. Patients improvise musical pieces with adapted instruments that are selected based on their preferences and abilities. Patients also select the type of music. During the sessions, a music therapist plays the piano and an occupational therapist and a second music therapist support patients to play musical instruments. Sessions can be done at the rehabilitation center or hospital.
Active music therapy approach Raglio et al., 2017	Music playing intervention that aims to enhance fine and gross motor skills, emotional well-being and communication. Patients are asked to interact and play with rhythmical-melodic instruments. Sessions are conducted by a music therapist at the rehabilitation center or hospital.
Therapeutic instrumental music performance Street et al., 2018	Music playing training to enhance motor function of the paretic extremity. Patients are asked to play acoustic musical instruments and virtual instruments using an electronic tablet. The training comprises 12 motor exercises and variations. A music therapist conducts the sessions at the patient's home and provides pulsed musical patterns with an acoustic guitar.
Rhythm- and music-based therapy Bunketorp-Käll et al., 2017b	Group music therapy to enhance global mobility. Patients are asked to perform coordinated rhythmic movements in response to visual and auditory cues. The difficulty of movement sequences is adapted to the patient's mobility and is increased in complexity over sessions. Sessions are conducted by a music therapist at the rehabilitation center or in community settings.
Musical sonification Scholz et al., 2016	Musical training to enhance gross movements of the paretic extremity. The setting for the training requires capturing the position and movement of the upper extremity in real time and transforming spatial information in different sounds. Patients sit at a desk with a three-dimensional space frame and perform movements to produce rhythms following the cues of a therapist. The training is delivered at the rehabilitation center or hospital.

2.1. Music-supported Therapy

One of the most investigated protocols of music-based interventions to treat hemiparesis after stroke is Music-supported Therapy (Schneider et al., 2007), where stroke patients are trained to play musical instruments with the affected upper extremity. In the training sessions, an electronic keyboard and/or drum pads are used in an adapted form to exercise fine and gross movements respectively. A standardised protocol of different exercises arranged into levels of increasing difficulty has been designed and allows the individualisation of the training depending on the severity of motor deficits. Patients may start playing simple sequences, which progressively increase in complexity, and eventually evolve into playing folk songs at the end of the training period. Music-supported Therapy is based on the principles of (i) mass repetition of finger and arm movements; (ii) audio-motor coupling and integration; (iii) shaping; and (iv) emotion-motivation effects (Rodriguez-Fornells et al., 2012; Schneider et al., 2007).

2.1.1. Effects on motor function

Music-supported Therapy has been shown to enhance the motor function and movement kinematics of the paretic upper extremity in subacute and chronic stroke patients (Fig. 1a; Fujioka et al., 2018; Schneider et al., 2007).

Two randomised controlled trials in the early subacute phase of stroke recovery have shown that adding Music-supported Therapy to the rehabilitation program was superior in improving the motor function of subacute stroke patients than standard care alone (Altenmüller et al., 2009; Schneider et al., 2007). However, a recent randomized controlled trial found that adding Music-supported Therapy to a standard program of rehabilitation was not superior to conventional therapy approaches in the recovery of upper extremity function in stroke patients during the subacute stage (Grau-Sánchez et al., 2018). This discrepancy might have resulted from differences in training intensity between studies. In the study of Schneider et al. (2007), patients in both the experimental and the control group received 13.5 h of standard rehabilitation, which included physical and occupational therapy sessions. In addition to that, the experimental group received 15 sessions (30 min each) of Music-supported Therapy, but no more extra sessions were provided to the control group. Similarly, Altenmüller et al. (2009) did not provide an extra time of therapy to the control group. In the study of Grau-Sánchez et al. (2018), both groups were enrolled in a standard rehabilitation program that consisted of 40 h of conventional treatment for four weeks. Apart from this standard program, patients in the experimental and control groups were provided with ten extra hours of training with either Music-supported Therapy or conventional therapy, respectively. The control group sessions included passive mobilization, stretch and progressive resistance exercises, and task-specific training. Therefore, the standard rehabilitation program was nearly three times more intense than in previous studies and patients in the control group received extra time of rehabilitation. Thus, it can be concluded that when the number of training hours is equal, there are no differences between Music-supported Therapy and conventional therapy. This can also be interpreted as Music-supported Therapy being able to promote the same amount of motor improvement as traditional approaches in the subacute stage.

Chronic stroke patients can enhance their upper extremity functionality when treated with Music-supported Therapy, even when the treatment is provided years after the stroke (Amengual et al., 2013; Rojo et al., 2011; Villeneuve and Lamontagne, 2013; Villeneuve et al., 2014). However, the only randomized controlled trial in the chronic phase, conducted by Fujioka et al. (2018), has shown that Music-supported Therapy was not superior to self-administered graded repetitive arm supplementary program (GRASP, Harris et al., 2009). In this study, both training protocols resulted in small improvements of motor

Table 2
Summary of studies investigating music-based interventions for the upper extremity motor rehabilitation in stroke.

Reference	Study design	Control treatment	Participants (n) Recovery phase	Primary outcome	Duration of intervention	Main results
Music-supported Therapy						
Altenmüller et al., 2009	RCT 2-armed	Standard care	62 Early subacute phase	Motor function ARAT	3 weeks 15 sessions 7.5 hours	The experimental group improved in the functional use of the affected extremity and movement kinematics. An enhancement of connectivity between motor and auditory regions was found in the music group.
Schneider et al., 2007	RCT 2-armed	Standard care	40 Early subacute phase	Motor function ARAT	3 weeks 15 sessions 7.5 hours	Major improvements in the functional use of the affected extremity and movement kinematics in the experimental group.
Grau-Sánchez et al., 2018	RCT 2-armed	Standard care	39 Early and late subacute phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Both groups improved in the functional use of the upper extremity and reduced their motor deficits and gains were maintained at 3-month follow-up. Patients treated with Music-supported Therapy reported better language abilities, increased their rate of verbal learning, and experienced less fatigue and negative emotions and a better quality of life after the treatment. Motor gains in the Music-supported Therapy group were related to the individual's capacity to experience pleasure from musical activities.
VanVugt et al., 2016	RCT 2-armed	Music-supported Therapy with delayed feedback	34 Early subacute phase	Motor function 9HPT	4 weeks 10 sessions 5 hours	Both groups improved upper extremity function, but improvements were more prominent in the delayed feedback group.
Tong et al., 2015	RCT 2-armed	Mute Music-supported Therapy	30 Late subacute and chronic phase	Motor function WMT	4 weeks 20 sessions 10 hours	Both groups improved but greater improvements were seen in the experimental group.
Fujioka et al., 2018	RCT 2-armed	GRASP	28 Chronic phase	Motor function CAHAI	10 weeks 30 sessions 30 hours	Minor motor improvements in both groups. Patients in the Music-supported Therapy group improved in processing speed and mental flexibility. Both groups reduced negative affect and improved overall quality of life.
Van Vugt et al., 2014	Experimental study	Music-supported Therapy in turns	28 Early subacute phase	Motor function 9HPT	3-4 weeks 10 sessions 5 hours	Patients treated in turns improved more in the functional use of the affected extremity. Both groups improved in movement kinematics. Both groups reported less fatigue and depressive symptoms.
Ripollés et al., 2016a Amengual et al., 2013	Experimental study	No	20 Chronic phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Improvement in the functional use of the affected extremity and movement kinematics, attention, speed of processing, and rate of verbal learning after the therapy. Patients increased their arousal, valence, positive affect and quality of life, and reported less depressive symptoms. A pattern of intrahemispheric reorganization within the lesioned cortex was observed after the therapy, with cortical map reorganization and increased excitability of the motor cortex, and functional coupling between motor and auditory areas.
Villeneuve et al., 2014	Experimental study	No	13 Chronic phase	Motor function BBT/9HPT	3 weeks 9 sessions 9 hours	Overall motor function improvement after the therapy.
Grau-Sánchez et al., 2013	Experimental study	No	9 Early and late subacute phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Patients improved in the functional use of the affected extremity and increased their quality of life after the therapy. Reorganisation within the affected hemisphere, as evidenced by increased excitability and cortical map reorganisation was found in a subgroup of 5 patients.
Villeneuve et al., 2013	Case series	No	3 Chronic phase	Motor function BBT/9HPT	3 weeks 9 sessions 9 hours	Improvement in note and timing accuracy within and across the training sessions together with motor function improvement after the therapy.
Music-supported Therapy						
Grau-Sánchez et al., 2017	Case-study ABAB design	Standard care	1 Chronic phase	Motor function ARAT	4 weeks 12 sessions 18 hours	Improvement in movement kinematics and in the functional use of the affected extremity after Music-supported Therapy. Improvement in a musical task within the first training sessions. Gains in motor function were maintained over time, and generalisation to daily life activities occurred at the end of training.

(*continued on next page*)

Table 2 (*continued*)

Reference	Study design	Control treatment	Participants (n) Recovery phase	Primary outcome	Duration of intervention	Main results
Rojo et al., 2011	Case-study	No	1 Chronic phase	Motor function ARAT	4 weeks 20 sessions 10 hours	Improvement in the functional use of the affected extremity and movement kinematics. Reorganisation within the lesioned hemisphere, with increased excitability, cortical map reorganisation and functional coupling between motor and auditory areas.
Music glove						
Zondervan et al., 2016	RCT 2-armed Cross-over design	Self-guided hand exercises	17 Chronic phase	Motor function BBT	3 weeks 9 hours	Both groups improved in the functional use of the upper extremity.
Friedman et al., 2014	RCT 2-armed	Self-guided hand exercises	12 Chronic phase	Motor function BBT	2 weeks 6 sessions 6 hours	Both groups improved but a major improvement was observed in the Music glove group.
Music upper limb therapy-integrated						
Raghavan et al., 2016	Experimental study	No	13 Chronic phase	Motor impairment FMA	6 weeks 12 sessions 9 hours	Reduced upper limb motor and sensory impairment, and activity limitation. Patients increased their well-being and participation.
Active music therapy approach						
Raglio et al., 2017	Experimental study	Standard care	38 Early subacute phase	Physical and cognitive disability FIM	7 weeks 20 sessions 10 hours	Increased grip strength in the experimental group. Both groups improved their quality of life, functional level and gross mobility.
Therapeutic instrumental music performance						
Street et al., 2018	RCT Cross-over design	No	10 Late subacute and chronic phase	Feasibility of treatment	6 weeks 12 sessions 6 hours	Participants perceived the musical intervention as motivating, and that instruments facilitated movements. Patients reported that fatigue was low. Music therapy seems feasible.
Rhythm- and music-based therapy						
Bunketorp-Käll et al., 2017a Bunketorp-Käll et al., 2017b	RCT 3-armed	Horse-riding therapy No treatment	122 Chronic phase	Perception of stroke recovery SIS, item 9	12 weeks 24 sessions Rhythm- and music-based therapy: 36 hours Horse-riding therapy: 96 hours	Perception of recovery was greater for patients treated with rhythm- and music-based therapy and horse-riding therapy and was maintained at 3 and 6-month follow up. Horse-riding therapy group improved in gait and balance, and rhythm- and music-based therapy group in balance and grip strength. Improvements were maintained at 6 months. Patients treated with rhythm- and music-based therapy showed increased working memory at 6 months. Caregiver burden was reduced in the rhythm- and music-based and horse-riding therapy groups after the therapy and at 3-month follow-up.
Musical sonification						
Nikmaram et al., 2019	Experimental study	Sham sonification	40 Early subacute phase	Motor impairment FMA	15 sessions Unknown hours and weeks	No differences between groups were found for the primary outcome. Patients undergoing musical sonification treatment showed slight improvements in movement smoothness.
Scholz et al., 2016	Experimental study	Sham sonification	25 Early subacute phase	Motor impairment FMA	10 sessions 5 hours Unknown weeks	Both groups improved the functional use of the affected extremity but the group treated with musical sonification therapy experienced a reduction in pain after training.

ARAT, Action Research Arm Test; BBT, Box and Blocks Test; CAHAI, Chedoke Arm and Hand Activity Inventory; CIMT, Constraint-induced movement therapy; FIM, Functional Independence Measure; FMA, Fugl-Meyer Assessment of Motor Recovery after Stroke; GRASP, graded repetitive arm supplementary program; RCT, Randomised Controlled Trial; SIS, Stroke Impact Scale; WMT, Wolf Motor Function Test; 9HPT, Nine Hole Pegboard Test.

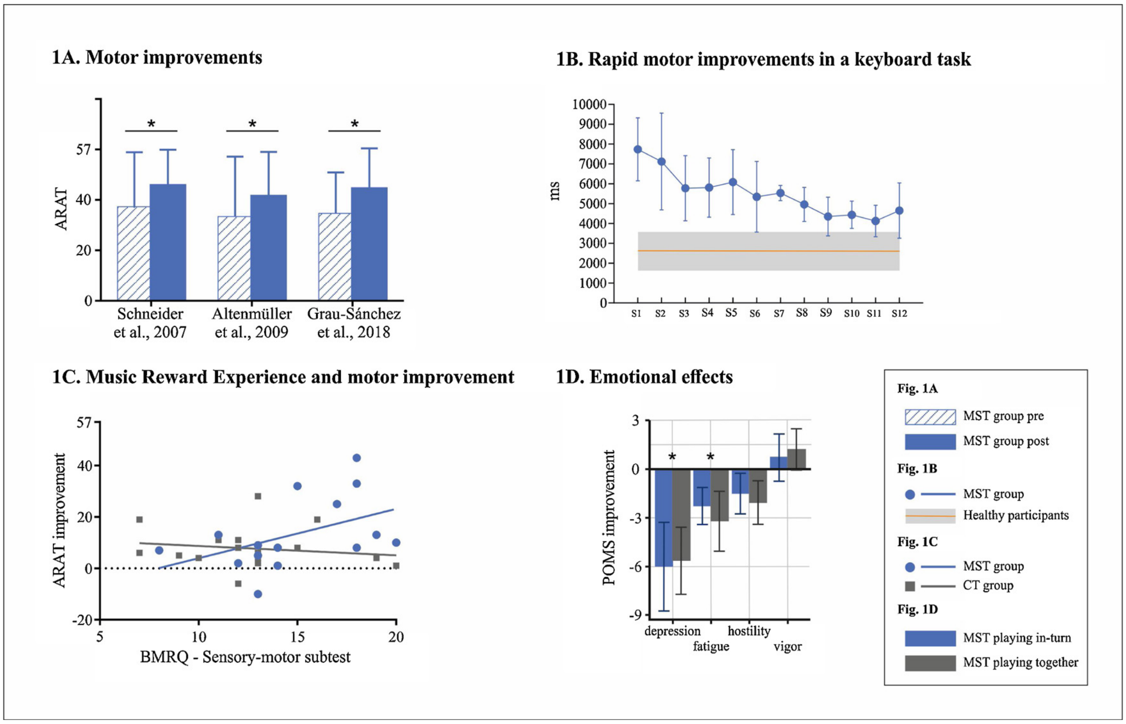

Fig. 1. Behavioural effects of Music-supported Therapy. A) Motor improvements in subacute stroke patients after Music-supported Therapy. This figure illustrates the scores in the *Action Research Arm Test* (ARAT, maximum possible score = 57) obtained before and after Music-supported Therapy in samples of three different studies (Schneider et al., 2007; Altenmüller et al., 2009; Grau-Sánchez et al., 2018). Stroke patients significantly improved the functionality of the paretic upper extremity after the training. * = $p < .001$ **B) Rapid motor improvements in a keyboard task in a patient treated with Music-supported Therapy.** The figure shows the time (in ms) a patient needed to complete a keyboard sequence across the sessions of the training program (sessions 1 to 12; S1-S12). A fast learning stage can be observed during the first training sessions. The time needed to complete the same task in a sample of healthy participants is shown in orange and grey (mean and standard deviation) (Grau-Sánchez et al., 2017). **C) Motor improvement and musical reward.** In this sample of subacute stroke patients, a correlation was encountered between the sensory-motor subtest of the *Barcelona Music Reward Questionnaire* (BMRQ) and motor improvement measured with the *Action Research Arm Test* (ARAT, maximum score = 57). This indicates that those patients with higher sensitivity to experience reward in musical activities were the ones who improved more in the group treated with Music-supported Therapy (Grau-Sánchez et al., 2018). **D) Emotional effects in subacute stroke patients treated with Music-supported Therapy.** Patients treated with Music-supported Therapy (either playing in-turn or together) experienced a significant reduction in depression and fatigue after the intervention * = $p < .001$ (Van Vugt et al., 2014). Data and figures are reproduced with permission from the authors. MST, Music-supported Therapy; CT, Conventional Therapy.

impairment and movement speed.

Only two studies have investigated the progression of motor gains over the course of the training (Fig. 1b; Grau-Sánchez et al., 2017; Villeneuve and Lamontagne, 2013). Improvements in velocity, key pressure and note accuracy were achieved rapidly during the first training sessions, which reflects the fast learning stage of motor learning. Rapid improvements occurred in the context of musical task performance, but functional gains and recovery of deficits were more evident at the end of the Music-supported Therapy program and were even more significant after a second training period. Generalisation of motor gains to activities of daily living has been explored in two randomized controlled trials in the subacute stage (Grau-Sánchez et al., 2018; Schneider et al., 2007). Patients improved in the performance of functional tasks and activities of daily living after the training and reported a transfer effect to every-day functions. Moreover, adding Music-supported Therapy to the standard rehabilitation program promotes the same retention of gains as conventional therapy at three months (Grau-Sánchez et al., 2018). Interestingly, patients who are more sensitive to experience reward in musical activities seem to show a larger motor improvement when treated with Music-supported Therapy (Fig. 1c; Grau-Sánchez et al., 2018).

2.1.2. *Effects on cognition, mood and quality of life*

Subacute patients report having better language abilities after Music-supported Therapy than those patients who are treated only with conventional therapy (Grau-Sánchez et al., 2018), probably because the processing of relevant features of music such as rhythm and beat share several networks with language processing (Patel, 2011). Moreover, chronic patients are able to improve their processing speed and mental flexibility after the training (Fujioka et al., 2018; Ripollés et al., 2016a). These results are in agreement with previous findings on the effects of passive music listening on cognitive functions in subacute stroke patients and music playing in traumatic brain injury (Särkämö and Soto, 2012; Särkämö et al., 2008).

Regarding the effects on mood and quality of life, patients treated with Music-supported Therapy have reported increased quality of life and positive emotions as well as a reduction of negative affect, fatigue and depressive symptoms (Fig. 1d; Fujioka et al., 2018; Grau-Sánchez et al., 2018; Ripollés et al., 2016a; Van Vugt et al., 2014). The results on mood and quality of life are of great significance, because one of the aims of stroke rehabilitation is to improve the patient's quality of life (Albert and Kesselring, 2012). The benefits of Music-supported Therapy at the emotional level are in line with previous research on music-based interventions promoting well-being in patients with other conditions (Fredenburg and Silverman, 2014; Ghetti, 2011; Segall, 2018) and healthy populations (for a review, see Daykin et al., 2018). Importantly, individuals with stronger musical engagement are the ones who show larger effects on well-being after a music-based intervention (Kreutz et al., 2008; Weinberg and Joseph, 2017; Zavoyskiy et al., 2016). Therefore, if Music-supported Therapy can promote similar motor improvements as conventional therapy but patients are in a better mood and increase their quality of life after the training, this argues in favour

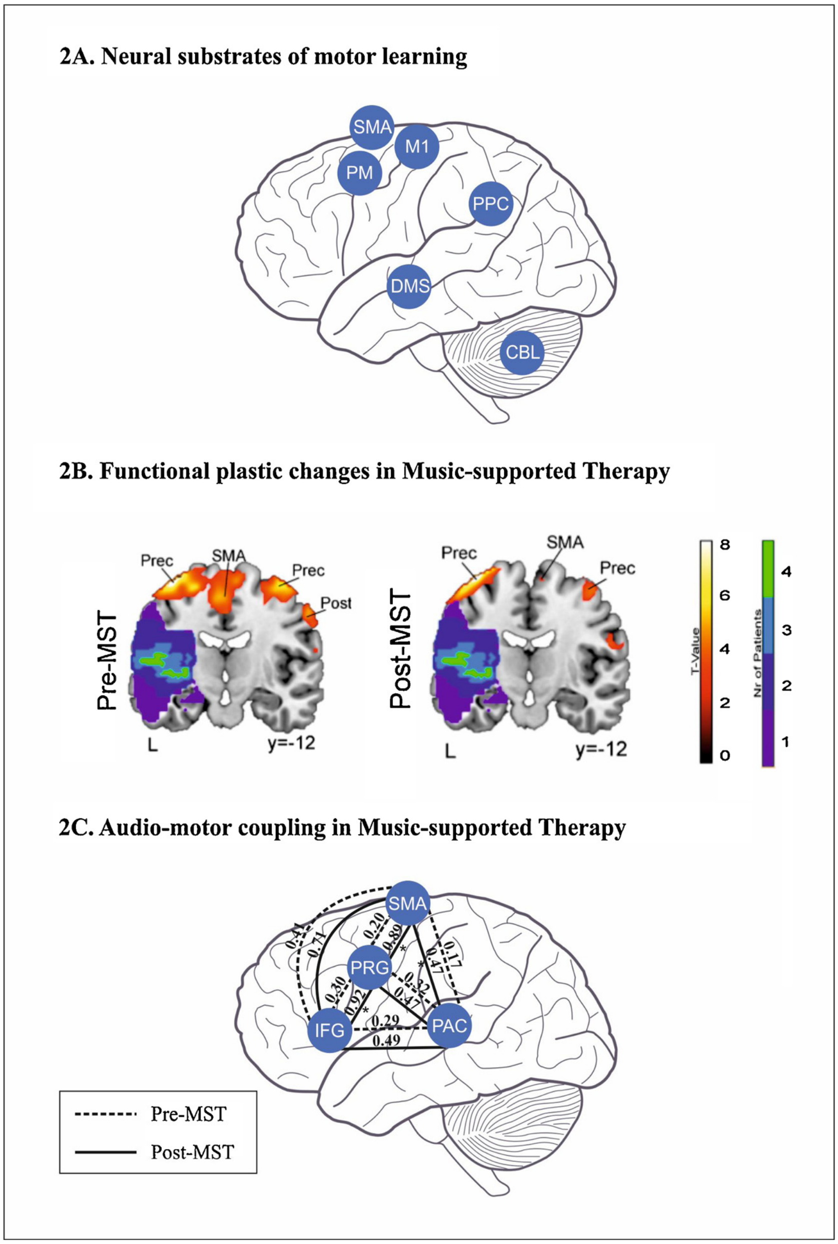

Fig. 2. Neural mechanisms of music-based interventions. A) Neural substrates of motor learning. Regions involved in motor learning include the primary motor cortex (M1), the premotor cortex (PM), the supplementary motor area (SMA), the posterior parietal cortex (PPC), the dorsomedial striatum (DMS) and the cerebellum (CBL). Adapted from Dayan and Cohen, 2011.**B) Functional plastic changes in Music-supported Therapy.** Results from a motor task with functional Magnetic Resonance Imaging before (Pre-MST) and after the intervention (Post-MST) in a sample of chronic patients. Before the intervention, movements of the paretic hand elicited bilateral activations in motor regions. These activations were reduced in the ipsilateral hemisphere, indicating a pattern of intra-hemispheric reorganisation in the affected hemisphere. In this image, lesions of patients are also shown (Ripollés et al., 2016a). **C) Audio-motor coupling in Music-supported Therapy.** A pattern of co-activation of auditory and motor regions was encountered in a sample of chronic stroke patients after being treated with Music-supported Therapy.

of Music-supported Therapy over conventional approaches.

2.1.3. Effects on plasticity

Two experimental studies have reported an increase in the excitability and a cortical motor map reorganization in the affected sensorimotor cortex of subacute and chronic stroke patients after Music-supported Therapy (Amengual et al., 2013; Grau-Sánchez et al., 2013). Similarly, in chronic stroke patients, a reduction in the involvement of the unaffected hemisphere during paretic movements has been reported. This could indicate a pattern of intrahemispheric reorganisation within the lesioned hemisphere after the training (Fig. 2b; Ripollés et al., 2016a). Moreover, a reestablishment of functional connectivity between auditory and motor regions has been described in chronic stroke patients (Fig. 2c). However, in these studies, the lack of a control group of patients undergoing a different therapy is a limitation when concluding that these changes are specific to Music-supported Therapy, since other types of motor therapies can promote similar cortical reorganisation and functional changes (Classen et al., 2014; Liepert et al., 2000).

2.2. Music glove

Music glove aims to facilitate the practice of movements with the affected extremity at home (Friedman et al., 2014; Zondervan et al., 2016). This device consists of a glove that produces different sounds when gripping and pinching movements are performed and challenges patients with an interactive computer game to play along with songs. One study found that the effects of Music glove were superior to self-guided hand exercises in chronic stroke patients (Friedman et al., 2014). However, in a randomised controlled trial, hand and finger home-based training with Music glove during three weeks lead to similar improvements as self-guided exercises following a booklet-based program (Zondervan et al., 2016). The superiority of Music glove over more conventional approaches for home training in the chronic stroke phase has not been well established. However, the device is feasible and offers the possibility to easily incorporate gamified music-based exercises for home stroke rehabilitation. One possible advantage of Music glove over other approaches is that the patient can perform different types of finger and hand movements that are more relevant for everyday activities. Key limitations of the few studies investigating motor rehabilitation using Music glove so far include the small sample sizes and lack of standardisation of exercise programs.

2.3. Classical approaches of music therapy

Group music therapy is different from other types of music-based interventions such as Music-supported Therapy or Music glove because sessions are conducted in small groups by a music therapist, and the main focus is on recreational and emotional aspects. These therapies have been mainly used in palliative care (McConnell et al., 2016; Schmid et al., 2018), oncology (Potvin et al., 2015), and mental health (Aalbers et al., 2017) although they could be feasible and motivating for stroke patients (Street et al., 2018). In Music upper limb therapy-integrated (MULTI), stroke patients are engaged in group sessions of interactive live music making (Raghavan et al., 2016). Together with the music therapist, patients improvise music with different adapted musical instruments. The instruments include maracas, drums, and piano among others that are selected based on the patient's preferences, abilities and motor deficits. In MULTI, specific attention is paid to offer a successful and fulfilling experience to the patients. It also aims to facilitate emotional expression through the selection of the type of music, interpersonal communication, and a sense of belonging to the group. A study with chronic stroke patients undergoing this treatment has shown that patients reduced their motor and sensory deficits, and increased their functionality, well-being and participation (Raghavan et al., 2016). Raglio et al. (2017) have tested the effectiveness of adding music therapy to a standard program of rehabilitation for subacute patients, where the music intervention involved social, communicative and relational aspects in group music playing. In this study, only patients treated with music therapy increased their grip strength after seven weeks of training. Patients also improved their quality of life, functional level and gross mobility although these improvements were also observed in the control group who received the standard program of rehabilitation alone (Raglio et al., 2017).

2.4. Moving to the music and moving to create music

Moving to the music and making music through movements have also been used to treat motor deficits after stroke. An example of the former is Rhythm- and music-based intervention, which is a multisensory stimulation therapy based on the Ronnie Gardiner Rhythm and Music method (RGRM™) developed by jazz drummer Ronnie Gardiner (Bunketorp-Käll et al., 2012). In this method, a note system with visual cues of different symbols and colours is used to prompt movements of the right and left hand and foot. Movements include clapping hands, tapping hands on knees, and stamping the feet on the floor. Using music as a background, the therapist displays the cues on a screen to move to the music. The difficulty of movement sequences is adapted to the patient's mobility and is increased in complexity over sessions. In a recent randomised controlled trial, Bunketorp-Käll et al. (2017b) compared the effects of Rhythm- and music-based therapy to horse riding and no treatment in chronic stroke patients (Bunketorp-Käll et al., 2017b). Patients treated with Rhythm- and music-based therapy reported a greater perception of recovery, and improved in balance, grip strength and working memory when compared to patients who did not receive any treatment. Importantly, patients in the horse-riding group also increased their perception of recovery and improved in gait and balance. In both active treatment groups, behavioural improvements were maintained over time, and caregiver burden was reduced (Bunketorp-Käll et al., 2017a, b).

Training through Musical sonification therapy has been used to enhance gross movements of the upper extremity in the early subacute phase of stroke recovery (Scholz et al., 2016). During the sessions, patients are seated at a desk with a three-dimensional space frame, and when they move their upper extremities forward, upward or to the left or right, sounds are produced with variations in scale and volume. Although patients need some time to familiarise themselves with the training setting through implicit learning, once they are aware of the rules of Musical sonification therapy, they are encouraged to perform exercises that increase in complexity. A randomised controlled trial comparing Musical sonification therapy to a mute version of the exercises found that this therapy was not superior to a silent condition. Patients in both groups enhanced the functional use of the affected upper extremity. However, only patients who listened to the music experienced a reduction in pain after the training (Scholz et al., 2016). In a larger multicentre study, Musical sonification therapy showed limited clinical benefits. Patients receiving this treatment showed slight improvements in movement smoothness (Nikmaram et al., 2019).

2.5. Interim summary: music in stroke rehabilitation

The studies presented above and summarised in Table 2 make use of different research designs. Overall, there are ten randomised controlled trials (48 %) and four experimental studies (19 %) that had a control group but did not randomize patients to the different treatment arms. Moreover, four experimental studies (19 %) have investigated music therapy but without comparing its effects to another treatment, and there is a case-series (5%) and two case-studies (9%). Nine of these studies (43 %) have tested music-based interventions in the early subacute phase of stroke recovery whereas twelve studies (57 %) focused on the late subacute or chronic phase. In the early subacute phase, music-based interventions were added to the standard program of rehabilitation. Music therapy as an add-on treatment was compared to other types of interventions or standard care. In the chronic phase, music-based interventions were compared to other types of treatment such as horse riding, self-guided hand exercises, or mute versions of the musical training.

Regarding the primary outcome, most of these studies (86 %) have investigated the effectiveness of music-based interventions primarily in improving the motor function or impairment of the upper extremity. Other studies, however, investigated the effectiveness of these therapies in improving the perception of recovery, and physical and cognitive disability.

It can be concluded that active music-based interventions in stroke motor rehabilitation can enhance the motor function in subacute and chronic stroke patients. Most of the studies (90 %) have demonstrated an equivalent or superior effect of music-based interventions in improving motor abilities when compared to conventional therapy. Notably, a general effect of music-based therapies on well-being has been reported in most of the studies. Stroke patients have better mood and quality of life after musical training and report having less fatigue and negative emotions.

3. Mechanisms behind music-based interventions in stroke rehabilitation

Playing musical instruments in stroke motor rehabilitation requires highly coordinated fine movements that need to be precise in their timing and spatial organization. It also requires processing of information from different modalities. These two components can also be found in other types of motor therapies (i.e. robotic therapy, virtual reality or mirror therapy). In addition, there is an emotional component that is exclusive to music-based interventions and is linked to the ability of music to induce positive feelings and regulate mood. Below, we examine these different factors and their contribution to the effectiveness of music-based therapies (Fig. 3).

3.1. Motor skill acquisition in music-based interventions

3.1.1. Components of motor learning during musical training

Theories of motor learning in healthy individuals might provide

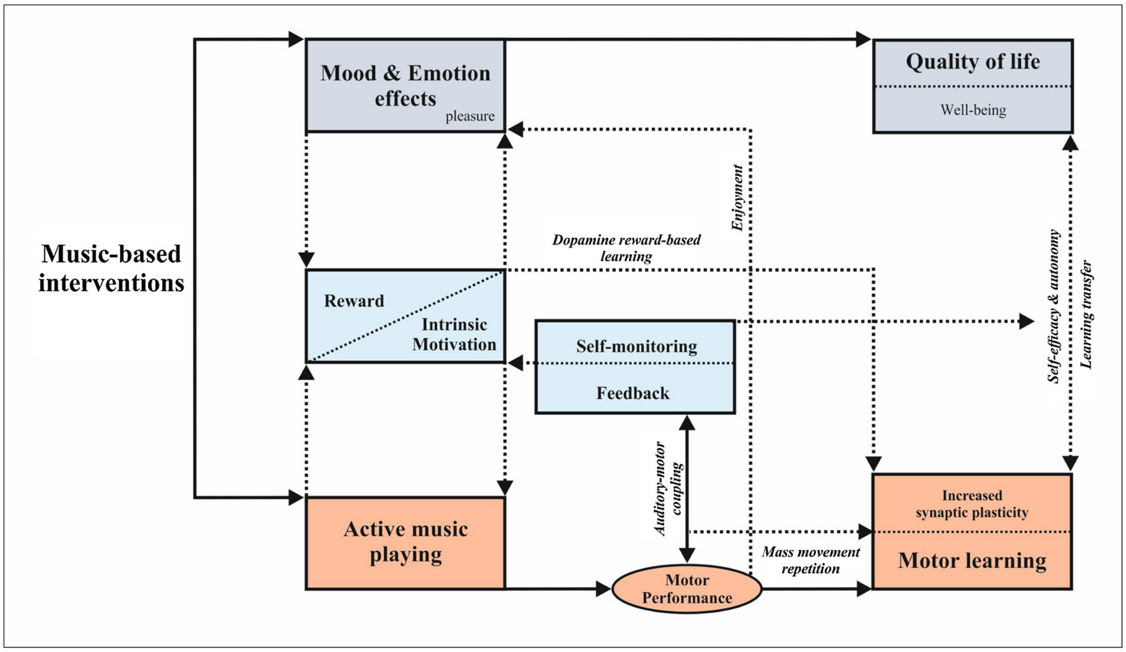

Fig. 3. Interacting components of music-based interventions. Music-based interventions involve mood and emotion effects as well as active music playing. On one hand, emotional aspects of music playing have a direct impact on boosting the individual's quality of life and well-being. On the other hand, playing an instrument requires mass repetition of movements and integration of auditory information, both elements contributing to motor learning. Specifically, the auditory information serves as a feedback and facilitates self-monitoring of the performance. A key element in music-based interventions is that music is linked to experiences of reward. Music playing in the context of rehabilitation can target intrinsic motivation. These two elements, reward and intrinsic motivation contribute to reward-based learning, boosting synaptic plasticity and increasing self-efficacy and autonomy.

insights about the optimal conditions to facilitate effective learning and better motor performance in stroke patients (Kitago and Krakauer, 2013). Wulf and Lewthwaite (2016) have recently developed the OPTIMAL model of motor learning, which proposes an explanation of how motivational and attentional factors influence motor learning (Wulf and Lewthwaite, 2016). Music-based interventions are *task-specific* since patients are trained to play a musical instrument, and therefore, aimed at learning a specific skill. Learning to play an instrument requires *mass repetition of movements*, which is a well-known principle of motor learning and rehabilitation. Exercises can be arranged into multiple levels of difficulty, which allows the gradual approximation to desired performance, known as *shaping*. Considering that patients have moderate-to-severe motor deficits, adapting the exercises can facilitate playing regardless of the patient's motor ability, *tailoring* the training to the individual needs of the patient. Besides, working with musical instruments allows exercising different types of movements, as well as performing different movement sequences depending on the musical piece, thereby contributing to *task variability*. In music-based interventions, the therapist provides *instructional language* and guidance, demonstrating the movements (*modelling*) or using verbal and visual cues for *prompting* movements, which can be progressively faded out as the patient improves. Similarly, electronic instruments can also be programmed to provide cues for patients (i.e. metronome clicks as a rhythmic cue). Instructions can be easily directed to the outcome of the performance, which is the sound of the musical instrument, focusing the *attention on the goal* of the movement. The *feedback* of the therapist and the auditory stimulus are sources of information about the patient's performance and may be considered extrinsic reinforcers. These serve to increase error awareness and to promote online motor adjustments. As the patient progresses, feelings of self-efficacy, satisfaction, and positive affect might act as intrinsic reinforcers.

3.1.2. Musical training and plasticity

One of the mechanisms that may underpin motor recovery in stroke patients treated with music-based interventions is that musical training promotes plasticity. Providing a context of motor skill acquisition, musical training in stroke aims to induce similar neural plastic changes as those occurring in healthy individuals when they learn to play an instrument. In the planning and execution of complex sequences of movements, the basal ganglia, supplementary motor area, premotor, motor and somatosensory cortical regions, and cerebellum are all involved (Fig. 2a; Zatorre et al., 2007). All these regions play different roles in sequencing movements in the correct timing, predicting and controlling movement trajectories, and monitoring errors for online motor adjustments.

Music training leads to functional and structural changes specially in motor brain regions (Altenmöller and Schlaug, 2015; Dayan and Cohen, 2011; Draganski et al., 2004; Draganski and May, 2008; Schlaug, 2015). For example, when non-musicians learn to play piano sequences, the cortical representation of flexor and extensor finger muscles can experience an enlargement that is associated with improved performance in the piano task (Pascual-Leone et al., 1995). Thus, this type of training could be beneficial to promote reorganization of the motor cortical map and the recovery of motor brain regions in stroke patients.

3.2. Multimodal stimulation in music-based interventions

In the following we give an account of the different processes and brain networks involved in the integration of auditory information during music playing. This account has been derived from multiple studies and, while containing a few loose ends, represents our current understanding.

Music-based interventions can incorporate many principles of stroke motor rehabilitation. What makes these interventions different from other motor rehabilitation techniques is the multisensory nature of musical activities, which may be beneficial for learning and could be a critical aspect in explaining the effectiveness of music-based therapies (Zimmerman and Lahav, 2012). In music playing, movements are performed to produce an outcome: the sound of the instrument. A precise mapping between the sound and the movement to produce it is needed when playing music (Chen et al., 2012). Parietal, sensorimotor and premotor areas, belonging to the dorsal auditory-motor cortical pathway (Vaquero et al., 2018; Zatorre et al., 2007) are responsible for controlling and adjusting movements in space and time. When listening to the instrument sound, projections from the primary auditory cortex to parietal regions are important to create auditory-motor transformations and enhance the association between sound and movement (Hickok et al., 2003; Hickok and Poeppel, 2004; Patel, 2006). The detection of errors from auditory information is crucial for learning and refining actions and involves frontal, parietal and temporal regions as well as the cerebellum (Herrojo Ruiz et al., 2017; Penhune and Steele, 2011; Proverbio et al., 2017). In this sense, there is a complex audio-motor interplay that involves the establishment and reinforcement of fast and precise feedforward and feedback loops (Vaquero et al., 2018; Wollman et al., 2018).

When planning a movement, internal motor representations are used to make predictions of what the outcome will be. The motor plan is modulated by these predictions and thus, anticipating the desired sound (movement outcome) influences the motor output in a feedforward loop. When the movement is performed, the sound is evaluated and compared to the auditory expectations that were created by internal representations. Thus, the auditory feedback is used to evaluate the motor performance and make on-line motor adjustments (D'Ausilio et al., 2010; Furuya and Soechting, 2010). This sensory-motor interplay requires the coactivation of auditory and motor regions. It has been shown that motor and premotor cortical regions are activated when musicians listen to well-trained melodies (Lahav et al., 2007; Haueisen and Knösche, 2001). On the other hand, when musicians play silent instruments, auditory regions can be activated. Moreover, incongruence between sound and action observation during playing triggers an error detection response in the anterior cingulate cortex, the superior temporal gyrus, the supplementary motor area and the cerebellum in musicians (Proverbio et al., 2014, 2017). These examples support the idea of audio-motor coupling in music making. Audio-motor coupling reflects the coupling between perception and action and has been observed not only in musicians but also in musically untrained individuals after short training sessions with a musical instrument (Bangert et al., 2006).

3.3. Emotional and motivational aspects in music-based interventions

Playing musical instruments is an activity that has real-world relevance, and is often perceived as enjoyable by patients. Motivation towards the task is an essential factor in motor learning. In stroke patients, mastering an instrument, even at a very basic level, could increase feelings of self-efficacy and agency. The crucial role of motivation in predicting rehabilitation success in stroke has been frequently recognised (Maclean et al., 2000; Siegert and Taylor, 2004) despite the initial recommendations to avoid the use of this term due to the lack of consensus across professionals when measuring motivation in patients and the peril of erroneously labelling patients in certain categories (King and Barrowclough, 1989). In the study of Grau-Sánchez et al. (2018), the capacity of patients to experience pleasure from musical activities was related to motor gains. This association was not found in the control group that underwent conventional rehabilitation. The reward that patients experience in musical activities and their motivation to be engaged in music-related experiences was evaluated using the Barcelona Music Reward Questionnaire (Mas-Herrero et al., 2013). The sensorimotor factor assessed by this questionnaire was related to motor gains in Music-supported Therapy. This means that those patients who often dance, tap or move when listening to melodies and hum or sing along to music were the ones that improved more in the Music-supported Therapy group.

Intrinsic motivation towards the task is a crucial component for reward-based learning and successful motor performance (Censor et al., 2012). Participation in pleasant musical activities is associated with activation of the midbrain-striatal reward-motivation brain networks and dopamine release (Ferreri et al., 2019; Salimpoor et al., 2011). Hence, it is possible that part of the effects of music on motor rehabilitation could depend on this neuromodulatory system. In favour of this idea, previous studies have shown that tegmental dopaminergic neurons project to primary motor cortex through the mesocortical dopaminergic system (Lindvall et al., 1974; Luft and Schwarz, 2009). These projections may modulate cortical reorganisation during learning (Bao et al., 2001), being especially relevant for improving motor skills (Molina-Luna et al., 2009). Dopamine effects on motor learning have also been observed to affect the strength of synaptic connections (Wickens et al., 2003). In this regard, a study by Hosp et al. (2011) showed that damage to midbrain dopamine neurons projecting to the motor cortex impaired motor skill learning and consequently early gene expression in motor neurons associated to synaptic plasticity (Hosp et al., 2011). Noticeable, in this study, learning was partially restored after a dopamine precursor (Levodopa) injection into the motor cortex. Finally, recent research in rodents has shown that primary motor and somatosensory neurons (with dense dopamine receptors) represent information regarding reward anticipation and delivery (in the form of *reward prediction errors* as recorded in midbrain dopaminergic neurons), suggesting a potential role of dopamine reward-based plasticity in motor learning (Ramakrishnan et al., 2017). This converges also with the positive effects observed in motor learning after administration of reward- and punishment-based feedback (Abe et al., 2011; Galea et al., 2015; Nikooyan and Ahmed, 2015; Wächter et al., 2009).

At the clinical level, initial research has suggested better motor recovery in stroke patients after administration of a dopamine precursor concurrent to physiotherapy (Floel et al., 2005; Scheidtmann et al., 2001). This effect has been called into question by the results of the DARS trial, which showed that dopaminergic therapy does not improve functional outcomes (Ford et al., 2019; see also comment by Stinear, 2019). The effects of reward feedback on motor learning in stroke patients have been further substantiated by recent studies (Goodman et al., 2014) with positive and negative feedback yielding similar results (Quattrocchi et al., 2017). Overall, it seems plausible that reward-based motivated learning might create an enriched training environment, enhancing arousal and attention (Engelmann and Pessoa, 2007; Small et al., 2005) and promoting faster motor learning and retention of motor gains (Quattrocchi et al., 2017). Future studies should evaluate the duration and transfer to real life of these effects when using augmented feedback to enhance motor recovery.

Recent studies have shown the importance of engaging in self-regulatory learning activities in which humans can regulate their own intrinsic reward experiences. For example, when healthy adults correctly evaluated their own performance in a problem-solving task (Ripollés et al., 2018; Ripollés et al., 2016b), increased activation was observed in the dopaminergic reward midbrain and ventral striatum. This activation was coupled with increased activation in the hippocampal memory system and pleasurable feelings. Similarly, recent research on curiosity highlights the importance of intrinsic motivation in triggering the activation in the dopaminergic reward system and potentiating retention effects (Gruber et al., 2014). This idea agrees well with the classic motivational framework of the self-determination theory (Ryan and Deci, 2000), and suggests that providing patients with more self-control and freedom of selection in their training (e.g., using more flexible, recreative, gaming-based and improvisational trained environments) could strengthen their feeling of self-efficacy, competence and autonomy and lead to better long-term learning outcomes (Deterding, 2011; Wulf and Lewthwaite, 2016). The promotion of self-regulation has been very important in increasing the efficacy of educational programs (Pintrich and de Groot, 1990).

The improvement of mood and quality of life seen after Music-supported Therapy could be driven either by the positive and rewarding experience associated with the music-enriched training environment or rather indirectly as a consequence of motor amelioration and increased autonomy. As stroke is often accompanied by post-stroke depression (Robinson, 2003; Robinson and Jorge, 2016), the mood enhancing effect of music-based interventions is important.

4. Future directions in music therapy research

There are several questions regarding music-based interventions that need to be addressed before implementing these treatments into widespread clinical practice. Aspects related to the training protocol, the evaluation of patients, the research methodology and the process of implementation are mentioned in this section in order to move music therapy in stroke motor rehabilitation forward.

4.1. Modifications to the protocol

The number of sessions in previous studies ranged from nine to thirty over a period of three to twelve weeks. The selection of the number of sessions and training hours and their distribution was dictated by convenience and feasibility rather than systematic evaluation. Evidence from basic research on motor learning can help in the design of the most optimal protocol regarding dosage for future studies. Basic research indicates that increasing the intensity and duration of training might lead to better results although this aspect should be investigated in depth in musical training programs for clinical populations (Kitago and Krakauer, 2013; Zeiler and Krakauer, 2013). Most of the studies included in this review used a protocol that consisted of daily short sessions, but it could be that distributing practice, leaving space to longer rest periods, and providing longer and more intense sessions lead to a better motor performance in stroke patients (Krakauer, 2006; Shadmehr and Brashers-Krug, 1997). Future studies, especially in the form of single-case designs, should explore the benefits of resting between sessions and the role of offline periods to boost motor memory consolidation (Doyon and Benali, 2005).

Formally educating therapists on protocols of music-based therapies could ensure fidelity on treatment administration. The implementation of music-based interventions can be improved by providing therapists with a standardised manual including instructions that are autonomy-supportive, and information about the type and appropriateness of feedback during the training (Wulf and Lewthwaite, 2016). Moreover, modifications to the therapy protocol that allow the patient to select their most preferred songs or musical style could increase the patient's motivation and feeling of autonomy. Since motor improvements seem to be related to the individual's capacity to experience reward from musical activities, future studies should consider stratifying patients with regard to this aspect (Grau-Sánchez et al., 2018). Until now, the instruments used in Music-supported Therapy have been an electronic keyboard and a drum set, but other instruments could be used as well following the principles of the training to involve other movements that are relevant for everyday life tasks and activities. Including novel input devices to produce music, e.g. the Music-glove or devices similar to the Theremin (Zaitsev, 2008), might be important to improve movement quality and range.

Individual sessions in inpatient rehabilitation centres or day hospital services are sometimes difficult to adopt and are constrained by the resources of health systems or insurance conditions. Music-based interventions can be adapted for home use as a part of a community reintegration model (Villeneuve et al., 2014). The use of technology may also allow introducing new elements in training such as modelling with videos or self-modelling by hearing the best trials played by the patient. The development of new technologies that allow tailoring exercises and monitoring patients' progress remotely in the sense of telerehabilitation could be important improvements. However, one difficulty when applying music-based interventions at home could be that it may only work for already motivated patients. In this line, new technologies also offer the possibility to improve training protocols by gamifying exercises and providing a more recreational context.

An important methodological issue is the control treatment in rehabilitation studies. Some of the studies presented in this review have compared music-based interventions to conventional therapy. However, rehabilitation services and programs vary across countries and even regions within the same country in the type of setting, duration, intensity and health professionals involved (Winstein et al., 2016). In studies of stroke rehabilitation, control treatments are poorly defined as pointed out by a recent systematic review including 215 studies (Lohse et al., 2018). In this sense, the template for intervention description and replication (TIDIeR) is an excellent tool for researchers to check if they are describing relevant aspects of the treatment when reporting results (Hoffmann et al., 2014).

4.2. Evaluation of patients

Future studies should use neuroimaging techniques to investigate the mechanisms underpinning improvements produced by music-based interventions. Moreover, the use of these measurements at baseline may allow stratifying patients according to potential confounding variables related to lesion size and location. For instance, the evaluation of the integrity of the corticospinal tract with Transcranial Magnetic Stimulation as a measure of structural reserve is one of the most important predictors for recovery in stroke patients (Di Pino et al., 2014; Stinear, 2010). Other techniques such as Voxel-based lesion-symptom mapping can be used to identify if lesion location and site can predict which patients respond better to the treatment.

A critical question concerns the best stage for applying music-based therapy. Most efforts have been devoted to the subacute phase, during which the potential for recovery might be optimal (Dancause and Nudo, 2011). However, numerous studies have found that functionality can be improved with training in the chronic phase. A multicentre study found that patients experience a functional deterioration five years after the stroke (Meyer et al., 2015) and learned non-use of the affected extremity is common in stroke patients, affecting the functionality of the patient in everyday life activities (Taub et al., 2006). Therefore, there is increasing interest in developing interventions that are feasible to apply once patients are discharged from rehabilitation services. In this sense, music-based interventions seem promising not only in the subacute phase but also in the chronic stage as a way of exercising and carrying out active and stimulating activities to prevent decline in functionality.

The retention of motor gains has been investigated in few studies in evaluations performed at three months after finishing the training but longer follow-up should be performed. Evaluation in the long-term can also explore possible negative side-effects of music-based interventions (Craig et al., 2008). Since most music-based interventions use a paradigm of motor learning, trying to avoid compensatory movements and promote recovery of the motor function, it could be that patients experience problems such as pain or muscle contractions, due to the forced used of effectors (Carmichael and Krakauer, 2013; Jones, 2017).

4.3. From the laboratory to the clinic: the example of Music-supported Therapy

Music-supported Therapy was designed in 2007 with a strong ground on basic research. By using the musician's brain as a model for neuroplasticity, the rationale behind Music-supported Therapy was to use elements of musical training to promote brain reorganisation and functional recovery in stroke patients. However, there is a long process between the design of a treatment and its implementation into clinical practice routinely.

From the first study of Music-supported Therapy by Schneider et al. (2007) to the present day, other studies have evaluated several aspects related to the effectiveness of this therapy. However, introducing Music-supported Therapy into clinical guidelines will require more high-quality randomised controlled trials, with larger samples, stratification of patients and recruitment at multiple rehabilitation centres. Only this will allow conducting meta-analyses and systematic reviews and draw a conclusion about its effectiveness.

The cost of Music-supported Therapy has never been evaluated, but it is a crucial aspect when implementing therapies that have been designed in the laboratory and need to be adopted in centres that belong to the public health system or involve health insurance companies. Once the therapy is included in clinical practice guidelines and implemented into clinical practice, further studies will be needed to monitor the administration of Music-supported Therapy, its adaptation and integration into real practice and its long-term effects, aspects that are difficult to explore using research designs.

5. Clinical considerations for implementation

Like other motor rehabilitation techniques, music-based interventions can be regarded as complex interventions. These therapies comprise numerous elements, all of them potentially contributing to treatment success, which are difficult to study separately. Some of these elements of complexity rely on the multimodal nature of the training and the fact that the therapist and patient's behaviour may influence the treatment effect. Moreover, training programs are tailored to the needs of the patient, and although the main target of the therapies described is the recovery of the motor function, they can affect other areas of functioning. Considering the Medical Research Council framework for developing, evaluating and implementing complex interventions, the following sections address how music-based interventions can be implemented.

5.1. Piloting, feasibility and evaluating music-based interventions

Music-based interventions seem feasible to apply, since they have already been tested at a group level in different studies in the subacute and chronic phase of stroke recovery (Altenmöller et al., 2009; Ripollés et al., 2016a; Schneider et al., 2007; Tong et al., 2015; Van Vugt et al., 2016). Voluntary withdrawal of patients undergoing music-based interventions has rarely been reported although further research is needed to investigate patients' satisfaction or intention to continue. Moreover, the acceptability of the music-based interventions by therapists and stakeholders is still unknown. Aspects such as the perceived appropriateness and suitability within organised stroke rehabilitation influence the extent to which a treatment is likely to be used. Focus groups, measures of satisfaction in randomised controlled trials or surveys before and during the intervention can provide insight into all these aspects that influence acceptability (Bowen et al., 2009).

5.2. Reporting the results and implementing music-based interventions

For music-based interventions to be included in clinical practice guidelines the number of published studies and their level of evidence needs to be enhanced. Currently, only ten randomised controlled trials (48 % of studies) have validated music-based interventions to treat motor deficits after stroke (Table 2). Future efforts should be directed to conduct multiple randomised controlled trials and meta-analyses. The second crucial aspect is the size of the treatment effect. Music-based interventions seem useful and effective in treating hemiparesis of the upper extremity after stroke. However, conflicting evidence exists regarding their superiority over conventional therapy. This aspect will influence the strength of the clinical recommendations to apply music-based interventions. Moreover, studies evaluating the cost-effectiveness of these therapies are necessary to allow the transition of music-based interventions from research to clinical practice.

Implementation is challenging because aspects such as practicality, adaptation, and integration of these therapies in rehabilitation program and centres have to be addressed. To implement music-based interventions, an analysis should be conducted of the resources needed including space, materials and therapist requirements. Moreover, monitoring of implementation to ensure the quality of administration or how a therapy is adapted to clinical practice will be necessary during the first years after introducing music-based interventions in clinical settings.

Declaration of Competing Interest

None.

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