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CONCISE REVIEW

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Putting music to trial: Consensus on key methodological challenges investigating music-based rehabilitation

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Abstract

Major advances in music neuroscience have fueled a growing interest in music-based neurological rehabilitation among researchers and clinicians. Musical activities are excellently suited to be adapted for clinical practice because of their multisensory nature, their demands on cognitive, language, and motor functions, and music's ability to induce emotions and regulate mood. However, the overall quality of music-based rehabilitation research remains low to moderate for most populations and outcomes. In this consensus article, expert panelists who participated in the *Neuroscience and Music VII* conference in June 2021 address methodological challenges relevant to

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music-based rehabilitation research. The article aims to provide guidance on challenges related to treatment, outcomes, research designs, and implementation in music-based rehabilitation research. The article addresses how to define music-based rehabilitation, select appropriate control interventions and outcomes, incorporate technology, and consider individual differences, among other challenges. The article highlights the value of the framework for the development and evaluation of complex interventions for music-based rehabilitation research and the need for stronger methodological rigor to allow the widespread implementation of music-based rehabilitation into regular clinical practice.

KEYWORDS
evidence-based medicine, methodology, music-based rehabilitation, neurology, patient-centered

INTRODUCTION

Neurological disorders are the leading cause of disability globally and, with continuing growth and aging of the population, the prevalence of these disorders is expected to increase, placing enormous pressure on health care and social systems.[1,2] Disorders, such as acquired brain injury, neurodegenerative diseases, and neurodevelopmental conditions, significantly impact individual functioning and quality of life.[1,3–6] These conditions alter a wide range of brain and body functions, resulting in movement and cognitive deficits as well as mood and emotional disorders that lead to limitations in daily activities and participation restrictions.[7–11] Individuals affected by neurological disorders undergo intensive, diverse, and long rehabilitation processes; require physical, social, and emotional support from close ones; and may need rehabilitative interventions throughout their lifespan.[12,13] In this context, the development and validation of evidence-based and cost-effective rehabilitative interventions targeting the recovery of lost functions, coupled with improvement and maintenance of autonomy during the acute and chronic phases of the disease, is a central research area and key clinical-translational goal.[14]

Recently, considerable interest has grown in music-based neurological rehabilitation among researchers and clinicians. This interest has been fueled by significant advances in neuroscience related to understanding the neural basis of music processing and the neuroplasticity changes underlying musical training.[15–19] Musical activities, such as listening, singing, playing, dancing, or score reading, are excellently suited to be adapted for clinical practice with rehabilitative purposes. These activities (1) require integration of information from different sensory modalities, (2) place high demands on cognitive functions, (3) are inherently motivating and evoke positive emotions, (4) promote social interaction and bonding, and (5) may involve skilled movements linked to auditory cues.[20,21] The multisensory nature of musical activities and music's ability to induce emotions and regulate mood can increase patients' engagement, motivation, and well-being when used during the rehabilitation process.[22–24] Moreover, musical activities are widely available and can be adjusted to different levels of cognitive and motor function, as evidenced by several studies conducted on stroke, Parkinson's and Alzheimer's disease, traumatic brain injury, or autism.[25–36] They can also be adapted to the individual's ability and to the different recovery stages, ranging from more passive modalities, such as music listening, to active and highly demanding activities, such as reading or playing music. Music-based rehabilitation can be applied in rehabilitation settings, but there are also home-based interventions that include self-administered sessions with or without the assistance of a caregiver that may be excellent to maintain and enhance functioning in chronic stages.

A basic search on *PubMed* in June 2022 combining the keywords "music" and "neurological rehabilitation" shows that the number of publications about music-based rehabilitation and neurological diseases has considerably increased from 2011 to 2022. However, while individual randomized controlled trials have shown positive emotional, motor, or cognitive effects of music interventions, the overall quality of evidence for the clinical efficacy of music-based rehabilitation remains low to moderate for most patient populations and outcomes.[37–39] Building consensus about the design and methodology of trials and fostering collaboration between music, rehabilitation, and neuroscience communities as well as across research laboratories in different countries is essential. Such a development would allow conducting larger multicenter clinical trials that would foster the development of the music rehabilitation field and, ultimately, allow the translation of music intervention methods from the laboratory to clinical practice.

This article is the result of an open discussion from a virtual workshop at the *Neuroscience and Music VII* conference in June 2021 in Aarhus, Denmark. In this workshop, 10 experienced researchers in music-based rehabilitation presented the methodology and preliminary results of ongoing clinical trials and discussed methodological and practical challenges in research. At a roundtable meeting after the conference, the expert panelists reviewed, discussed, and formed a consensus on priority methodological areas relevant to music-based rehabilitation research. As a result of this dialogue, this paper outlines the main challenges related to treatment, outcomes, research designs, and implementation of music-based neurological rehabilitation and proposes different ideas to approach these challenges and propel music in neurorehabilitation research forward (Table 1).

TREATMENT

Defining music-based rehabilitation in research

Music-based interventions in neurological rehabilitation are complex interventions by nature because several interacting components need to be disentangled. Some of these components are related to the task demands, the body and cognitive functions involved, the music and instruments used, or the therapeutic relationship. The structure and standardization of intervention protocols should define the core components and describe them in detail. Adequate reporting of interventions ensures treatment fidelity in future studies, enhancing validity, replicability, and clinical application of findings.[40] However, a recent systematic review, including 187 music-based intervention studies, concluded that the overall quality of reporting was poor, with poor reporting of intervention content and inconsistent terminology.[41] The Template for Intervention Description and Replication (TIDieR) checklist for reporting interventions is a checklist that guides the reporting of interventions in research studies.[42,43] The TIDieR checklist proposes identifying the intervention's name, aim, and rationale, describing in detail the sessions' materials and procedures, including how and by whom the intervention was delivered, alongside information about the location, timing, intensity, tailoring, modifications, and the assessment of adherence or fidelity. In addition to the TIDieR checklist, the Reporting Guidelines for Music-based Interventions, developed by Robb et al., guide the reporting of music-based interventions, considering the factors that are unique to music.[44] These guidelines are composed of seven components specific to music-based interventions, including providing the intervention theory with a rationale for the music selected, who selected the music in the intervention, which music was used and how was delivered, the therapist's qualifications and credentials, or ambient sound, among others. With regard to the intervention's targets, a description of the neural structure and function involved, cognitive or motor abilities, emotional state, and quality of life is also essential for the translation of research outcomes into clinical practice.

A crucial factor when defining music-based interventions is treatment fidelity, as most studies do not describe which strategies were used to keep the intervention delivery consistent across patients, therapists, and the course of the study.[41] Different approaches, such as specific therapist training, manualized protocols, and protocols to track core session components, reduce intervention variability within a study.[45,46] In conclusion, a comprehensive description of training protocols, including strategies for ensuring treatment fidelity, will allow the dissemination of research methods into clinical practice and foster sharing of resources among the rehabilitation community.

Determining control treatments

The multicomponent nature of music-based interventions represents a challenge when deciding which control intervention is the most appropriate for a given study.[47] In neurorehabilitation studies, control groups allow to consider other influences on health outcomes, such as developmental maturation in studies with children; degeneration in older adults; spontaneous recovery in stroke and brain injury patients; placebo effects; the learning or test-retest effects in repeated outcome measures; and fluctuations of the disease, either spontaneous or in response to drug treatments.[48] Passive control groups do not account for the effects of the experimental group when it comes to experiencing a change in routine, engaging in activities that promote health, and social desirability. Moreover, in acute conditions with rapid clinical evolution, it would be unethical to leave patients without treatment.

In active control groups, participants receive other treatments that can be under the umbrella of standard care or a standardized and well-defined intervention as a single comparator. Having designs where only two interventions are compared is often not possible, as patients might also receive their usual and standard rehabilitation to address their deficits and limitations in activities of daily living. Usual and standard treatments, such as rehabilitation programs, including physical, occupational, speech, and neuropsychological therapy, may have synergistic effects on recovery and outcome measures.[49] These interventions aim to improve functioning at different levels, having a significant impact on patients' emotional well-being, quality of life, and autonomy as they experience progress. These potential synergistic effects should be taken into account and if possible controlled for. Ideally, the addition of music-based interventions to a neurorehabilitation program or an ongoing treatment should be compared with extra sessions of other types of activities to match intervention intensity between study groups. Some control intervention examples are listening to audiobooks in studies investigating the effects of music listening, or physical therapy exercises in music-based sonification studies.[27,50]

In exploratory and pragmatic trials that test the efficacy and effectiveness of music-based interventions, an appropriate control group should include all ingredients of the music-based intervention that are not under investigation, selecting an intervention with the same goal that requires similar motor, cognitive, or emotional functions. Defining and dissecting the core components of the music-based intervention can be useful in deciding which components need to be similar in the control intervention and which ones remain unique to the nature of music. A detailed reporting of all components of the control intervention is needed to identify the unique elements of the music-based intervention that promote the therapeutic effect.

Tailoring

Tailoring intervention sessions is essential in patient-centered rehabilitation processes. When designing and implementing the music intervention, it is important to find a balance between making it structured and manualized enough to enable treatment fidelity and replicability while retaining enough flexibility. It is crucial to define which elements of the musical intervention can be adapted without interfering with the fidelity of the intervention, leaving the core components the same for all participants within a study group. These core elements should be monitored across sessions and participants, implementing strategies to ensure consistent delivery and reduce unintended intervention

TABLE 1 Consensus to address challenges related to treatment, outcomes, research designs, and implementation in music-based rehabilitation research

Intervention
Definition of music-based rehabilitation
• Describe the intervention's protocol in detail following the TIDieR checklist.[42]
• Describe the intervention's target at the neural structure and function, and motor and cognitive abilities.
Selection of a control treatment
• Choose active control interventions and match intervention intensity between study groups.
• Select a control intervention with the same goal that requires similar motor, cognitive, or emotional functions.
• Describe the control intervention's aim, rationale, training protocol, and target.
Tailoring
• Define which intervention elements can be adapted without interfering with treatment fidelity.
• Adjust exercises to participant ability.
• Allow choices in some intervention elements to increase motivation (i.e., type of music).
• Register intervention adjustments during data collection.
• Consider intervention adjustments in the analysis and results interpretation.
• Describe which elements of the training program were tailored when reporting.
The use of technology
• Consider low-cost and highly available technologies.
• Codesign new technologies with all stakeholders and potential users (patients, caregivers, and clinicians).
• Conduct proof-of-concept studies to assess the feasibility, usability, and effectiveness of technologies.
• Evaluate whether telerehabilitation is comparable to in-person or face-to-face protocols.
• Assess the limits of the intervention and make music technologies more interactive.
Outcomes
Selection of appropriate outcomes
• Differentiate study outcomes evaluating effectiveness, mechanistic effects, and feasibility.
• Build consensus between researchers and clinicians about evaluation protocols.
• Consider other relevant indicators of improvements (i.e., effect size, MDC, or MCID).
Consideration of individual differences
• Follow the NICE PPI policy[77] to ensure intervention feasibility and meaning for the targeted population.
• Screen participants for any deficits in basic auditory functions, music perception, music-evoked pleasure, or possible proneness to adverse effects triggered by music.
• Consider musical background, music-related auditory-perceptual and motor skills, and sensitivity to music reward in the analysis and results interpretation.
• Collect information about musical preferences and interests from the participant or their relatives.
• Assess prepost changes in musical skills and determine how they relate to transfer effects.
Theory-based predictions for targeted outcomes
• Use specific mechanism-based predictions.
• Consider skill transfer to extra-musical functions and other activities.
Research designs
Framework for complex interventions
• Consider the framework for the development and evaluation of complex interventions.[114,115]
• Consider all the different levels of evidence and clinical research designs.
• Choose case series or smaller experimental studies for new interventions.
• Conduct high-quality and multicenter clinical trials for interventions with solid evidence.
• Create clear and explicit specifications for the intervention protocols in multicenter studies.
• Consider pragmatic and preference trials to reproduce clinical practice conditions.

(Continues)

TABLE 1 (Continued)

Research designs
Stronger methodological rigor in designing and reporting
• Match intervention groups based on symptom severity and general functional ability.
• Provide a clear sociodemographic and clinical description of participants.
• Report information from participants who withdraw from the study.
Implementation
• Address specific subgroups within the population and tailor interventions to make them culturally, sociologically, and neurologically appropriate.
• Consider participants' perspectives and needs on treatment and outcomes.
• Choose outcomes that are relevant and common for clinical practitioners.
• Engage musicians and music instructors in the study and intervention design.
• Involve stakeholders (i.e., patients, caregivers, clinicians, or policymakers) when developing and evaluating music-based interventions.

Abbreviations: MCID, minimal clinically importance difference; MDC, minimal detectable change; PPI, patient and public involvement.

variability.[41,51] The core components may expand beyond the "active ingredients" of the music-based intervention and include aspects related to the dosage, procedure, and quality of the intervention. A comprehensive analysis of the intervention allows determining components of fidelity and designing strategies to monitor and ensure treatment fidelity. A good example of this type of analysis and monitoring strategies design is the study conducted by Wiens and Gordon, where they developed an approach to address treatment fidelity in a music-based intervention to improve grammar skills in children with specific language impairment.[45] The authors focused on four components of fidelity: treatment design, provider training, treatment administration, and treatment receipt. The strategies included the development of an intervention manual, therapist certification, and recording sessions to give feedback to the therapist about the quality and quantity of treatment to ensure consistency. Importantly, a coding system was designed to measure the type of events during the intervention (e.g., instructions and participant responses) and their proportion, measuring content and dosage through observational methods.

With regard to the elements that can be adapted, one of the main adaptations of the music-based intervention can include deciding if sessions are more active or receptive for the patient depending on their abilities and previous experience with music.[52] Apart from adjusting the exercises to the level of participants' ability, elements of the intervention can be chosen by patients to increase motivation and adherence to the intervention. It is common to allow the selection of different types of music according to the participant's preferences or the ideal time to do the intervention session in home-based interventions.[53,54] These individual adjustments should be registered during data collection to consider them in the analysis or results interpretation. Articles reporting the effectiveness of music-based interventions should describe which elements of the training program were tailored and which were strategies to ensure treatment fidelity. Importantly, the nature of within-subjects experimental designs (including cross-over randomized controlled trials, where each participant receives each intervention) allows investigating more personalized interventions and adjusting the sessions considering individual differences and the person's goals as cornerstones in person-centered rehabilitation.[55]

The use of technology

The use of technology coupled with dedicated or general-purpose devices (e.g., mobile devices) is progressively increasing in music-based interventions.[56] Participation of technology in music applications spans a variety of approaches, techniques, and clinical populations, including music information retrieval,[57] to design music materials for sessions, enhanced feedback and sonification for stroke rehabilitation,[58,59] serious games for Parkinson's disease,[60] and recent developments in robotics and human–computer interaction in dementia.[56,61] In these examples, technology can be used for music classification and instrument recognition, for providing sound feedback to the patients' movements using inertial sensors, for training rhythmic skills through a game where success depends on the patients' performance or for listening to music after a social robot interaction. Of particular interest is the line of research dedicated to movement sonification, where kinematic and dynamic movement parameters are transformed into artificially produced sounds to enhance motor perception and performance.[62] The use of real-time movement sonification has been extensively investigated in sports training, showing that it optimizes movement control and execution by improving performance self-awareness through auditory feedback (for a review, see Ref. 63). Movement sonification is a promising therapeutic tool and it has been applied to neurologic rehabilitation to improve gait in individuals with Parkinson's disease or upper-limb movement in stroke survivors.[63–65]

The use of touch-sensitive or multimodal devices, such as tablets and sets of dedicated sensors, is ideally suited for people with disabilities as a way to foster interaction, participation, and compliance during the intervention.[66] Some of these applications can be implemented in off-the-shelf devices, such as tablets and smartphones,[67,68] which are low-cost, highly available to the public, and usable in a home environment for self-rehabilitation. Importantly, these devices allow applying machine learning and artificial intelligence to data collected in real-time during the training sessions. This information can be of great help to better tailor sessions according to progress, difficulty, motivation, or preferences, leading to more personalized interventions.[69] Several music-based interventions using technology are being adapted to be delivered as a form of telerehabilitation,[56] a technological transformation boosted by the recent COVID-19 pandemic crisis.[70] Telerehabilitation can make interventions more accessible, inclusive, and cost-effective, thus contributing to their widespread implementation. They allow reaching patients from rural areas, delivering treatments in the chronic phase, or not putting vulnerable neurologic patients at risk in pandemic scenarios.

When developing and evaluating new technologies for music-based interventions, it is essential to consider acceptance and usability.[71] Therefore, a critical step prior to using technology in music-based interventions is to run proof-of-concept studies for testing feasibility, usability, and effectiveness.[72] These types of studies should include a detailed assessment of the clinical group and users' needs, analyzing how new technology can address these needs and which technical features or requirements are important for users.[73] In the iterative prototype development, the codesign with all stakeholders involved (patients, caregivers, and clinicians) increases the likelihood of acceptance, and qualitative studies with all potential users can provide valuable insights about usability, learnability, acceptability, reliability, and satisfaction.[74] Some of the challenges specific to the use of technology are that devices need to be cognitively accessible for patients and user-friendly. On top of validating the intervention in view of running a randomized clinical trial, proof-of-concept studies allow assessing whether the effect of the intervention is comparable or not (e.g., in the case of telerehabilitation) to in-person or face-to-face protocols in the clinic.

An important aspect to consider is that the relational aspect of music is transformed with technology. Music brings people together, and this relational aspect may be absent or hindered using technological devices or telerehabilitation. The extent to which the relational aspect is critical to the success of the intervention should be assessed to identify the limits of the intervention or foster further developments to make music technologies more interactive. There is a growing interest to design and implement new and cost-effective online treatments using technological advances.[75,76] It is important to adequately consider the impact of incorporating technology on treatment success and patients' recovery. Crucially, the trade-off between face-to-face interventions and telerehabilitation needs to be well assessed and balanced in music-based rehabilitation.

OUTCOMES

Selecting appropriate outcomes in neurological music-based rehabilitation studies

The selection of appropriate outcomes depends on the study aim and research questions and design. It is important to differentiate between outcomes evaluating the effectiveness of the intervention, the mechanistic effects, or the feasibility of the intervention. In effectiveness studies, the selection of the primary and secondary outcomes is a challenge since music-based interventions can target multiple deficits and impairments (e.g., motor, cognitive, and language deficits, mood, social interaction, and quality of life). In the field of neurorehabilitation, there are several validated tests and assessments but there is a general lack of agreement in music-based neurological rehabilitation research regarding the most relevant tests, questionnaires, and measures for a given population and outcomes, making the comparison between music-based studies difficult. In this regard, it is necessary to build consensus between music-based rehabilitation researchers, clinicians, patients, and caregivers about evaluation protocols to decide on generalizable outcome measures that are standardized, reliable, and clinically meaningful. It is also important to consider other relevant indicators of improvement beyond the statistical significance, such as the effect size, the minimal detectable change, or the minimum clinically important difference.

Considering individual differences

Music is a highly personal experience, influenced by many auditory-cognitive, aesthetic, emotional, and autobiographical factors, individual musical preferences, and previous experiences of musical activities across life. Given that the experience of pleasure and reward derived from music is at the heart of all musical activity, it is important to give due consideration to these factors across all stages of music intervention research, from designing the intervention, enrolling participants in the trial, implementing the intervention, and analyzing the results.

During the design phase, piloting the intervention, and getting direct feedback from patients, following the NICE Patient and Public Involvement policy[77] is important to ensure that the intervention is feasible and meaningful for the targeted clinical population and also takes individual limitations (e.g., in sensory/motor functions) into account in the accessibility of its implementation.

When enrolling participants in a music-based intervention study, one might consider screening participants for any deficits in basic auditory functions (e.g., hearing loss), music perception (congenital or acquired amusia), music-evoked pleasure (musical anhedonia), or possible proneness to adverse effects triggered by the music stimulus or the training (e.g., tinnitus, epileptic seizures, and falls), which can be expected to detract from the applicability or safety of the intervention. These individual factors should be considered when implementing and adapting the intervention.

In testing the effectiveness of the intervention, it is essential to give consideration to individual factors in the experimental and control group. Each rehabilitation trajectory is unique and individual and the patient's experiences with music and music background can play a major role in mediating the treatment success. To control and account for this, the analysis of results of the music intervention trial should include baseline measures of musical background (e.g., formal/informal musical training and musical hobbies), music-related auditory-perceptual and motor skills (e.g., melodic and rhythmic perception, beat entrainment), and sensitivity to experience reward and emotions from music-related activities in all intervention groups. Collecting these variables in the experimental and control group may provide valuable information about factors that mediate the efficacy of the intervention, which can help develop the intervention further and better target its use in the clinical population.[78] At baseline assessment, it is important to gather information from the relatives on the previous patient's musical preferences and interests, as in some cases, in acute stages, self-assessment could be severely biased by the onset of the disease and consequent mood and affective changes (e.g., depression, anhedonia, and apathy) as well as severe life changes experienced. Possibly, it can be useful to assess prepost changes in musical skills and determine how they relate to the transfer effects in the cognitive, motor, emotional, or social functions targeted by the intervention. Importantly, to investigate possible transfer effects, musical skills should be assessed as well in the control group. Together with data on the frequency and intensity of the training, this can help determine the extent to which active engagement and musical improvement during the intervention mediate its clinical efficacy (transfer effects).

Theory-based predictions for targeted outcomes

Practicing music is a complex activity that likely trains and transfers to several different processes, such as cognitive abilities,[79,80] verbal abilities,[81–83] and socioemotional development.[84] Complex training, such as musical practice, is more likely to show transfers than a specific training because it involves different processes. However, it may be challenging to find the sufficient level of training intensity required to empirically test for skill transfer with this approach. A series of small but significant effects of short experimental music training in typical and atypical development have shown skill transfer to inhibition[85–87] and phonological awareness.[88–90] These studies used specific mechanism-based predictions and highlighted the pertinence of this approach to improve skill transfer efficiency.

One of the most investigated aspects is the underlying mechanisms supporting the use of music for motor recovery.[63] There is extensive evidence on the role of auditory stimuli in enhancing motor planification, performance, and adjustment.[91–94] A distributed neuroanatomical network connecting auditory and motor systems, with regions that are highly interconnected at the subcortical and cortical level, is responsible for audio-motor coupling and the interplay between sound and movement.[63] The auditory system detects temporal patterns at an impressively high temporal resolution and primes the motor system in a process of auditory-motor entrainment. The temporal references provided by auditory regions allow movement anticipation and preparation in a feedforward loop. When a movement is performed in musical playing or movement sonification, the auditory stimuli resulting from the movement serve as feedback of movement performance, reinforcing, adjusting, and correcting movement trajectories.[91] The audio-motor coupling and its influence on motor learning have been extensively investigated in healthy individuals and musicians.[95–97] It is proposed as the underlying mechanism for the effectiveness of some music-based interventions, such as Rhythmic Auditory Stimulation, movement sonification, or Music-supported Therapy for individuals with Parkinson's disease or stroke.[32,78,98,99]

When considering the potential effects of music preferences and sensitivity to reward in patients' recovery, it is important to bear in mind that pleasure and enjoyment during treatment might potentially increase the effects of rehabilitation, boosting motivation and treatment adherence, most probably through the engagement of reward-related mesolimbic and dopaminergic networks.[78] As pleasant musical activities activate midbrain-striatal reward-motivation brain networks and dopamine release,[22,100] it is possible to conceive that music could modulate motor rehabilitation through this neuromodulatory system. Support for this idea comes from studies showing that midbrain dopaminergic neurons project to the primary motor cortex,[101,102] and this functional and structural connectivity could modulate cortical reorganization during learning.[103,104] Supporting evidence from a sample of subacute stroke patients shows a positive association between music reward sensitivity and motor improvement.[35] The potential involvement of reward-dopaminergic networks during recovery also converges with the positive effects observed in motor learning after administration of reward- and punishment-based feedback.[105–108] Notice, however, that there is contradictory evidence on the direct effects of dopamine precursor administration in motor recovery.[109–112] Overall, the current hypothesis is that music provides a reward-based motivated learning process that constructs an enriched training environment that could potentially promote faster recovery and retention of gains as well as improve concomitant emotional side-effects as depression and anhedonia.[78] In the future, modifications to existing training protocols should go in the direction of enhancing intervention components that boost reward-based learning, tailoring the sessions to increase motivation, pleasure, and enjoyment.

RESEARCH DESIGNS AND LEVELS OF EVIDENCE

Considering the framework for the development and evaluation of complex interventions

Although well-designed and properly conducted randomized controlled trials can provide the most reliable evidence on intervention effects,[113] it is important to consider all the different levels of evidence and clinical research designs when designing and evaluating interventions. The framework for the development and evaluation of complex interventions[114,115] is excellent to be followed in our field and guides the different steps for developing, testing, and implementing. The framework was developed in 2000, revised in 2006, and updated in 2021, taking into account recent theory and methods development. The new version of the framework identifies four research phases: development or identification of the intervention, feasibility, evaluation, and implementation. These phases allow including other research perspectives and questions beyond effectiveness and efficacy, such as cost-effectiveness, the interplay of mechanisms and context, or how the intervention is adapted to a system. The framework also identifies common core elements in each phase regarding the context, program theory, stakeholders, key uncertainties, intervention refinement, and economic considerations. In the case of music-based interventions, this framework can help to identify the research questions depending on the development phase of the intervention and consider all the relevant core components to advance with research and achieve implementation. Excellent examples of interventions that have followed all the research phases, thereby achieving wide acceptance and implementation, are Rhythmic Auditory Stimulation for gait rehabilitation in individuals with Parkinson's disease and stroke and Neurologic Music Therapy in stroke or traumatic brain injury patients.[116–118]

With regard to research designs, case series or smaller experimental studies are initially more appropriate for new interventions than large clinical trials. The steps involved in developing and evaluating a complex intervention follow roughly the same steps as those for pharmaceutical development, however, with theory development and the modeling of components and mechanisms replacing preclinical and phase I clinical development.[114] For those interventions with solid evidence from such smaller studies, efforts should be made to then conduct high-quality and multicenter clinical trials. Conducting such trials internationally across a range of therapists from various centers may prove logistically and conceptually challenging and require clearer and more explicit specifications of the intervention protocol.[42,114,119–121] Pragmatic and preference trials[120,121] are a solution to some of the challenges related to reproducing what happens in clinical practice or addressing individual differences in motivation and preference for music interventions. Other challenges are related to recruitment, such as the clinical heterogeneity of samples and biases to participate in music studies.

While there are now some examples of successfully conducted pragmatic multicenter trials,[122,123,124] such trials have often shown negative results, which is a reflection of their rigorous methodology but may also indicate that the intervention is not well enough understood and developed yet[125] or that the outcome measures used are not able to capture the real-life effects of the intervention. The framework for the development and evaluation of complex interventions is useful in these cases as it also offers a "circular" or iterative model where a new observational phase follows a pragmatic phase.[114] This recommendation is pertinent for music interventions: They are typically "out there" in the field already, so it is meaningful to ask whether they are effective as they are being conducted (e.g., pragmatic trials), but it is then also meaningful to "go back" and investigate mechanisms and to start the circle with a refined intervention.

Stronger methodological rigor in designing and reporting longitudinal studies

Designing music-based interventions in clinical settings often poses methodological challenges, especially in more naturalistic contexts. However, a balance between the generalizability of a study and the internal validity of the design must be considered carefully. It is important to match intervention groups based on symptom severity, baseline impairment, and general functional ability in order to reduce possible confounds stemming from nonequivalent groups not balanced on these clinical parameters. This is especially relevant for neurodevelopmental disorders, such as autism, that show heterogeneous symptom severity profiles and verbal abilities often ranging from being minimally verbal to neurotypically verbal.[37] In conditions where the recovery trajectory is linked to the onset of diseases, such as stroke or traumatic brain injury, groups should be matched based on the recovery stage. As discussed in the subsection on individual differences, it is important to consider matching intervention groups regarding experiences with music, music background, and musical skills as factors that can mediate the effectiveness of the intervention.

A clear description of the intervention group characteristics, such as the randomization procedure, training intensity, symptom severity, baseline functioning, age, gender, and social support of participants using means, range, and standard deviations, should be calculated and reported. Means, ranges, and standard deviations of groups before and after the interventions should be calculated and reported in order to (1) form a coherent composite overview of the size of an effect, (2) properly account for covariance arising from multiple measurements per participant, and (3) reduce small-sample biases when assessing studies in a meta-analysis. Finally, more consideration should be given to potential biases or confounds resulting from attrition by reporting information about individuals who failed to complete the study.

IMPLEMENTATION OF MUSIC-BASED INTERVENTIONS IN CLINICAL SETTINGS

Music interventions face many challenges for widespread implementation in clinical or even community settings. Some challenges for the wide implementation of music-based interventions in clinical settings are related to (1) failure to match specific interventions to the target population, (2) problems in integrating outcome measurements in clinical practice, (3) lack of acceptance and familiarity with music-based interventions from clinicians working in other fields, (4) the need of clinical expertise to be delivered, and (5) insufficient consideration or attention to stakeholders' opinions (patients, caregivers, clinicians, or policymakers) about barriers and facilitators to implement the intervention and how to address them.

Many diseases and disorders are heterogeneous in presentation, and often affect the diversity of a nation's population differently. The lack of trials addressing specific subgroups within populations (e.g., African Americans with cognitive impairment, women with Parkinson's disease, and stroke survivors with sensory problems) could result in the inappropriateness or mismatch of a given intervention for specific populations. Work must be done to translate and tailor music-based interventions for given subgroups of populations such that the interventions are culturally, sociologically, and neurologically appropriate, effective, and satisfying for the intended patient population. Organizations, such as the Patient-Centered Outcomes Research

Institute or the StrokeNet in the United States, attempt to enhance the patient's perspectives and individual and societal needs for particular treatments and the importance of appropriate and relevant outcome measures. Such an approach is necessary for the field of music-based rehabilitation research.

Regarding the problems in integrating outcomes in clinical practice, the challenge relates to the transferability of evaluations performed in clinical trials to clinical practice. It is common to have long evaluation protocols in research designs but, if a given outcome that was successfully modified in a trial is not a regular part of clinical practice, healthcare professionals cannot compare and evaluate if the implemented intervention was successful. Outcomes relevant to a given physician or clinician type should be investigated to influence the clinician uptake and understanding of the potential treatment, including music treatments.

The implementation of music-based rehabilitation requires expertise and formal clinical music training. In some contexts and in some parts of some countries, neurologic music therapists are part of the healthcare team and music-based interventions are central to comprehensive rehabilitation programs, particularly in specialized neurorehabilitation hospitals or private centers or systems with high resources. However, the inclusion of neurologic music therapists in teams may not be the norm in general hospitals, intermediate care hospitals, community rehabilitation facilities, or nursing homes. In these contexts, training healthcare professionals is time-consuming and resource-intensive and can limit the implementation of music-based rehabilitation. If both musical expertise and clinical licensure are required, implementation barriers arise. As such, music programs that require minimal expertise or training should be investigated for their efficacy. An alternative approach is to engage musicians and music instructors with a clinical interest in music-based rehabilitation, which could provide a wonderful opportunity for some talented individuals to blend their love of music with clinical care. Investments in new generations of clinically minded musicians will help countries achieve stronger music as medicine programs and rehabilitation.

Inadequate consideration of stakeholders' needs, perceptions, attitudes, and desires when developing or implementing music therapies in a clinical setting hinders the acceptability of the interventions. At this time, little research has been performed that involves stakeholders (patients, caregivers, families, healthcare professionals, and decision-makers) in developing patient-centered musical treatment. Research done in partnership with stakeholders is necessary, for example, involving people with prodromal Alzheimer's disease from the ground up in the development and refinement of a music treatment so that the treatment is more specific, appropriate, effective, and satisfying for the constituents that the treatment purports to serve. Determining preferences for settings, times of day, duration of treatment, group numbers, and the type of music are just a few considerations that could be discussed and piloted with a patient group and their family members. That said, music is often universal, and the experience could be more entertaining and gratifying than similar research conducted about a less attractive therapy.

CONCLUSIONS

Music-based interventions for neurological rehabilitation are complex interventions, and this article highlights the main methodological research challenges related to treatment, outcomes, research designs, and implementation. We emphasize the need for a better definition and description of music-based interventions as well as control treatments in research articles. Major technological advances allow incorporating devices into music-based interventions, for example, by adapting interventions as a form of telerehabilitation. This technological transformation and telerehabilitation can make interventions more accessible and cost-effective, contributing to their widespread implementation, while facilitating the tailoring of interventions to individual patients (e.g., treatment personalization). Regarding outcomes, their adequate selection according to the study aim is critical as well as the need to consider individual differences in the evaluation process and analysis. The framework for the development and evaluation of complex interventions is excellent for the field of music-based rehabilitation research since it provides guidance on the different research steps to generate evidence according to the different levels of intervention development. Addressing the mentioned methodological challenges will improve the translation of research evidence into clinical practice. Importantly, the transferability of the evidence on music-based interventions relies on addressing the aspects mentioned in this consensus article, leading to the widespread implementation of these interventions into regular clinical practice.

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AUTHOR CONTRIBUTIONS

All authors participated in the workshop at the Neuroscience and Music VII conference in June 2021 and at a roundtable meeting afterward. All authors reviewed, discussed, and formed a consensus on the priority methodological areas relevant to music-based rehabilitation research. J.G.-S. prepared a draft of the paper. All authors made a critical revision of the article and approved the final version to be published.

COMPETING INTERESTS

The authors declare no competing interests.

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