THE CLINICAL NEUROSCIENCE OF MUSIC: EVIDENCE BASED APPROACHES AND NEUROLOGIC MUSIC THERAPY

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THE CLINICAL NEUROSCIENCE OF MUSIC: EVIDENCE BASED APPROACHES AND NEUROLOGIC MUSIC THERAPY

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EDITORIAL
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Editorial: The Clinical Neuroscience of Music: Evidence Based Approaches and Neurologic Music Therapy

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Editorial on the Research Topic

The Clinical Neuroscience of Music: Evidence Based Approaches and Neurologic Music Therapy

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Modern music therapy, starting around the middle of the Twentieth century as an organized profession has traditionally been rooted in concepts of social science. The basic value of music in therapy was considered to derive from emotional and social functions in personal life experiences and a society's culture. Emotional expression, social roles to facilitate group association, integration, and relationship building, as well as general concepts of well-being and health were considered and are still today core functions to explain music as a therapeutic modality.

As the content of this special Research Topic clearly indicates, driven by new insights from research in music and brain function, a new understanding of the capabilities of music as a complex auditory language in therapy and rehabilitation has emerged over the past 25 years. Research has shown that music engages complex perceptual, cognitive, affective, speech/language, and motor control processes in the human brain. Furthermore, translational research approaches have shown that brain processes in music perception, music cognition, and music production can engage and shape non-musical perceptual, cognitive, language, and motor functions to effectively retrain the injured brain in neurorehabilitation and neurodevelopment. Music has become a language of science again as well as a new language to change the brain.

This transition is well-reflected in the research studies in this special topic as a critical step in the historical understanding of music as therapy. Rather than viewed as an ancillary or complimentary discipline to enhance other core therapies music has now been accepted to be applied effectively in core areas of training and retraining the injured or developing brain in motor, speech/language, and cognitive domains.

The most clearly developed clinical model has been encoded in Neurologic Music Therapy [NMT] which was formally established in 1999/2000. Translational biomedical research in music had led to the emergence of scientific clusters of scientific evidence for specific music based interventions. In the late 1990s researchers and clinicians in music therapy, neurology, and rehabilitation and brain sciences classified these evidence clusters into as system of standardized therapeutic techniques for sensorimotor, speech/language and cognitive rehabilitation. NMT is medically recognized as evidence based therapy [e.g., by the World Federation of Neurorehabilitation], is represented in over 60 countries by certified NMT-Therapists, and one prominent NMT technique [Rhythmic Auditory Stimulation for gait rehabilitation] has been included in the official clinical stroke care guidelines in the US [Departments of Veteran Affairs and Defense] and Canada [Heart & Stroke Foundation], Similar efforts are underway in several other countries.

This special topic represents an important step to further advance the scientific basis of this exciting development. Fourteen studies cover the breadth of new research from clinical trials to investigations of neural mechanisms underlying clinical NMT techniques to comprehensive reviews of the current evidence status of music-based interventions. The topic also includes projects breaking new ground, e.g., looking at signal coherence in EEG hyperscanning between parents and non-verbal children (Samadani et al.), including different art forms beyond music in the aging brain (Alain et al.), and NMT applications to motor deficits in neurotoxic cancer therapies (Ghai and Ghai).

It comes as no surprise that of the 14 papers half are dedicated to music in motor rehabilitation and the other to applications in the cognitive rehabilitation domain.

Included clinical research focuses on NMT in gait (Crosby et al.; Mainka et al.) and upper extremity training in stroke (Nikmaram et al.; Tian et al.). The study by Buard et al. combines clinical outcome measures with MEG based brain connectivity measures for upper extremity training in Parkinson's disease. The study by Koshimori et al. is looking at the effect of rhythmic auditory cues on dopamine release in the basal ganglia in young health adults as a prequel to further studies with Parkinson's disease. Music-based attention interventions are the topic of studies by van Alphen et al. and Kasuya-Ueba et al.. Berger Morris et al. take an integrative approach investigating the role of music beyond clinical applications on conceptual and emotional levels in persons with Parkinson's disease. Finally, important comprehensive reviews provide updates on the evidence base for music and NMT in upper extremity stroke rehabilitation (Ghai) and in cognitive interventions in Alzheimer's disease (Leggieri et al.).

The compilation of papers in this special Research Topic cannot claim complete representation of all important areas of translational research and effective clinical applications. For example, critical music based research areas in speech and language, hemi-spatial neglect, memory, executive, and psychosocial function are not covered but readers are encouraged to acquaint themselves with those results. They are fully covered in the NMT treatment model of 20 standardized clinical techniques across 3 rehabilitation domains. However, each of the papers in this topic presents critical new information in the continuous advancement of understanding the role and function of music as a complex auditory language in helping to advance brain rehabilitation. Twenty years ago, this topic would not have been possible as a major contribution to brain research and neurorehabilitation. The rehabilitative effects of music based interventions on meaningful clinical outcomes and brain plasticity were not known. However, the enormous progress in the basic neuroscience of music perception, cognition, and production has led to a translational clinical research path in music that has made the development and establishment of a medically recognized treatment system such as Neurologic Music Therapy possible in a comparatively short time span, from "bench" to "therapy."

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Effects of Real-Time (Sonification) and Rhythmic Auditory Stimuli on Recovering Arm Function Post Stroke: A Systematic Review and Meta-Analysis

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Background: External auditory stimuli have been widely used for recovering arm function post-stroke. Rhythmic and real-time auditory stimuli have been reported to enhance motor recovery by facilitating perceptuomotor representation, cross-modal processing, and neural plasticity. However, a consensus as to their influence for recovering arm function post-stroke is still warranted because of high variability noted in research methods.

Objective: A systematic review and meta-analysis was carried out to analyze the effects of rhythmic and real-time auditory stimuli on arm recovery post stroke.

Method: Systematic identification of published literature was performed according to PRISMA guidelines, from inception until December 2017, on online databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST. Studies were critically appraised using PEDro scale.

Results: Of 1,889 records, 23 studies which involved 585 (226 females/359 males) patients met our inclusion criteria. The meta-analysis revealed beneficial effects of training with both types of auditory inputs for Fugl-Meyer assessment (Hedge's g: 0.79), Stroke impact scale (0.95), elbow range of motion (0.37), and reduction in wolf motor function time test (−0.55). Upon further comparison, a beneficial effect of real-time auditory feedback was found over rhythmic auditory cueing for Fugl-meyer assessment (1.3 as compared to 0.6). Moreover, the findings suggest a training dosage of 30 min to 1 h for at least 3–5 sessions per week with either of the auditory stimuli.

Conclusion: This review suggests the application of external auditory stimuli for recovering arm functioning post-stroke.

Keywords: cueing, stability, rehabilitation, cognitive-motor interference, hemiplegia, spasticity, paresis

INTRODUCTION

According to World health organization, stroke accounts as the third main cause of disability across the world (1). The incidence of stroke related disability have almost doubled in the developing countries in the past decade (2, 3). The disability affects basic day to day life activities (4), which further increase dependency (5), anxiety, depression (6), social isolation (7), and promote a poor quality of life (8, 9). Moreover, the disability inflicts substantial economic burden on patients (10).

Typically, patients affected from stroke exhibit sensorimotor dysfunctions on the contralateral side of the affected brain region (11). These deficits can be exhibited focally, segmentally, unilaterally, or bilaterally (12). The symptoms are typically characterized by progressive inefficient movement synergy patterns (13), abnormal muscle tone (14), force production (15), compromised dexterity (16), poor coordination (17), and more (18). Moreover, hyper/hypokinetic movement disorders are also common [see Handley et al.,(12)]. Additionally, cognitive and sensory dysfunctions are also common in patients with stroke (19). Despite advancements in rehabilitation, poor prognosis in stroke is still prevalent, especially for recovering arm function (5, 20). Studies suggest that upper limb recovery is an important predictor for determining the health status outcome, and quality of life for stroke patients (21, 22).

The poor gross and fine motor performance in upper extremities can be due to abnormal co-contraction of antagonists/agonists (23), disruptions in force production/adaptation (24), and regulation of stretch reflex (15, 25). Besides, these musculoskeletal dysfunctions can considerably impair joint kinematics (26, 27). According to Hara et al. (28) impaired activation of motor units in terms of firing rate and synchronization might result in such deficits. Furthermore, as the disease progresses, these changes increase fatigue (29), reduce coordination (30), and with the progression of time promote development of joint contractures (31), and subluxations/dislocations (32). Likewise, discrepancies in sensory perceptions, memory, cognition, and behavior further impact the prognostic outcome of a stroke patient (33–35).

Neuroimaging studies suggest site specific lesions and silent infarcts at medial temporal lobe (36), gray (37), and white matter (38), further leading to a wide array of cognitive dysfunctions (39) [see Makin, (40) and Sperber and Karnath (41).] Similarly, deficits in corticospinal (42, 43), thalamocortical (44), superior occipito-frontal (41), and superior-longitudinal pathways (45), might overload the already impaired cognitive-motor pathways. Such a constraining impact on the impaired cognitive pathways might increase "internal" conscious monitoring by the patients to control their movements [see movement re-investment (46–48)]. This increase in attention is aimed to safeguard the stability of a movement (49, 50), it retrospectively impairs autonomic execution of a movement and promotes movement failure (46–48). Likewise, dysfunctions in sensory perception could affect perceptuomotor representations in the brain, thereby affecting motor planning and execution (35). Together, these cognitive and sensorimotor dysfunctions affect the prognosis of a stroke patient.

Common treatment strategies to curb cognitive motor dysfunctions in stroke patients include training with virtual-reality (51), mental imagery (52), biofeedback (53), physical therapy (54), exercise (55), prosthesis (56–58), dual-task priority training, and more (59). Recently studies have tried to enhance the stroke recovery by simultaneously addressing the sensory deficits with motor rehabilitation by applying external sensory stimulation as a neuro-prosthetic (59–62). Studies have analyzed the effects of different sensory stimuli in auditory, visual and tactile domain on motor performance (59, 61, 62). However, the literature predominantly supports the beneficial role of auditory stimuli (50, 63, 64). The main reasons which underlie the beneficial effects are thought to be multifaceted. Firstly, rich neuroanatomical interconnectivity has been reported between auditory and motor cortex (65–67). Here, inference can be drawn from literature evaluating auditory startle reflex on animal models (68, 69). Studies using Double-labeling experiments have revealed that cochlear root neurons in the auditory nerve can project bilaterally to sensorimotor paths, including synapsing on reticulospinal neurons (65, 68, 70). Likewise, patterns of thalamocortical and corticocortical inputs unique to auditory cortex have also been reported [for a detailed review see (71)]. In humans, neuroimaging data confirms the presence of cortico-subcortical network involving putamen, supplementary motor area, premotor cortex, and the auditory cortex especially for perceiving and processing rhythmic auditory stimuli (72–75). Secondly, the human auditory system can consistently perceive auditory cues 20–50 ms faster as compared to its visual and tactile counterparts (76–78). Thirdly, the auditory system has a strong bias to identify temporal patterns of periodicity and structure as compared to other sensory perceptual systems (78–80). For instance, auditory rhythmic perception has been reported to exist well beyond the limits of temporal resolution of visual modalities i.e., when periodicities are presented at a rate of ∼300–900 ms (80, 81).

In the literature, however, rhythmic auditory cueing (67), and real-time kinematic auditory feedback (82), also termed as sonification, are the most widely studied approaches in upper limb stroke rehabilitation. Both the methods possess differential influence over neurophysiological and musculoskeletal domains. Firstly, rhythmic auditory cueing can be defined as repetitive isosynchronous stimulations applied with an aim to simultaneously synchronize motor execution (83, 84). Here, neuroimaging data for rhythmic auditory stimuli suggests facilitated activations in premotor cortex, insula, cuneus, supplementary motor area, cerebellum, and basal ganglia (73, 80, 85–87). Moreover, training with rhythmic auditory cueing has been reported to modulate neuromagnetic β oscillations (88, 89), biological motion perception (82, 90), auditory-motor imagery (91–93), shape variability in musculoskeletal activation patterns (94), cortical reorganization, neural-plasticity (95, 96), and also movement specific re-investment (97). Real-time kinematic auditory feedback on the other hand is a comparatively new approach. Such type of an intervention involves mapping of movement parameters on to the sound components, such as pitch, amplitude with a very minimal or no latency (82). The feedback has been reported to alleviate sensory perceptions like proprioception (98), by enhancing sensorimotor representation while facilitating activations in action observation system (90), and inducing neural plasticity (99). Moreover, the feedback has been reported by Effenberg et al. (82) to extend the benefits of discrete rhythmic auditory cueing stimuli. Here, the authors suggest that the continuous flow of information might allow a participant to better perceive their movement amplitudes and positioning, thereby resulting in development of both feedback and feed-forward models (82). Moreover, by allowing additional influence over the action observation system the real-time auditory stimuli might also enrich the internal stimulation of the executed movement (50, 82, 90). This methodology involves delivering action relevant auditory feedback, where the characteristics of stimuli (e.g., frequency, amplitude) are mapped to the specific joint kinematics in real-time, for an example see (98). Schmitz et al. (90) in a neuroimaging study reported that observation of a convergent audio (sonification)-visual feedback led to enhanced activations in fronto-parietal networks, action observation system i.e., superior temporal sulcus, Broadman area 44, 6, insula, precentral gyrus, cerebellum, thalamus and basal ganglia (90). The authors mentioned that the multimodal nature of the stimuli can enhance the activation in areas associated with biological motion perception and in sub-cortical structures involving striatal-thalamic frontal motor loop. This then might improve perceptual analysis of a movement thereby resulting in efficient motor planning and execution (90).

Till date, no study has analyzed the influence of real-time auditory feedback on upper limb recovery post-stroke. Moreover, no study has compared the influence of rhythmic and real-time auditory stimuli on upper limb recovery post stroke. This information might serve to be an important source of information for future research and for developing efficient rehabilitation protocols in stroke community. Only four systematic reviews have analyzed the influence of rhythmic auditory stimulations on arm recovery post stroke (100–103), in which only two reviews included a statistical meta-analysis (102, 103). In these studies limitations persisted in terms of meta-analysis approach i.e., no heterogeneity analysis. Therefore, interpretation of results from the statistical analyses might indicate biasing. Therefore, the aim of the present systematic review and meta-analysis is to develop a state of knowledge where both qualitative and quantitative data for different auditory stimuli delivery methods can be interpreted for the use of stroke patients and medical practitioners alike. Moreover, a meta-analysis approach will be used to determine specific training dosage for auditory stimuli in recovering arm function post-stroke.

METHODS

This systematic review and meta-analysis was conducted according to the guidelines outlined by PRISMA statement: Preferred Reporting Items for Systematic Reviews and Meta-analysis (104).

Data Sources and Search Strategy

Academic databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane central register of controlled trials, EMBASE, and PROQUEST were searched from inception until December 2017. A sample search PICOS strategy for the review has been provided in (**Table 1**) (105).

Data Extraction

Upon selection for review, the following data were extracted from each article; author, date of publication, selection criteria, sample size, sample description (gender, age, health status, duration of stroke), applied intervention, characteristics of auditory stimuli i.e., rhythmic/real-time, applied dual-task (if any), outcome measures, results, and conclusions. The data were then summarized and tabulated (**Table 2**).

The inclusion criteria for the studies was (i) The experimental studies were either randomized controlled trials, cluster randomized controlled trials or controlled clinical trials; (ii) The included studies reported reliable and valid measures to analyse arm function, and/or kinematic parameters; (iii) The included studies analyzed subjective analysis of stroke outcome; (iv) The included studies scored ≥4 score on the PEDro methodological quality scale; (v) The experiments conducted on human participants; (vi) The included studies were published in a peer-reviewed academic journal, conference proceeding; (vii) The included studies were published in English, Hindi, Punjabi, and German languages.

Quality and Risk of Bias Assessment

The quality of the included experimental studies was assessed using the PEDro methodological quality scale (127). This scale consists of 11 items which address both external, internal validity. Moreover, its interpretation can effectively detect potential bias with fair to good reliability, and validity (127). A blinded scoring for the methodological quality was carried out by the primary reviewer (S.G). If any ambiguous issues were there concerning rating of the studies. These issues were discussed with a second reviewer (Dr. Ishan Ghai). Included studies were interpreted according to a scoring of 9–10, 6–8, and 4–5 considered as "excellent," "good," and "fair" quality, respectively (128).

Data Analysis

For a better interpretation of the intervention effects, a meta-analysis was included (129). The absence of presence of heterogeneity asserted the use of either fixed or random effect meta-analysis (130), respectively. A narrative synthesis of the findings structured around the intervention, population characteristics, duration of stroke, auditory signal characteristics, methodological quality, and type of outcome are provided (**Table 2**). A meta-analysis was conducted between pooled homogenous studies using CMA (Comprehensive meta-analysis V 2.0, USA). Heterogeneity between the pooled studies was assessed and interpreted using I^2 statistics. The data in this present review was systematically distributed and pooled for each variable. Thereafter, forest plots with effect size and 95% confidence intervals were plotted. The effect sizes were weighted

TABLE 1 | Sample search strategy EMBASE.

PICOS	DATABSE	EMBASE
	DATE	**10/12/2017**
	STRATEGY	**#1 AND #2 AND #3 AND #4 AND #5 AND #6**
P	#1	("Stroke" OR "Apoplexy" OR "CVA" OR "Cerebral Stroke" OR "Cerebrovascular accident" OR "Cerebrovascular Accident, Acute" OR "Cerebrovascular Apoplexy" OR "Cerebrovascular Stroke" OR "Stroke, Acute" OR "Vascular Accident, Brain" OR "Hemiplegia, Crossed" OR "Hemiplegia, Flaccid" OR "Hemiplegia, Spastic" OR "Hemiplegia, Transient" OR "Monoplegia" OR "Upper Extremity Paresis" OR "Muscular Paresis" OR "Muscle Paresis" OR "Monoparesis" OR "Hemiparesis")/de OR (Stroke OR Apoplexy OR CVA OR Cerebral Stroke OR Cerebrovascular accident OR Cerebrovascular Accident, Acute OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Stroke, Acute OR Vascular Accident, Brain OR Hemiplegia, Crossed OR Hemiplegia, Flaccid OR Hemiplegia, Spastic OR Hemiplegia, Transient OR Monoplegia OR Upper Extremity Paresis OR Muscular Paresis OR Muscle Paresis OR Monoparesis OR Hemiparesis):ti,ab
I	#2	("rhythmic auditory cueing" OR "rhythmic auditory cueing" OR "rhythmic acoustic cueing" OR "rhythmic auditory entrainment" OR "metronome cueing" OR "metronome" OR "rhythmic metronome cueing" OR "acoustic stimulus" OR "acoustic cueing" OR "acoustic cueing" OR "external stimuli" OR "external cueing" OR "external cueing" OR "music therapy" OR "Neurological music therapy" OR "tempo" OR "beat" OR "rhythm" OR "RAC" OR "NMT" OR "real-time auditory feedback" OR "sonification")/de OR (rhythmic auditory cueing OR rhythmic auditory cueing OR rhythmic acoustic cueing OR rhythmic auditory entrainment OR metronome cueing OR metronome OR rhythmic metronome cueing OR acoustic stimulus OR acoustic cueing OR acoustic cueing OR external stimuli OR external cueing OR external cueing OR music therapy OR Neurological music therapy OR tempo OR beat OR rhythm OR RAC OR NMT OR real-time auditory feedback OR sonification)ti,ab
C	n/a	n/a
O	#3	("Range of Motion" OR "Passive Range of Motion" OR "Joint Range of Motion" OR "Joint Flexibility" "elbow" OR "shoulder" OR "wrist" OR "Fugl Meyer Assessment" OR "Fugl-Meyer assessment for upper extremity" OR "FMA" OR "Wolf motor assessment" OR "WMA" OR "Wolf motor test" OR "Nine hole peg test" OR "NHPT" OR "9HPT" OR "Action reach arm test" OR "ARAT" OR "Stroke index scale" OR "SIS" OR "BATRAC" OR "Bilateral arm training with rhythmic auditory cueing" OR "Unilateral arm training with rhythmic auditory cueing" OR "Arm reach training" OR "BBT" OR "Box and block test" OR "Motor activity log" OR "MAL" OR "Cincinnati Stroke Scale" OR "Los Angeles Prehospital Stroke Scale" OR "ABCD Score" OR "Canadian Neurological Scale" OR "European Stroke Scale" OR "Hemispheric Stroke Scale" OR "NIH Stroke Scale" OR "Modified Rankin Scale" OR "Stroke Specific Quality of Life Measure" OR "Health Survey SF-36" OR "Health Survey SF-12")/de OR (Range of Motion OR Passive Range of Motion OR Joint Range of Motion OR Joint Flexibility elbow OR shoulder OR wrist OR Fugl Meyer Assessment OR Fugl-Meyer assessment for upper extremity OR FMA OR Wolf motor assessment OR WMA OR Wolf motor test OR Nine hole peg test OR NHPT OR 9HPT OR Action reach arm test OR ARAT OR Stroke index scale OR SIS OR BATRAC OR Bilateral arm training with rhythmic auditory cueing OR Unilateral arm training with rhythmic auditory cueing OR Arm reach training OR BBT OR Box and block test OR Motor activity log OR MAL OR Cincinnati Stroke Scale OR Los Angeles Prehospital Stroke Scale OR ABCD Score OR Canadian Neurological Scale OR European Stroke Scale OR Hemispheric Stroke Scale OR NIH Stroke Scale OR Modified Rankin Scale OR Stroke Specific Quality of Life Measure OR Health Survey SF-36 OR Health Survey SF-12);ti,ab
S	#6	("intervention study" OR "cohort analysis" OR "longitudinal study" OR "cluster analysis" OR "crossover trial" OR "cluster analysis" OR "randomized trial" OR "major clinical study")/de OR (longitudinal OR cohort OR crossover trial OR cluster analysis OR randomized trial OR clinical trial OR controlled trial);ti,ab
	#4	("rehabilitation" OR "treatment" OR "rehab" OR "management" OR "therapy" OR "physiotherapy" OR "physical therapy" OR "prevention" OR "risk prevention")/de OR (rehabilitation OR treatment OR rehab OR management OR therapy OR physiotherapy OR physical therapy OR prevention OR risk prevention);ti,ab
	#5	("age groups" OR "adolescent" OR "young" OR "elderly" OR "old" AND ("gender" OR "male" OR "female")/de OR [age groups OR adolescent OR young OR elderly OR old AND (gender OR male OR female)];ti;ab

and reported as Hedge's g (131). Thresholds for interpretation of effect sizes are as follows; a standard mean effect size of 0 meant no intervention effect, negative effect size meant a negative intervention effect, and a positive effect size meant a positive intervention effect. Further, a mean effect size of 0.2 was interpreted as a *small* effect, 0.5 interpreted as a *medium* effect, and 0.8 interpreted as a *large* effect (132). Interpretation of heterogeneity made from I^2 statistics was as following: 0–0, 25, 75% was interpreted as negligible, moderate, and substantial heterogeneity, respectively. The alpha level was set at 95%.

RESULTS

Characteristics of Included Studies

A detailed search criterion has been demonstrated in **Figure 1.** Out of 1,889 studies, only 23 studies qualified our inclusion criteria. A total of 385 studies could not be included in the manuscript due to limitations in access by University's search database. The author (S.G) made attempts to contact the respective corresponding authors for retrieving the manuscripts. Although these studies could not be included in the review, the abstracts for all the studies were individually screened by

TABLE 2 | Effects of auditory stimuli on arm function post-stroke.

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Bang (106)	Effect of R-af on arm function in patients affected from stroke	Exp: 4F, 6M (61.3 ± 4.8) Ct: 5F, 5M (58.2 ± 5.1)	9	Exp: 8.9 ± 3.1 years Ct: 10.3 ± 3.7 years	ARAT, FMA, motor activity log (quality of movement, amount of use) and modified Ashworth scale	Pre-test, modified constraint induced movement therapy with/without R-af for 1 h/day, 5 days/week for 4 weeks, post-test	R-af (proportional to reduced pressure by shoulder on the sensor) Frequency faded off with progression from every 1/3rd trial	Significant enhancement in ARAT, FMA, motor activity log (quality of movement, amount of use), modified ashworth scale after training with R-af and in Exp as compared to Ct
Scholz et al. (107)	Effects of R-af on gross motor functions on participants affected from stroke (right hemiparesis).	Exp: 1F (59), 1M (85) Ct: 2M (61.5 ± 3.5)	4	–	FMA, ARAT, BBT, 9-HPT, and SIS	Patients moved their arms in a 3D R-af space, for 9 days of training with R-af (30 min/day)	X axis: Brightness mapped, increased from left to right Y axis: Pitch mapped, increased from bottom to up Z axis: Volume, increased when closed to the participant	Exp: Enhancements were observed for participants in FMA, ARAT, 9-HPT, and SIS Ct: No enhancements were observed for, but minimally for one participants in FMA, and the other in SIS
Malcolm et al. (108)	Effect of RAC on arm kinematics in patients affected from stroke	5M (72.8 ± 6.5)	4	0.7 ± 0.4 years	Movement time, reach velocity, wolf motor function test, FMA, and motor activity log	Pre-test, 1-h session followed by 2 h of home training, 3 times/week for 2 weeks with RAC and reaching performed in sagittal, frontal and diagonal planes, post-test	RAC at patients preferred pace of movement	Significantly enhanced reaching velocity, FMA, and motor activity log after training with RAC Significantly reduced reaching time, wolf motor function test performance time after training from RAC
Speth (109)	Effect of RAC on arm reaching in patients affected from stroke	8 stroke patients	4	–	BBT for (paretic/non-paretic side)	BBT performance with/without RAC i.e., waltz music, metronome	RAC (200 bpm), waltz music (200 bpm) cueing	Enhanced performance for BBT with waltz music>RAC>no feedback for both paretic and non-paretic arms
	Effect of RAC on robot-assisted arm reaching in patients affected from stroke	11F, 22M (51.6 ± 15.9), severe: 18, moderate: 8, mild: 8 Exp: 14 [A; severe (11), moderate (4), mild (4)] [B: 2–6 months' post stroke (8), >12months post stroke (9)] Ct: 14 [A: severe (6), moderate (4), mild (4)] [B: 2-6 months' post stroke (9), >12months post stroke (5)]		1.2 ± 1.3 years	BBT, 9-HPT, and intrinsic motivation inventory	Pre-test, robot assisted arm training "Amadeo" with (Exp)/without (Ct) RAC (polymetric music, game-related action feedback) for 45 min for 9 times for 3–4 weeks, post-test, retention measurement after 8 weeks' post-test	RAC by polymetric music (rhythmic adaptability to multi-joint movements in hand and finger movement e.g., first 3/4 m containing 2 bars, second 2/4 m containing 3 bars, 3rd 3/8 m containing 4 bars: all sounds played in one absolute time frame) and game related sounds (error feedback, natural sounds) together	Significant enhancement in mean BBT for moderate and mild affected patients, for Exp as compared to Ct Significant reduction in mean box and block test for severely affected patients, for Ct as compared to Exp Enhancement in 9-HPT for Exp as compared to Ct Significant enhancement in intrinsic motivation inventory for (interest/enjoyment, perceived competence, relaxation, perceived choice) for Exp as compared to Ct
Scholz et al. (60)	Effects of R-af on gross motor functions on participants affected from stroke (right hemiparesis).	Exp: 7F, 8M (68.8 ± 13.6) Ct: 4F, 6M (72.2 ± 8.4)	6	Exp: 32.5 days Ct: 28 days	FMA, ARAT, BBT, 9-HPT, and SIS	Patients moved their arms in a 3D sonification space, for 10 days of sonification training (30 min/day).	X axis: Brightness mapped, increased from left to right Y axis: Pitch mapped, increased from bottom to up Z axis: Volume, increased when closed to the participant	Exp: Significant enhancements were observed for participants in movement smoothness, FMA, SIS as compared to Ct Enhancements were observed in ARAT, BBT and 9-HPT Ct: No significant enhancements were observed post sham training
van Delden et al. (110)	Effects of RAC on arm reaching in patients affected from stroke	Exp: 8F, 11M (62.6 ± 9.8) Ct I: 3F, 16M (56.9 ± 12.7) CT II: 8F, 14M (59.8 ± 13.8)	7	Exp: 7.8 ± 4.9 weeks Ct I: 9.2 ± 6.8 weeks Ct II: 11.1 ± 6.8 weeks	ARAT, motricity index, FMA, 9-HPT, Erasmus modification of Nottingham sensory assessment, motor activity log test and SIS	Pre-test, BATRAC (Exp), modified constrained induced movement therapy (Ct I), conventional therapy (Ct II), for 60 min session, 3 times/week, post-test, 6 weeks follow up post-test	RAC (rhythmic flexion-extension at the wrist joint)	Significant enhancement in ARAT with BATRAC No differences in between Exp, Ct I, Ct II

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Schmitz et al. (111)	Effect of R-af on reaching task in patients affected from stroke	Exp: 1F, 3M (65 ± 14.8) Ct: 3F (56 ± 5.3)	4	-	ARAT, 9HPT, and BBT	I: Reaching and retraction task by affected arm. II: Patients repositioned a ball on objects of different shapes. Training for 5 days for 5 sessions of 20 min each	Arm velocity: modulates amplitude of sound Elevation angle: modulates frequencies between 133.3 and 266.6 Hz. Radial arm amplitude: modulates brightness	Significant enhancements were observed in BBT for Exp as compared to Ct. Enhancements were observed in 9HPT and ARAT. Ct: No significant enhancements were observed
Kim et al. (112)	Effects of RAC on arm reaching performance in patients affected from stroke	7F, 9M (49.2 ± 17.6)	4	1.9 ± 2.2 years	Movement time, movement unit, elbow extension range of motion by 3D motion detection, triceps, biceps brachii muscle activation and co-contraction ratio from EMG	Repetitive reaching task performed with/without RAC from affected arm	RAC at patients preferred pace of movement	Significant enhancement in elbow range of motion, tricpes brachii activation with RAC Significant reduction in co-contraction ratio, movement time and movement unit with RAC
Shahine and Shafshak (113)	Effect of RAC on arm function in patients affected from stroke	Exp: 19F, 21M (61.4 ± 5.5) Ct: 17F, 19M (62.7 ± 3.1)	9	Exp: 2.6 ± 1.8 years Ct: 2.9 ± 0.7 years	FMA and transcutaneous magnetic stimulation eliciting motor evoked potential in paretic abductor pollicis brevis (motor evoked potential resting threshold, central motor conduction time)	Pre-test, BATRAC for 1-h session/day, 3seesions/week, for 8 weeks, post-test	RAC at patients preferred pace of movement (frequency 0.25–1/s)	Significant enhancement in FMA, motor evoked potential amplitude ratio after BATRAC Significant reduction in motor evoked potential resting threshold, central motor conduction time after bilateral arm training with RAC, and in Exp as compared to Ct
Dispa et al. (114)	Effect of RAC on arm reaching in patients affected from stroke	1F, 9M (66 ± 11.1)	8	2.3 ± 2.6 years	Grip lift parameters (preloading-loading phase, maximum grip force, hold ratio, cross correlation coefficient, time shift), digital dexterity, activity limitation manual ability, satisfaction in activities, and participation	Pre-test, post-test after 4 weeks of no-training, unilateral-bilateral (modified BBT) repetitive grip lift task oriented training with RAC for 1-h session, 3 days/week for 4 weeks, post-test at 4 weeks after training, retention measurement after 4 weeks	RAC at patients preferred pace of movement	Reduction in preloading phase of grip lift parameters for the paretic hand after 4 weeks of training and during retention measurement. Enhancement in loading phase of grip lift parameters for the paretic hand after 4 weeks of training and during retention measurement. No effect on grip lift parameters (maximum grip force, hold ratio, cross correlation coefficient, time shift), digital dexterity, activity limitation manual ability, satisfaction in activities, and participation after 4 weeks of training or during retention measurement.
Whitall et al. (115)	Effect of RAC in arm reaching patients affected from stroke	Exp: 16F, 26M (59.8 ± 9.9) Ct: 26F, 24M (57.7 ± 12.5) fMRI: Exp: 10F, 7M (61.2 ± 13.8) Ct: 10F, 11M (54.8 ± 13.1)	6	Exp: 4.5 ± 4.1 years Ct: 4.1 ± 5.2 years	FMA, wolf motor test (time, weight, function, SIS (emotion, hand, strength), isokinetic strength (elbow flexion-extension nonparetic side, elbow extension paretic side) and isometric strength (shoulder extension, wrist flexion-extension nonparetic side, shoulder extension, wrist extension, elbow flexion paretic side)	Pre-test, BATRAC for 1-h session, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, wolf motor test (weight, function), SIS (hand, strength), isokinetic strength (elbow extension nonparetic side, elbow extension paretic side), isometric strength (shoulder extension, wrist extension nonparetic side, shoulder extension) assessment in Exp after training with RAC Significant reduction in wolf motor test (time) in Exp after training with RAC Significant enhancement in isokinetic strength (elbow flexion nonparetic side), isometric strength (wrist flexion, nonparetic side, wrist extension paretic side) in Exp as compared to Ct

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
		Exp: 3.9 2.7 Ct: 3.3 2.1						Significant enhancement in activation for ipsilesional precentral, anterior cingulate, postcentral gyri, supplementary motor area in Exp after training with RAC as compared to Ct. Significant enhancement in contralesional superior frontal gyrus in Exp after training with RAC, as compared to Ct
Chouhan and Kumar (116)	Effect of RAC on gait and arm reaching in patients affected from stroke	Exp: 3F, 12M (56.7 ± 5.9) Ct I: 3F, 12M (58.1 ± 4.1) Ct II: 3F, 12M (57.3 ± 5.5)	5	–	Dynamic gait index and FMA	Pre-test, gait, reaching task training with RAC (0% of preferred cadence initially, increased by +10% every week if comfortable for patient: for gait) (Exp) or visual feedback (Ct I) for 2 h training, 3 time/week session for 3 weeks, post-tests at 7, 14, 21, 28 days	RAC at 0% and +10% on following weeks of preferred movement pace, and gait (cadence)	Significant enhancements in FMA, dynamic gait index (14, 21, 28 days only) after 7, 14, 21, 28 days of training with RAC and in Exp as compared to Ct II
Secoli et al. (117)	Effect of RAC on tracking task in patients affected from stroke.	Exp: (affect left hemisphere) 8F, 6M (56.3 ± 12.3) Ct: (affect right hemisphere) 1F, 4M (61.8 ± 5) Healthy: 2F, 12M (27 ± 7.5)	4	4.6 ± 1 years	Arm movements with robot assisted force production to execute task in Z dimension Positioning error in Z dimension	Patients performed tracking task with robot assisted device in with/without visual distractor task and/or with/without RAC	Tonal beeps sampled at frequency of 800 Hz and lasting for 0.1 s Frequency manipulated proportionally to vector magnitude of position tracking error within dead-zone. Error direction determined by left and right channel of auditory input	Significant reduction in robot assisted force in Exp when auditory input was delivered, suggesting significant enhancement in arm functioning Significant reduction in robot assisted force for the paretic side as compared to healthy side with RAC No effect on position tracking accuracy
Thielman (118)	Effect of RAC on arm reaching in patients affected from stroke	Exp: 2F, 6M (62.9 ± 6.5) Ct: 4F, 4M (63 ± 9.2)	4	Exp: 2.2 ± 0.7 years Ct: 1.8 ± 1.4 years	Reaching performance scale for near and far targets, FMA, wolf motor function test, shoulder flexion range of motion, motor activity log, grip strength and elbow active range of motion	Pre-test (<5days before training), training for arm reaching with pressure sensor generated auditory feedback (Exp), stabilizer (restrained Ct) on arm reaching for 40-45 minutes' session, 2-3days/week (12 total sessions), post-test (<2days after training)	R-af (proportional to reduced pressure by shoulder on the sensor) Frequency faded off with progression from every 1/3rd trial.	Significant enhancement in reaching performance scale for near-far targets, FMA in Exp after training with R-af Significant reduction in wolf motor function test in Exp after training with R-af Enhancement in shoulder flexion, motor activity log and elbow active range of motion in Exp after training with R-af

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Johannsen et al. (119)	Effect of RAC on arm reaching and gait in patients affected from stroke	Exp I: 3F, 8M (59.5 ± 13.4) Exp II: 3F, 7M (68.1 ± 10.1)	6	5.2 ± 4.2 years	FMA (upper/lower extremity), 10-m walking test, treadmill (step length) and repetitive foot/hand aiming task	Pre-test, BATRAC (arm: Exp I/leg: Exp II) for 45 min session, 2 times/week for 5 weeks, post-test, follow up post-test after 18 weeks	RAC at patients preferred pace of movement (increased at patient's preference) Bilateral training for lower extremities: increased pacing during training from 36.7 ± 6.5 to 45.9 ± 9.5 beats per minute BATRAC: increased pacing during training from 39.8 ± 5.6 to 46.3 ± 5.9 beats per minute	Significant enhancement in treadmill step length on both paretic and non-paretic side after bilateral leg training in Exp II as compared to Exp I (no effects), during immediate follow-up test. No effects in follow up post-test. Enhancement in FMA test for lower extremity in Exp II> Exp I at post-test. No enhancements in follow up post-test Enhancement in fugl meyer motor test for upper extremity in Exp I> Exp II at post-test. No enhancements in follow up post-test Enhancement in treadmill step length on both paretic and non-paretic side after bilateral arm training in Exp I as compared to Exp II for 18 week follow up post-test Enhancement in repetitive foot and arm aiming task on both paretic and non-paretic side after bilateral leg training in Exp II during immediate post-tests. No effects on follow up post-tests
Stoykov et al. (120)	Effects of RAC on arm reaching in patients affected from stroke	Exp I: 3F, 9M (63.8 ± 12.6) Exp II: 5F, 7M (64.7 ± 11.1)	6	Exp I: 9.5±5.4 years Exp II: 10.2±10.1 years	Motor assessment scale (upper arm function, hand movements, upper limb items, advanced hand activities), motor status scale (total, shoulder-elbow, wrist-hand scale), shoulder flexion strength and wrist flexion-extension strength	Pre-test, arm reach training with bilateral (Exp I), unilateral (Exp II) arm training with RAC (for 4 tasks), for 60 minutes' session, 3 times/week for 8 weeks, post-test, RAC (rhythmic flexion-extension at the wrist joint)	RAC at patients preferred pace of movement (0.25-1.5 Hz) incremented gradually during training	Significant enhancement in motor assessment scale (upper arm function, upper limb items) for Exp I Significant enhancement in motor status scale (total, shoulder-elbow, wrist-hand scale), shoulder flexion strength, wrist flexion-extension strength for Exp I and Exp II Enhancement in motor assessment scale (advanced hand activities) in Exp I No differences in motor assessment scale for unilateral arm training for Exp II
Richards et al. (121)	Effects of RAC on arm reaching in patients affected from stroke	5F, 9M (64.4 ± 12.8)	4	5.4±4 years	FMA, wolf motor function test and motor activity log (use, ability)	Pre-test, BATRAC for 1-hour session, 3 times/week, for 6 weeks, post-test	RAC at patients preferred pace of movement	Enhancement in FMA, motor activity log (ability and use) in Exp after training with RAC No effect on wolf motor function test in Exp after training with RAC
Jeong and Kim (122)	Effects of RAC on range of motion, flexibility in patients affected from stroke	Exp: 5F, 11M (58 ± 7.1) Ct: 5F, 12 M (62.2 ± 8.1)	4	Exp: 5.4 ± 4.5 years Ct: 7.2 ± 5.3 years	Shoulder flexion, ankle flexion-extension range of motion and back-scratch test for flexibility upwards/downward the affected arm, profile of mood states, relationship change scale and stroke specific quality of life scale	Pre-test, training for motor activities with RAC for 2 hours/ week for 8 weeks (functional ambulatory training), and self-training at home, post-test	RAC (music) at patients preferred pace of movement	Significant enhancement of range of motion for shoulder flexion, ankle flexion-extension, shoulder flexibility in Exp as compared to Ct, on the affected side Significant enhancement of mood states, interpersonal relationships in Exp Enhancement in quality of life in Exp

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Waller and Whitall (123)	Effects of RAC on arm reaching in patients affected from stroke	Right hemisphere lesion: 2F, 9M (64.3 ± 10) Left hemisphere lesion: 3F, 8M (58.6 ± 17)	5	6.5 ± 4.1 years	FMA, University of Maryland questionnaire for stroke, wolf motor arm test (weight, time), active range of motion elbow flexion, shoulder extension and strength (shoulder extension-abduction-adduction, wrist flexion-extension)	Pre-test, BATRAC for 1-h session, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, University of Maryland questionnaire, active range of motion elbow flexion, shoulder extension (left hemisphere only), strength (shoulder extension (left hemisphere only)-abduction (left only)-adduction, wrist flexion-extension), wolf motor arm test (weight) for stroke for right and left hemisphere lesion patients after training with RAC Significant reduction in wolf motor arm test (time) for patients with left hemisphere lesions as compared right hemisphere lesions after training with RAC Significant enhancement in University of Maryland questionnaire for stroke, wolf motor assessment test (weight, time), active range of motion elbow flexion, shoulder extension, strength (shoulder extension-abduction-adduction, wrist flexion-extension) for patients with left hemisphere lesions as compared to right hemisphere lesions after training with RAC
Luft et al. (95)	Effect of RAC on arm function in patients affected from stroke	Exp: 2F, 7M (63.3 ± 15.3) Ct: 7F, 5M (59.6 ± 10.5)	6	6.2 (3.1–7) years	FMA, shoulder, elbow strength, Wolf motor arm test (weight, time), University of Maryland arm questionnaire for stroke and functional magnetic resonance imaging	Pre-test, BATRAC for 1-h session/day, 3 times/week for 6 weeks, post-test	RAC at patients preferred pace of movement (0.67–0.97 Hz)	After exclusion of 3 patients from Exp: Significant enhancement in FMA in Exp as compared to Ct. Enhancement in shoulder, elbow strength, Wolf motor arm test (weight), University of Maryland arm questionnaire for stroke in Exp as compared to Ct. Reduction in wolf motor arm test (time) in Exp as compared to Ct. Significant enhancements in cerebellum, precentral and postcentral gyri activation after BATRAC
Thaut et al. (124)	Effects of RAC on arm reaching task in patients affected from stroke	8F, 13M (52.7 ± 13.7)	4	–	Wrist trajectory, elbow, shoulder kinematic and optimization model of peak acceleration of wrist joint coordinates	Reaching tasks initiated with/without rhythmic auditory feedback/external time cueing (counterbalanced)	RAC at patients preferred pace of movement 1,000 Hz square wave tone 50 ms pattern	Significant enhancement in elbow range of motion with RAC Significantly reduced trajectory variability of wrist joint, deviation of acceleration curves from optimal coordinates of wrist joint with RAC No effect on arm timing, shoulder joint displacement

(Continued)

TABLE 2 | Continued

Author	Research question(s)/ hypothesis	Sample description, age: (M ± S.D)	PEDro	Disease duration	Assessment tools	Research design	Auditory stimuli characteristics	Conclusion
Maulucci and Eckhouse (125)	Effects of R-af on reaching task in patients affected from chronic stroke	Healthy: 15F, 9M Exp: 3F, 5M Ct:4F, 4M	4	–	Normal trajectory region for end effectors and reach parameters	Normal participants performed and established generalized repeatability for the experimental groups. Reach trials performed for 42 trials 3 times/week for 6 weeks. Residual performance evaluated post 2 weeks without auditory feedback	Regulated R-af of magnitude and existence of error from normal ellipsoid reach area.	Significant enhancement in trajectory performance for Exp group as compared to Ct group Significant enhancement in both Exp and Ct group for reach trajectory
Whitall et al. (126)	Effects of RAC on arm motor function in patients affected from stroke	6F, 8M (63.7 ± 12.6)	6	5.5 ± 7.9 years	Active, passive range of motion of upper extremity, isometric shoulder, elbow, wrist force (flexion/extension) assessment, FMA, wolf motor function test and modified University of Maryland arm questionnaire for stroke	Pre-test, BATRAC for four 5-min sessions, 3 times a week for 6 weeks, post-test, 8-week retention post-test	RAC at patients preferred pace of movement	Significant enhancement in FMA, Wolf motor function test and modified University of Maryland arm questionnaire for stroke with RAC Significant enhancement in elbow, wrist flexion for paretic and non-paretic arm with RAC Significant enhancement in active range of motion for shoulder extension, wrist flexion and thumb opposition and passive range of motion for wrist flexion on the paretic side with RAC Significant enhancements sustained during the 8-week retention post-test across all range of motion, strength variables and qualitative assessment tools with RAC

ARAT, Action reach arm test; 9HPT, 9-hole peg test; FMA, Fugl Meyer assessment for upper extremity; BBT, Box and block test; EMG, Electromyography; RAC, Rhythmic auditory cueing; BATRAC, Bilateral arm training with rhythmic auditory cueing; R-af, Real-time auditory feedback; SIS, Stroke impact scale; Exp, Experimental group; Ct, Control group; F, Females; M, Males.

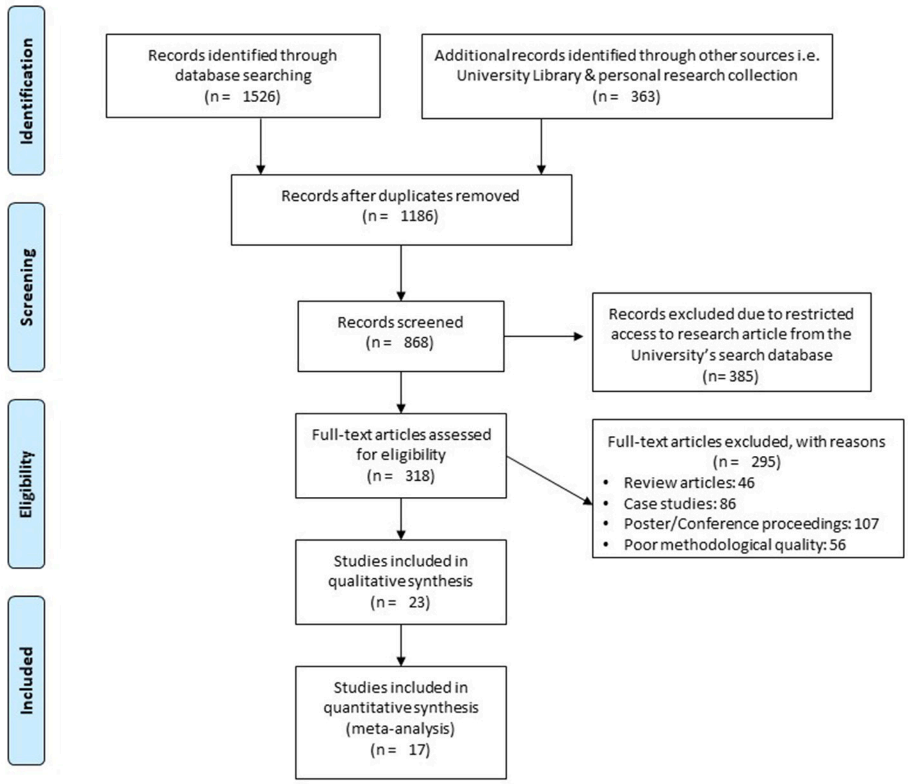

FIGURE 1 | PRISMA flow chart for the inclusion of studies.

the reviewers. The reviewers did not find any counterbalancing data. Data from each included study has been summarized in (**Table 2**). In the included studies, 10 were randomized controlled trials, and 13 were controlled clinical trials. Interventions in all the included studies were performed by either physiotherapists or medical practitioners. However, two studies in addition to training in clinics/laboratories included a phase of self-training administered by the patients themselves, at home (108, 122). Here, in both the studies guidance was provided by the researchers to the patients via telephone.

Participants

In total, the 23 included studies evaluated 585 participants of mixed gender population. The included studies had the gender distribution as follows: 226 females, and 359 males. Descriptive statistics concerning age (mean ± standard deviation) of the participants were tabulated across the studies. Disease duration of stroke patients has also been mentioned for better interpretation of the reader. However, five studies did not mention these details (107, 109, 111, 124, 125).

Risk of Bias

Studies scoring ≥4 on PEDro methodological scale were included in the review. Individual scores have been reported (**Table 2**, Supplementary Table 1). The average PEDro score for the 23 included studies was computed to be 5.3 ± 1.6 out of 10, indicating "fair" quality of the overall studies. Here, two studies scored nine (excellent quality), one study scored eight (excellent quality), three studies scored seven (good quality), six studies scored six (good quality), two studies scored five (fair quality), and 11 studies scored four (fair quality) (**Table 2**, Supplementary Table 1). **Figure 2** illustrates risk of bias across the studies. Further, publication bias was analyzed by plotting the evaluated weighted effect size i.e., Hedge's g values against standard error (**Figure 3**). Here, any asymmetry concerning mean in the funnel plot might suggest the presence of publication related bias.

Meta-Analysis

Outcomes

The results clearly suggest a positive influence of training with rhythmic auditory cueing and real-time auditory feedback on arm recovery post-stroke. Out of 23 included studies, significant enhancement was reported in 19 studies, three studies reported enhancements, and only one study reported significant reduction in arm function post training with auditory stimuli (**Table 2**).

Meta-Analysis Report

Application of a strict inclusion criterion was also meant to limit the amount of heterogeneity between the pooled studies (133). Nevertheless, despite these attempts some amount of unexplained heterogeneity was still observed. Thereafter, attempts were made to pool and analyze the studies further in sub-groups. The meta-analysis evaluated arm-functioning parameters, such as Fugl-Meyer assessment scores, Wolf motor time test, Action reach arm test, Stroke impact scale, 9-hole peg test, and elbow range of motion. The reliability and validity of these tests has been proven in the literature (134). Further, sub-group analyses were conducted to analyze specific training dosages, and to compare the effects of rhythmic auditory cueing and real-time auditory feedback. The main reasons for excluding the studies from statistical analysis was either major differences in between assessment methods, for instance considerably different auditory stimuli, disease duration, and/or lack of descriptive statistics within the manuscript. In this case, attempts were made by the primary reviewer (S.G) to contact respective corresponding authors.

Fugl Meyer Assessment Score

Fugl Meyer assessment scores for arm performance were assessed in 11 studies. Here, two studies evaluated the score on stroke patients while using real-time auditory feedback, whereas nine studies utilized rhythmic auditory cueing. The analysis of studies revealed (**Figure 4**) a *large* effect size in the positive domain (g: 0.79, 95% C.I: 0.38–1.09) and moderate heterogeneity was observed in between the studies (I^2: 29.3%, $p > 0.05$). Further, on separating the studies for comparing the effects of rhythmic auditory cueing and real-time auditory feedback, nine studies were analyzed for their effects on rhythmic auditory cueing and three studies for real-time auditory feedback.

An analysis for effects of rhythmic auditory cueing on Fugl Meyer assessment revealed (Supplementary Figure 1), positive

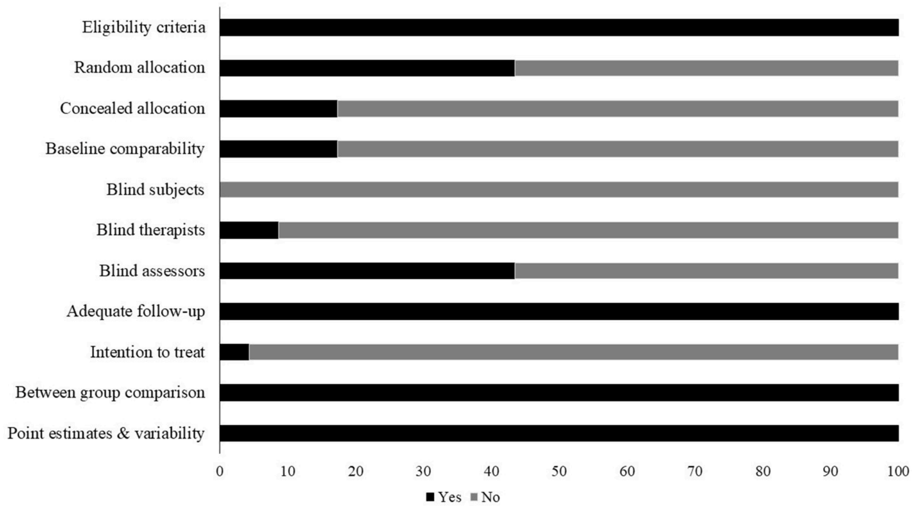

FIGURE 2 | Risk of bias across studies.

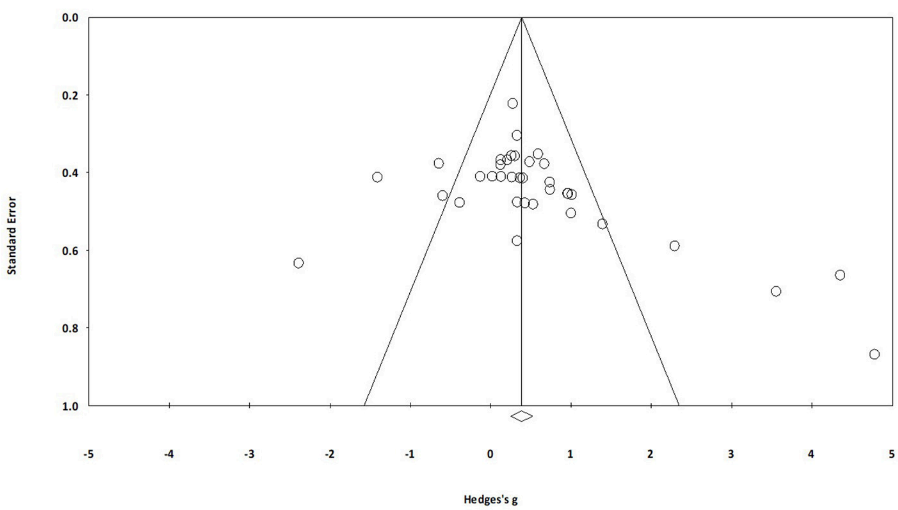

FIGURE 3 | Funnel plot for Hedge's g and standardized effect for each value in the meta-analysis. Each of the effect is represented in the plot as a circle. Funnel boundaries represent area where 95% of the effects are expected to lie if there were no publication biases. The vertical line represents the mean standardized effect of zero. Absence of publication bias is represented by symmetrical distribution of effect's around the mid-line.

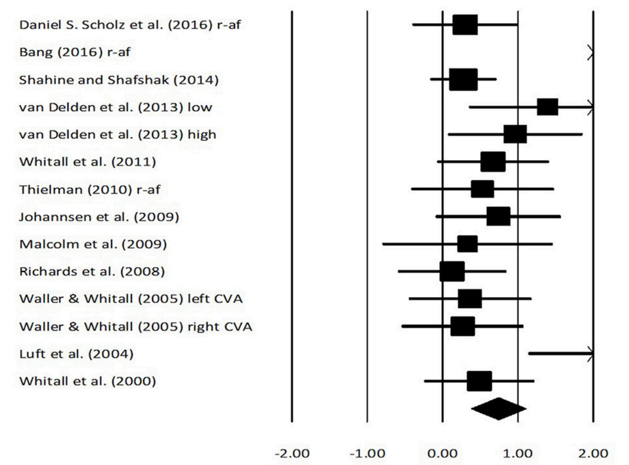

FIGURE 4 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on Fugl Meyer assessment scores on arm function amongst post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in Fugl Meyer scores depicting poor arm functioning; a positive effect size indicated enhancement in Fugl Meyer scores depicting better arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

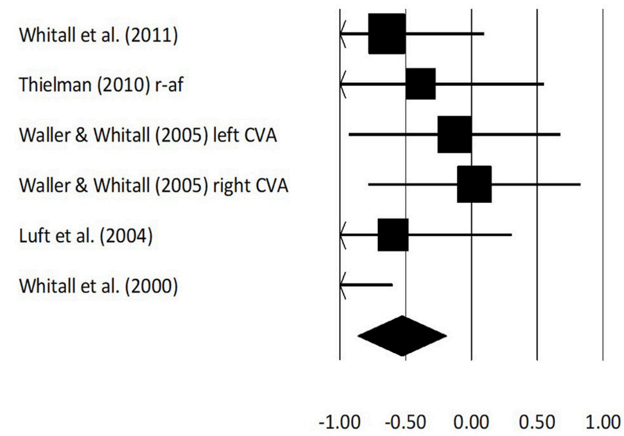

FIGURE 5 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on Wolf motor time assessment scores for arm function amongst post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in Wolf motor scores depicting a better arm functioning; a positive effect size indicated enhancement in Wolf motor scores depicting poor arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

medium effect size with negligible heterogeneity (g: 0.6, 95% C.I: 0.30–0.91, I^2: 10.7%, $p > 0.05$). An analysis for effects of real-time auditory feedback on Fugl Meyer assessment revealed (Supplementary Figure 2), a larger positive *large* effect size with moderate heterogeneity (g: 1.3, 95% C.I: −0.25 to 2.8, I^2: 40.3%, $p > 0.05$).

A further sub-group analysis based on the amount of training dosage (30 min to 1 h, ≥3 sessions per week) for rhythmic auditory cueing revealed (Supplementary Figure 3), positive *medium* effect size with moderate heterogeneity (g: 0.54, 95% C.I: 0.3–0.78, I^2: 43.8%, $p = 0.06$). Only one study (126), performed a training with rhythmic auditory cueing for <30 min, and hence was not included in further analysis. For the real-time auditory feedback Supplementary Figure 2 also illustrates the effects of training dosage for 30–45 min per session, and for >10 sessions of training.

Wolf Motor Time Assessment

An analysis for effects of rhythmic and real-time auditory stimuli on Wolf motor time assessment revealed (**Figure 5**) a negative *medium* effect size with moderate heterogeneity (g: −0.52, 95% C.I: −0.86 to −0.19, I^2: 33.2%, $p = 0.18$). Further, an analysis for only rhythmic auditory cueing revealed (Supplementary Figure 4) a similar negative *medium* effect size with negligible heterogeneity (g: −0.55, 95% C.I: −1.04 to −0.05, I^2: 0%, $p > 0.05$).

A further sub-group analysis based on the amount of training dosage (30 min to 1 h, ≥3 sessions per week) for rhythmic auditory cueing revealed (Supplementary Figure 5), negative *medium* effect size with negligible heterogeneity (g: −0.34, 95% C.I: −0.71 to 0.02, I^2: 0%, $p > 0.05$).

Elbow Range of Motion

Analysis for effects of rhythmic and real-time auditory stimuli on elbow range of motion revealed assessment revealed (**Figure 6**) a positive *medium* effect size with negligible heterogeneity (g: 0.36, 95% C.I: 0.03–0.7, I^2: 0%, $p > 0.05$). Further, a sub-group analysis for only rhythmic auditory cueing revealed a similar positive *medium* effect size with negligible heterogeneity (g: 0.37, 95% C.I: 0.01–0.72, I^2: 0%, $p > 0.05$). Further sub-group analysis was not performed because two studies did not include a training regime (112, 124), and one study analyzed the effects of real-time auditory feedback (118).

Action Reach Arm Test

Analysis for effects of rhythmic and real-time auditory inputs on Action reach arm test revealed (Supplementary Figure 6) a positive *large* effect size with substantial heterogeneity (g: 0.95, 95% C.I: 0.49–1.42, I^2: 87%, $p = 0.01$). Further, a sub-group analysis for only real-time auditory feedback training (30–45 min per session, and for >10 sessions of training) revealed a similar positive *large* effect size with substantial heterogeneity (g: 0.91, 95% C.I: 0.26–1.55, I^2: 95.6%, $p = 0.001$). Here, heterogeneity could be affirmed to considerable differences in the characteristics of real-time auditory feedback provided to the patients (see **Table 2** for details in auditory signal characteristics).

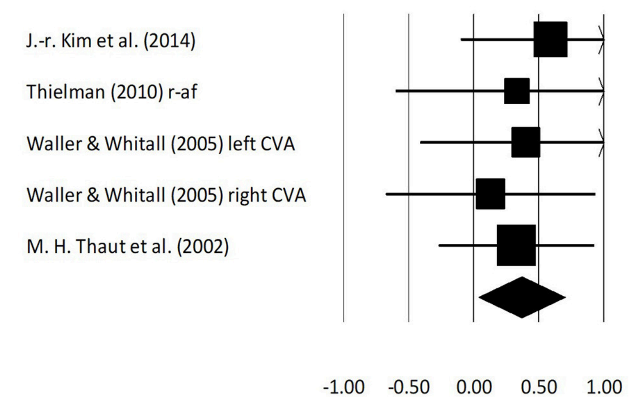

FIGURE 6 | Forest plot illustrating individual studies evaluating the effects of rhythmic auditory cueing, and real-time auditory feedback on elbow range of motion among post stroke patients. Weighted effect sizes; Hedge's g (boxes) and 95% C.I (whiskers) are presented, demonstrating repositioning errors for individual studies. The (Diamond) represents pooled effect sizes and 95% CI. A negative effect size indicated reduction in elbow range of motion depicting poor arm functioning; a positive effect size indicated enhancement in elbow range of motion depicting better arm functioning. (r-af, Real-time auditory feedback; low, Low performance group; high, High performance group; left CVA, Left sided cerebrovascular accident; right CVA, Right sided cerebrovascular accident).

Nine-Hole Peg Test

Analysis for effects of rhythmic and real-time auditory stimuli on Nine-hole peg test revealed (Supplementary Figure 7) a positive *small* effect size with substantial heterogeneity (g: 0.12, 95% C.I: −0.32 to 0.58, I^2: 85.2%, $p = 0.01$).

Further, a sub-group analysis for only rhythmic auditory cueing training (>30 min training session, 3 sessions per week) revealed a similar positive *small* effect size with substantial heterogeneity (g: 0.12, 95% C.I: −0.32 to 0.58, I^2: 90.15%, $p = 0.001$). Here, heterogeneity could be affirmed to considerable differences in the characteristics of rhythmic auditory cueing provided to the patients (**Table 2**).

Stroke Impact Scale

Analysis for effects of rhythmic and real-time auditory stimuli on Stroke impact scale revealed (Supplementary Figure 8) a positive *large* effect size with substantial heterogeneity (g: 0.95, 95% C.I: 0.49–1.42, I^2: 87%, $p = 0.01$). Further, a sub-group analysis for only rhythmic auditory cueing (>30 min of training, 3 sessions per week) revealed a similar positive *large* effect size with substantial heterogeneity (g: 0.91, 95% C.I: 0.26–1.55, I^2: 95.6%, $p = 0.001$). Here, substantial amount of heterogeneity could be due to considerable differences in the characteristics of real-time auditory feedback provided to the patients (**Table 2**).

DISCUSSION

The objective of this systematic review and meta-analysis was to analyze the current state of knowledge for the effects of rhythmic auditory cueing and real time kinematic auditory feedback for recovering arm function post-stroke. The current meta-analysis reports beneficial *small*-to-*large* standardized effects for both rhythmic auditory cueing and real-time kinematic auditory feedback in this aspect. Normally, patients with stroke exhibit poor spatiotemporal parameters during gross and fine motor skills performance for the upper extremities (135). Research suggests that assessment of arm function from Fugl Meyer test (136), Wolf motor assessment (137), Action reach arm test (138), 9-hole peg test (139), reliably reveal the severity of gross and fine motor function impairment post-stroke (136). In the current meta-analyses, we report beneficial effects of rhythmic auditory cueing on Fugl Meyer test (g: 0.6), Action reach arm test (g: 0.95), Wolf motor time test (g: −0.55), elbow range of motion (0.37), Nine-hole peg test (0.12), and Stroke impact scale (g: 0.91). Similarly, beneficial effects of real-time auditory feedback have also been reported for Fugl Meyer test (1.3), and action reach arm test (0.91). Therefore, indicating beneficial effects of external auditory stimuli for enhancing arm recovery, quality of life post-stroke.

Several reasons ranging from physiological, psychological and cognitive domains can be asserted for the beneficial effects of auditory stimuli on motor performance (64, 67, 83, 140, 141). Firstly, from a neurophysiological aspect, the auditory stimuli could have mediated multifaceted benefits. First and foremost, the stimuli could have facilitated or bypassed the deficit internal cueing system, often impaired in stroke patients exhibiting movement disorders (12). Here, a direct stimuli could have bypassed the deficit putamen directly to thalamus, and then from pre-motor area directly to primary motor cortex (76, 142). Secondly, the external stimuli could have modulated the oscillatory pattern of neuromagnetic β waves (a functional measure of auditory motor coupling) in auditory cortex, cerebellum, inferior frontal gyrus, somatosensory area and sensorimotor cortex (88, 143). Thirdly, enhanced neurological activation in inferior colliculi, cerebellum, brainstem, and sensorimotor cortex post training with rhythmic auditory cueing could have enhanced motor performance. In addition, enhanced neural re-organization especially in cortico-cerebellar circuits, and phase-periodic corrections (144) could have also been important reasons for enhancements in upper limb motor performance. Similarly, external auditory stimuli have also been suggested to facilitate neural plasticity (89, 96). In the present meta-analysis, we report beneficial effects of a training duration of 30 min−1 h with rhythmic and real-time auditory stimuli to result in enhanced performance measures for upper arm. According to the results of, this seems rational. The authors in their research reported enhanced electroencephalographic co-activity in the right hemispheric regions after just 20 min of audio-motor training, thereby implying a timeline for instigating plasticity (96). The authors also suggested the necessity of such time frame for establishing links between the perceptual modalities. Additionally, bilateral training could have also played an integral role in facilitating recovery observed in most of the studies (145). This training strategy has also been reported to facilitate neuroplasticity, cortical reorganization (110). Research suggest that bilateral training can facilitate plasticity by increasing bi-hemispheric activation, disinhibiting motor cortex, and upwardly regulating the descending propriospinal neurons.

In addition to these changes, the external auditory stimuli could also mediate debilitating cognitive dysfunctions commonly observed in patients with stroke (49). Published literature has often reported a direct relationship between the cognitive decline and movement failure (46, 146, 147). Masters and Maxwell (48) suggested that a cognitive decline might predispose patients to internally monitoring their movement patterns. This could then cause interferences with the autonomic functioning of the neural pathways, and might result in information overload (46), which further could lead to movement failure. Here, two explanations have been suggested in literature to counteract this cognitive overload. Firstly, the external auditory stimuli have been suggested to act as an external distractor (148). This could have allowed the patient to direct their focus away from their movements, thereby enhancing automatic control. Choi et al. (149) for instance, analyzed static and dynamic balance in chronic stroke patients during a cognitive-motor dual task. Here, the authors reported balance improvements when auditory cues were used during the dual task. The authors suggested that auditory cues might induce appropriate attention allocation i.e., engage higher attentional resources during auditory perception, which then could have facilitated motor performance. Secondly, enhanced cross modal processing between auditory and proprioceptive signals due to their high spatiotemporal proximity could have circumvented information overload in the native sensory modality by directing task-irrelevant information toward the underused sensory modality (98, 150). Here, inferences can be drawn from the Multiple resource theory (151, 152). The theory states that separate pools of attentional resources exist for different sensory channels and processes. Therefore, utilizing congruent stimuli together through different sensory modalities might reduce attentional interference by distributing the load amongst both the utilized modalities. Research analyzing the influence of cross-modal cueing between sensory modalities for instance audio-tactile domain have reported significant enhancements in performance under dual-task conditions as compared to performances under single sensory modality (150, 153) [for a detailed meta-analysis see (154)].

Moreover, recent research also suggests that in addition to mediating cognitive overload in patients with stroke, the external auditory cueing via music might facilitate, reorganize deficit cortical structures (155–157). For instance, merging the external auditory stimuli with music can allow facilitation of neural network including prefrontal, and limbic cortex this in turn has been associated with cognitive and emotional recovery post-stroke (155). Future research is strongly recommended to address this gap in literature as it might allow in developing of a rehabilitation protocol that focuses not only on motor recovery but also neural re-generation and/or organization (158).

In addition to the cognitive and motor deficits, the external auditory stimuli can also mediate lower sensory perceptual thresholds exhibited in patients in stroke (35). Here, external auditory stimuli might enhance the saliency of the perceptual modalities, which could then support the development of feedback, and feedforward models necessary for motor planning and execution (82, 159–161). Also, cross-sensory impacts between the perceptual modalities due to high spatiotemporal proximity between the sensory modalities might result in the auditory stimuli to support the deficit proprioceptive modality (98). Recent research evaluating the rhythmic auditory cueing suggests that mediating the auditory signal characteristics in terms of ecologically valid action relevant sounds might further enrich the precepted spatio-temporal information and allow extended enhancements in motor execution (142, 162) i.e., as compared to isosynchronous cueing. Patients with stroke due to their sensory impairments usually have higher thresholds for perception of sensory stimuli (35, 163). Therefore, enhancing the saliency of sensory information delivered through ecologically valid action relevant auditory stimuli such as walking on gravel, snow might be beneficial (50, 142, 164). According to Young et al. (165) action relevant auditory stimuli not only specify the temporal but also the spatial information, thereby enriching the feed-forward mechanisms to execute a motor task efficiently (166). The authors also affirmed beneficial effects of action relevant auditory stimuli on gait performance due to putative function of "sensori-motor neurons" (166). Furthermore, it can be expected that modifications in auditory signal characteristics such as modulation of timbre at a higher intensity further merged with a broad ascending melody and rich harmony might motivate a stroke patient to exert more force (50, 142, 167). This however, was not evaluated in any of the studies included in this review and should be a possible topic of research for future studies.

Moreover, research suggests the extended benefits of real-time auditory feedback with respect to rhythmic auditory stimuli. suggested that mapping the movements with real-time auditory feedback could allow a patient to better perceive their self-generated movement amplitudes. Further allowing them to compare it with the sound of a desirable auditory movement model. This could then result in development of an auditory reference framework model, which could amplify internal simulations of movements, and allow a patient to better perceive spatio-temporal parameters as compared to discrete rhythmic component (168). A contextual comparison of neuroimaging data from rhythmic (85, 86), and real-time auditory stimuli (90), suggests a large number of neurological structures having overlapped activation between both the auditory stimuli. However, enhanced activation of the areas associated with action observation such as, superior temporal sulcus, premotor cortex (169, 170), have been reported with real-time auditory feedback in one study (90). Here, the main reasons for the enhanced activation in areas associated with motion perception can be attributed to the findings of Shams and Seitz (171) and Lahav et al. (172). Here, the authors suggested that a convergent audio-visual motion would enhance accuracy of perception and motor performance due to the enhanced multimodal congruent nature (90, 171). Further, Lahav et al. (172) hypothesized that an audio-visual mirror neuron system with the premotor areas might be involved in serving as an "action listening" and "hearing & doing mirror neuron system," with the latter being largely dependent on a person's motor repertoire. Likewise, Vinken et al. (173) demonstrated that mapping real-time auditory feedback with real life activities lead to enhanced accuracy in judgement of actions, thereby demonstrating enhanced potential for improving motor perception, control, and learning. In the present meta-analysis enhanced scores for Fugl Meyer scores with real time kinematic auditory feedback (g: 1.3) were observed as compared to rhythmic auditory cueing (0.60).

The auditory stimuli could have also influenced the musculoskeletal structure of the upper extremities. For example, research suggests that intricate neuroanatomical interconnections between the auditory and motor cortex could allow the auditory stimuli could possibly mediate the firing and recruitment rate of motor units (28). This could then result in smoothening of motor movements, further resulting in enhanced joint kinematics, and movement scaling parameters (174). Likewise, regularized muscle co-activation rate has also been documented in electromyographic studies (175–177). This was also demonstrated in our meta-analysis concerning enhancement in elbow range of motion with rhythmic auditory cueing.

Moreover, the application of these interventions can be promoted in a cost-effective manner due to their high viability (50, 142). The strategies could prove to be efficient in developing countries where higher costs of rehabilitation promote stroke associated morbidity and mortality (178, 179). Here, the medical practitioners or tele-stroke (179), helplines can promote the use of mobile applications which can be utilized by patients at their home. Few smartphone applications have been reported in published literature, however, their feasibility in terms of costs is too high (180, 181). Future studies are recommended to address this gap and develop open source applications for the use of stroke patients. Here, the global position sensors, gyroscope and accelerometers present usually in a smartphone can be utilized to direct kinematic information, which could then assist in projecting either optimal rhythmic cueing pattern or converted/mapped in real-time to produce sonified auditory feedback. Further, applications can be developed to generate different types of ecologically valid sounds.

Finally, as the current review mentions a sole author (S.G), concerns regarding biasing, methodological flaws in the study's design and outcomes could be expected (182). Here, the reader is assured that this present systematic review and meta-analysis was carried out by two authors. Dr. Ishan Ghai (I.G) acted as an additional reviewer and statistician in the current study. His role is duly mentioned in the methodological, and acknowledgment sections. Dr. Ishan Ghai has himself consented to be excluded from this study as a co-author. Moreover, to ensure transparency in the methodological parts of the current review and analyses sufficient description has been provided for reciprocating the search strategy (**Table 1**), and the statistical analysis. Additionally, the corresponding author is willing to share the entire data with any reader upon request.

In conclusion, this present review for the first time analyzed the effects of rhythmic and real time auditory stimuli on arm recovery in post-stroke patients. The present findings are in agreement with systematic reviews and meta-analysis carried out to analyze auditory entrainment effect on aging (50), cerebral palsy (164), stroke (183), multiple sclerosis (184), and parkinsonism (63, 185). This review strongly suggests the incorporation of rhythmic and real-time auditory stimuli with a training dosage of 30 min to 1 h of training, for >3 sessions week for enhancing arm function recovery post-stroke.

AUTHOR CONTRIBUTIONS

SG conceptualized the study, carried out the systematic review, statistical analysis, and wrote the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00488/full#supplementary-material

REFERENCES

1. World Health Organization. *Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012.* Geneva: WHO (2014).
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol.* (2007) 6:182–7. doi: 10.1016/S1474-4422(07)70031-5
3. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* (2009) 8:355–69. doi: 10.1016/S1474-4422(09)70025-0
4. Cerniauskaite M, Quintas R, Koutsogeorgou E, Meucci P, Sattin D, Leonardi M, Raggi A. Quality-of-life and disability in patients with stroke. *Am J Phys Med Rehabil* (2012) 91:S39–47. doi: 10.1097/PHM.0b013e31823d4df7
5. Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. *Cochrane Database Syst Rev.* (2013) CD010820. doi: 10.1002/14651858.CD010820
6. White JH, Attia J, Sturm J, Carter G, Magin P. Predictors of depression and anxiety in community dwelling stroke survivors: a cohort study. *Disabil Rehabil*. (2014) 36:1975–82. doi: 10.3109/09638288.2014.884172
7. Haun J, Rittman M, Sberna M. The continuum of connectedness and social isolation during post stroke recovery. *J Aging Stud* (2008) 22:54–64. doi: 10.1016/j.jaging.2007.03.001
8. King RB. Quality of life after stroke. *Stroke* (1996) 27:1467–72. doi: 10.1161/01.STR.27.9.1467
9. Franceschini M, La Porta F, Agosti M, Massucci M. Is health-related-quality of life of stroke patients influenced by neurological impairments at one year after stroke? *Eur J Phys Rehabil Med.* (2010) 46:389–99.
10. Godwin KM, Wasserman J, Ostwald SK. Cost associated with stroke: outpatient rehabilitative services and medication. *Top Stroke Rehabil.* (2011) 18(Suppl. 1):676–84. doi: 10.1310/tsr18s01-676
11. Krakauer JW. Arm function after stroke: from physiology to recovery. *Semin Neurol.* (2005) 25:384–95. doi: 10.1055/s-2005-923533
12. Handley A, Medcalf P, Hellier K, Dutta D. Movement disorders after stroke. *Age Ageing* (2009) 38:260–6. doi: 10.1093/ageing/afp020

13. Barker RN, Brauer S, Carson R. Training-induced changes in the pattern of triceps to biceps activation during reaching tasks after chronic and severe stroke. *Exp Brain Res*. (2009) 196:483–96. doi: 10.1007/s00221-009-1872-8
14. Watkins C, Leathley M, Gregson J, Moore A, Smith T, Sharma A. Prevalence of spasticity post stroke. *Clin Rehabil* (2002) 16:515–22. doi: 10.1191/0269215502cr512oa
15. Kokotilo KJ, Eng JJ, Boyd LA. Reorganization of brain function during force production after stroke: a systematic review of the literature. *J Neurol Phys Ther*. (2009) 33:45–54. doi: 10.1097/NPT.0b013e31819824f0
16. Santisteban L, Térémetz M, Bleton JP, Baron JC, Maier MA, Lindberg PG. Upper limb outcome measures used in stroke rehabilitation studies: a systematic literature review. *PLoS ONE* (2016) 11:e0154792. doi: 10.1371/journal.pone.0154792
17. Clark DJ, Ting LH, Zajac FE, Neptune RR, Kautz SA. Merging of healthy motor modules predicts reduced locomotor performance and muscle coordination complexity post-stroke. *J Neurophysiol.* (2010) 103:844–57. doi: 10.1152/jn.00825.2009
18. Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD. Characterization of incident stroke signs and symptoms. Findings from the atherosclerosis risk in communities study. *Stroke* (2002) 33:2718–21. doi: 10.1161/01.STR.0000035286.87503.31
19. Foerch C, Misselwitz B, Sitzer M, Berger K, Steinmetz H, Neumann-Haefelin T. Difference in recognition of right and left hemispheric stroke. *Lancet* (2005) 366:392–3. doi: 10.1016/S0140-6736(05)67024-9
20. Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb. *Stroke* (2003) 34:2181–6. doi: 10.1161/01.STR.0000087172.16305.CD
21. Dobkin BH. Rehabilitation after stroke. *N Engl J Med* (2005) 352:1677–84. doi: 10.1056/NEJMcp043511
22. Perez-Marmol JM, Garcia-Rios MC, Barrero-Hernandez FJ, Molina-Torres G, Brown T, et al. Functional rehabilitation of upper limb apraxia in poststroke patients: study protocol for a randomized controlled trial. *Trials* (2015) 16:508. doi: 10.1186/s13063-015-1034-1
23. Silva A, Sousa AS,Tavares JM, Tinoco A, Santos R, Sousa F. Ankle dynamic in stroke patients: agonist vs. antagonist muscle relations. *Somatosens Mot Res*. (2012) 29:111–6. doi: 10.3109/08990220.2012.715099
24. Lee CJ, Sanders RH, Payton CJ. Changes in force production and stroke parameters of trained able-bodied and unilateral arm-amputee female swimmers during a 30 s tethered front-crawl swim. *J Sports Sci*. (2014) 32:1704–11. doi: 10.1080/02640414.2014.915420
25. Trumbower RD, Ravichandran VJ, Krutky MA, Perreault EJ. Contributions of altered stretch reflex coordination to arm impairments following stroke. *J Neurophysiol.* (2010) 104:3612–24. doi: 10.1152/jn.00804.2009
26. Messier S, Bourbonnais D, Desrosiers J, Roy Y. Kinematic analysis of upper limbs and trunk movement during bilateral movement after stroke. *Arch Phys Med Rehabil.* (2006) 87:1463–70. doi: 10.1016/j.apmr.2006.07.273
27. van Dokkum L, Hauret I, Mottet D, Froger J, Metrot J, Laffont I. The contribution of kinematics in the assessment of upper limb motor recovery early after stroke. *Neurorehabil Neural Repair* (2014) 28:4–12. doi: 10.1177/1545968313498514
28. Hara Y, Masakado Y, Chino N. The physiological functional loss of single thenar motor units in the stroke patients: when does it occur? Does it progress? *Clin Neurophysiol.* (2004) 115:97–103. doi: 10.1016/j.clinph.2003.08.002
29. Young CA, Mills RJ, Gibbons C, Thornton EW. Poststroke fatigue: the patient perspective. *Top Stroke Rehabil.* (2013) 20:478–84. doi: 10.1310/tsr2006-478
30. Pelton T, van Vliet P, Hollands K. Interventions for improving coordination of reach to grasp following stroke: a systematic review. *Int J Evid Based Healthcare* (2012) 10:89–102. doi: 10.1111/j.1744-1609.2012.00261.x
31. Lannin NA, Cusick A, McCluskey A, Herbert RD. Effects of splinting on wrist contracture after stroke. A randomized controlled trial. *Stroke* (2007) 38:111–6. doi: 10.1161/01.STR.0000251722.77088.12
32. Pop T. Subluxation of the shoulder joint in stroke patients and the influence of selected factors on the incidence of instability. *Ortoped Traumatol Rehabil* (2013) 15:259–67. doi: 10.5604/15093492.1058421
33. Jellinger KA. Pathology and pathogenesis of vascular cognitive impairment-a critical update. *Front Aging Neurosci*. (2013) 5:17. doi: 10.3389/fnagi.2013.00017
34. Weinstein G, Preis SR, Beiser AS, Au R, Kelly-Hayes M, Kase CS, et al. Cognitive performance after stroke–the Framingham Heart Study. *Int J Stroke* (2014) 9(Suppl. A100): 48–54. doi: 10.1111/ijs.12275
35. Bolognini N, Russo C, Edwards DJ. The sensory side of post-stroke motor rehabilitation. *Restor Neurol Neurosci* (2016) 34:571–86. doi: 10.3233/RNN-150606
36. Grau-Olivares M, Bartres-Faz D, Arboix A, Soliva JC, Rovira M, Targa C. Mild cognitive impairment after lacunar infarction: voxel-based morphometry and neuropsychological assessment. *Cerebrovasc Dis.* (2007) 23:353–61. doi: 10.1159/000099134
37. Stebbins GT, Nyenhuis DL, Wang C, Cox JL, Freels S, Bangen K, et al. Gray matter atrophy in patients with ischemic stroke with cognitive impairment. *Stroke* (2008) 39:785–93. doi: 10.1161/STROKEAHA.107.507392
38. Fazekas F, Wardlaw JM. The origin of white matter lesions. A further piece to the puzzle. *Stroke* (2013) 44:951–2. doi: 10.1161/STROKEAHA.111.000849
39. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. *Ann Transl Med.* (2014) 2:80. doi: 10.3978/j.issn.2305-5839.2014.08.05
40. Makin SDJ, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *J Neurol Neurosurg Psychiatry* (2013) 84:893–900. doi: 10.1136/jnnp-2012-303645
41. Sperber C, Karnath HO. Topography of acute stroke in a sample of 439 right brain damaged patients. *Neuroimage Clin.* (2016) 10:124–8. doi: 10.1016/j.nicl.2015.11.012
42. Maraka S, Jiang Q, Jafari-Khouzani K, Li L, Malik S, Hamidian H, et al. Degree of corticospinal tract damage correlates with motor function after stroke. *Ann Clin Transl Neurol.* (2014) 1:891–9. doi: 10.1002/acn3.132
43. Puig J, Blasco G, Schlaug G, Stinear CM, Daunis EP, Biarnes C, et al. Diffusion tensor imaging as a prognostic biomarker for motor recovery and rehabilitation after stroke. *Neuroradiology* (2017) 59:343–51. doi: 10.1007/s00234-017-1816-0
44. Tennant KA, Taylor SL, White ER, Brown CE. Optogenetic rewiring of thalamocortical circuits to restore function in the stroke injured brain. *Nat Commun.* (2017) 8:15879. doi: 10.1038/ncomms 15879
45. Kamali A, Flanders AE, Brody J, Hunter JV, Hasan KM. Tracing superior longitudinal fasciculus connectivity in the human brain using high resolution diffusion tensor tractography. *Brain Struct Funct* (2014) 219:269–81. doi: 10.1007/s00429-012-0498-y.
46. Ghai S, Driller MW, Masters RSW. The influence of below-knee compression garments on knee-joint proprioception. *Gait Posture* (2018) 60:258–61. doi: 10.1016/j.gaitpost.2016.08.008
47. Masters RSW. Knowledge, knerves and know-how: the role of explicit versus implicit knowledge in the breakdown of a complex motor skill under pressure. *Br J Psychol.* (1992) 83:343–58. doi: 10.1111/j.2044-8295.1992.tb02446.x
48. Masters RSW, Maxwell J. The theory of reinvestment. *Int Rev Sport Exerc Psychol.* (2008) 1:160–83. doi: 10.1080/17509840802287218
49. Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Interven Aging* (2017) 12:557–77. doi: 10.2147/CIA.S125201
50. Ghai S, Ghai I, Effenberg AO. Effect of rhythmic auditory cueing on aging gait: a systematic review and meta-analysis. *Aging Dis.* (2017) 131–200. doi: 10.14336/AD.2017.1031
51. Laver KE, Lange B, George S, Deutsch JE, Saposnik G, Crotty M. Virtual reality for stroke rehabilitation. *Cochrane Database Syst Rev*. (2017) CD008349. doi: 10.1002/14651858.CD008349.pub4
52. Tong Y, Pendy JT Jr., Li WA, Du H, Zhang T, Geng X, et al. Motor imagery-based rehabilitation: potential neural correlates and clinical application for functional recovery of motor deficits after stroke. *Aging Disord*. (2017) 8:364–71. doi: 10.14336/AD.2016.1012
53. Del Din S, Bertoldo A, Sawacha Z, Jonsdottir J, Rabuffetti M, Cobelli C, et al. Assessment of biofeedback rehabilitation in post-stroke patients combining fMRI and gait analysis: a case study. *J Neuroeng Rehabil* (2014) 11:53. doi: 10.1186/1743-0003-11-53
54. Pollock A, Baer GD, Langhorne P, Pomeroy VM. Physiotherapy treatment approaches for stroke. *Stroke* (2008) 39:519–20. doi: 10.1161/STROKEAHA.107.492710

55. Billinger SA, Arena R, Bernhardt J, Eng JJ, Franklin BA, Johnson CM, et al. Physical activity and exercise recommendations for stroke survivors. A statement for healthcare professionals From the American Heart Association/American Stroke Association. *Stroke* (2014) 45:2532–53. doi: 10.1161/STR.0000000000000022
56. Figueiredo EM, Ferreira GB, Maia Moreira RC, Kirkwood RN, Fetters L. Efficacy of ankle-foot orthoses on gait of children with cerebral palsy: systematic review of literature. *Pediatr Phys Ther.* (2008) 20:207–23. doi: 10.1097/PEP.0b013e318181fb34
57. Ghai S, Driller M, Ghai I. Effects of joint stabilizers on proprioception and stability: a systematic review and meta-analysis. *Phys Ther Sport* (2017) 25:65–75. doi: 10.1016/j.ptsp.2016.05.006
58. Ghai S. *Proprioception and Performance: The Role of Below-Knee Compression Garments and Secondary Tasks*. Hamilton: University of Waikato (2016). Available online at: https://hdl.handle.net/10289/10575
59. Hatem SM, Saussez G, della Faille M, Prist V, Zhang X, Dispa D, et al. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Front Hum Neurosci.* (2016) 10:442. doi: 10.3389/fnhum.2016.00442
60. Scholz DS, Rohde S, Nikmaram N, Brückner HP, Großbach M, Rollnik JD et al. Sonification of arm movements in stroke rehabilitation – a novel approach in neurologic music therapy. *Front Neurol.* (2016) 7:106. doi: 10.3389/fneur.2016.00106
61. Lam P, Hebert D, Boger J, Lacheray H, Gardner D, Apkarian J, et al. A haptic-robotic platform for upper-limb reaching stroke therapy: preliminary design and evaluation results. *J Neuroeng Rehabil.* (2008) 5:15. doi: 10.1186/1743-0003-5-15
62. Urra O, Casals A, Jane R. The impact of visual feedback on the motor control of the upper-limb. *Conf Proc IEEE Eng Med Biol Soc.* (2015) 2015:3945–8. doi: 10.1109/EMBC.2015.7319257
63. Spaulding SJ, Barber B, Colby M, Cormack B, Mick T, Jenkins ME. Cueing and gait improvement among people with Parkinson's disease: a meta-analysis. *Arch Phys Med Rehabil.* (2013) 94:562–70. doi: 10.1016/j.apmr.2012.10.026
64. Thaut MH, Abiru M. Rhythmic auditory stimulation in rehabilitation of movement disorders: a review of current research. *Music Percept.* (2010) 27:263–9. doi: 10.1525/mp.2010.27.4.263
65. Ermolaeva VY, Borgest A. Intercortical connections of the auditory areas with the motor area. *Neurosci Behav Physiol* (1980) 10:210–5. doi: 10.1007/BF01182212
66. Felix RA, Fridberger A, Leijon S, Berrebi AS, Magnusson AK. Sound rhythms are encoded by postinhibitory rebound spiking in the superior paraolivary nucleus. *J Neurosci.* (2011) 31:12566–78. doi: 10.1523/JNEUROSCI.2450-11.2011
67. Thaut MH, McIntosh GC, Hoemberg V. Neurobiological foundations of neurologic music therapy: rhythmic entrainment and the motor system. *Front Psychol.* (2014) 5:1185. doi: 10.3389/fpsyg.2014.01185
68. Nodal FR, López DE. Direct input from cochlear root neurons to pontine reticulospinal neurons in albino rat. *J Compar Neurol.* (2003) 460:80–93. doi: 10.1002/cne.10656
69. Mirjany M, Preuss T, Faber DS. Role of the lateral line mechanosensory system in directionality of goldfish auditory evoked escape response. *J Exp Biol.* (2011) 214:3358–67. doi: 10.1242/jeb.052894
70. de la Mothe LA, Blumell S, Kajikawa Y, Hackett TA. Cortical connections of the auditory cortex in marmoset monkeys: core and medial belt regions. *J Compar Neurol.* (2006) 496:27–71. doi: 10.1002/cne.20923
71. Read HL, Winer JA, Schreiner CE. Functional architecture of auditory cortex. *Curr Opin Neurobiol.* (2002) 12:433–40. doi: 10.1016/S0959-4388(02)00342-2
72. Chen JL, Zatorre RJ, Penhune VB. Interactions between auditory and dorsal premotor cortex during synchronization to musical rhythms. *Neuroimage* (2006) 32:1771–81. doi: 10.1016/j.neuroimage.2006.04.207
73. Grahn JA, Rowe JB. Feeling the beat: premotor and striatal interactions in musicians and nonmusicians during beat perception. *J Neurosci.* (2009) 29:7540–8. doi: 10.1523/JNEUROSCI.2018-08.2009
74. Tecchio F, Salustri C, Thaut MH, Pasqualetti P, Rossini PM. Conscious and preconscious adaptation to rhythmic auditory stimuli: a magnetoencephalographic study of human brain responses. *Exp Brain Res.* (2000) 135:222–30. doi: 10.1007/s002210000507
75. Giovannelli F, Innocenti I, Rossi S, Borgheresi A, Ragazzoni A, Zaccara G, et al. Role of the dorsal premotor cortex in rhythmic auditory–motor entrainment: a perturbational approach by rTMS. *Cereb Cortex* (2012) 24:1009–16. doi: 10.1093/cercor/bhs386
76. Nombela C, Hughes LE, Owen AM, Grahn JA. Into the groove: can rhythm influence Parkinson's disease? *Neurosci Biobehav Rev.* (2013) 37:2564–70. doi: 10.1016/j.neubiorev.2013.08.003
77. Spidalieri G, Busby L, Lamarre Y. Fast ballistic arm movements triggered by visual, auditory, and somesthetic stimuli in the monkey. II. Effects of unilateral dentate lesion on discharge of precentral cortical neurons and reaction time. *J Neurophysiol.* (1983) 50:1359–79. doi: 10.1152/jn.1983.50.6.1359
78. Thaut M, Kenyon G, Schauer M, McIntosh G. The connection between rhythmicity and brain function. *IEEE Eng Med Biol Magaz.* (1999) 18:101–8. doi: 10.1109/51.752991
79. Repp BH, Su YH. Sensorimotor synchronization: a review of recent research (2006–2012). *Psychon Bull Rev.* (2013) 20:403–52. doi: 10.3758/s13423-012-0371-2
80. Grahn JA. See what I hear? Beat perception in auditory and visual rhythms. *Exp Brain Res.* (2012) 220:51–61. doi: 10.1007/s00221-012-3114-8
81. van Noorden L, Moelants D. Resonance in the perception of musical pulse. *J New Music Res.* (1999) 28:43–66. doi: 10.1076/jnmr.28.1.43.3122
82. Effenberg AO, Fehse U, Schmitz G, Krueger B, Mechling H. Movement sonification: effects on motor learning beyond rhythmic adjustments. *Front Neurosci.* (2016) 10:219. doi: 10.3389/fnins.2016.00219
83. Schaefer RS. Auditory rhythmic cueing in movement rehabilitation: findings and possible mechanisms. *Philos Trans R Soc B Biol Sci.* (2014) 369:20130402. doi: 10.1098/rstb.2013.0402
84. Thaut MH, Hoemberg V. *Handbook of Neurologic Music Therapy*. Oxford: Oxford University Press (2014).
85. Grahn JA, Henry MJ, McAuley JD. FMRI investigation of cross-modal interactions in beat perception: audition primes vision, but not vice versa. *Neuroimage* (2011) 54:1231–43. doi: 10.1016/j.neuroimage.2010.09.033
86. Grahn JA. Neural mechanisms of rhythm perception: current findings and future perspectives. *Top Cogn Sci.* (2012) 4:585–606. doi: 10.1111/j.1756-8765.2012.01213.x
87. Hove MJ, Fairhurst MT, Kotz SA, Keller PE. Synchronizing with auditory and visual rhythms: an fMRI assessment of modality differences and modality appropriateness. *Neuroimage* (2013) 67:313–21. doi: 10.1016/j.neuroimage.2012.11.032
88. Fujioka T, Trainor LJ, Large EW, Ross B. Internalized timing of isochronous sounds is represented in neuromagnetic beta oscillations. *J Neurosci.* (2012) 32:1791–802. doi: 10.1523/JNEUROSCI.4107-11.2012
89. Ross B, Barat M, Fujioka T. Sound-making actions lead to immediate plastic changes of neuromagnetic evoked responses and induced beta-band oscillations during perception. *J Neurosci.* (2017) 37:5948–59. doi: 10.1523/JNEUROSCI.3613-16.2017
90. Schmitz G, Mohammadi B, Hammer A, Heldmann M, Samii A, Münte TF, et al. Observation of sonified movements engages a basal ganglia frontocortical network. *BMC Neurosci.* (2013) 14:32. doi: 10.1186/1471-2202-14-32
91. Heremans E, Nieuwboer A, Spildooren J, De Bondt S, D'hooge AM, Helsen WI et al. Cued motor imagery in patients with multiple sclerosis. *Neuroscience* (2012) 206:115–21. doi: 10.1016/j.neuroscience.2011.12.060
92. Heremans E, Nieuwboer A, Feys P, Vercruysse S, Vandenberghe W, Sharma N, et al. External cueing improves motor imagery quality in patients with Parkinson disease. *Neurorehabil Neural Repair* (2012) 26:27–35. doi: 10.1177/1545968311411055
93. Lima CF, Lavan N, Evans S, Agnew Z, Halpern AR, Shanmugalingam P, et al. Feel the noise: relating individual differences in auditory imagery to the structure and function of sensorimotor systems. *Cereb Cortex* (2015) 25:4638–50. doi: 10.1093/cercor/bhv134
94. Miller RA, Thaut MH, McIntosh GC, Rice RR. Components of EMG symmetry and variability in parkinsonian and healthy

elderly gait. *Electroencephalogr Clin Neurophysiol.* (1996) 101:1–7. doi: 10.1016/0013-4694(95)00209-X
95. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in chronic stroke: a randomized controlled trial. *J Am Med Assoc.* (2004) 292:1853–61. doi: 10.1001/jama.292.15.1853
96. Bangert M, Altenmüller EO. Mapping perception to action in piano practice: a longitudinal DC-EEG study. *BMC Neurosci.* (2003) 4:26. doi: 10.1186/1471-2202-4-26
97. Rochester L, Baker K, Nieuwboer A, Burn D. Targeting dopa-sensitive and dopa-resistant gait dysfunction in Parkinson's disease: selective responses to internal and external cues. *Mov Disord.* (2011) 26:430–5. doi: 10.1002/mds.23450
98. Ghai S, Schmitz G, Hwang TH, Effenberg AO. Auditory proprioceptive integration: effects of real-time kinematic auditory feedback on knee proprioception. *Front Neurosci.* (2018) 12:142. doi: 10.3389/fnins.2018.00142
99. Dyer J, Stapleton P, Rodger M. Transposing musical skill: sonification of movement as concurrent augmented feedback enhances learning in a bimanual task. *Psychol Res.* (2017) 81:850–62. doi: 10.1007/s00426-016-0775-0
100. Wolf A, Scheiderer R, Napolitan N, Belden C, Shaub L, Whitford M. Efficacy and task structure of bimanual training post stroke: a systematic review. *Top Stroke Rehabil.* (2014) 21:181–96. doi: 10.1310/tsr2103-181
101. Latimer CP, Keeling J, Lin B, Henderson M, Hale LA. The impact of bilateral therapy on upper limb function after chronic stroke: a systematic review. *Disabil Rehabil.* (2010) 32:1221–31. doi: 10.3109/09638280903483877
102. Zhang Y, Cai J, Zhang Y, Ren T, Zhao M, Zhao Q. Improvement in stroke-induced motor dysfunction by music-supported therapy: a systematic review and meta-analysis. *Sci Rep.* (2016) 6:38521. doi: 10.1038/srep38521
103. Yoo GE, Kim SJ. Rhythmic auditory cueing in motor rehabilitation for stroke patients: systematic review and meta-analysis. *J Music Ther.* (2016) 53:149–77. doi: 10.1093/jmt/thw003
104. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* (2009) 151:W65–94. doi: 10.7326/0003-4819-151-4-200908180-00136
105. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res.* (2014) 14:579. doi: 10.1186/s12913-014-0579-0
106. Bang DH. Effect of modified constraint-induced movement therapy combined with auditory feedback for trunk control on upper extremity in subacute stroke patients with moderate impairment: randomized controlled pilot trial. *J Stroke Cerebrovasc Dis.* (2016) 25:1606–12. doi: 10.1016/j.jstrokecerebrovasdis.2016.03.030
107. Scholz DS, Rhode S, Großbach M, Rollnik J, Altenmüller E. Moving with music for stroke rehabilitation: a sonification feasibility study. *Ann NY Acad Sci.* (2015) 1337:69–76. doi: 10.1111/nyas.12691
108. Malcolm MP, Massie C, Thaut M. Rhythmic auditory-motor entrainment improves hemiparetic arm kinematics during reaching movements: a pilot study. *Top Stroke Rehabil.* (2009) 16:69–79. doi: 10.1310/tsr1601-69
109. Speth F. The role of sound in robot-assisted hand function training post-stroke. Humboldt-Universität zu Berlin, Kultur-, Sozial-und Bildungswissenschaftliche Fakultät (2016).
110. van Delden AL, Peper CL, Nienhuys KN, Zijp NI, Beek PJ, and Kwakkel G. Unilateral versus bilateral upper limb training after stroke. *Stroke* (2013) 44:2613–6. doi: 10.1161/STROKEAHA.113.001969
111. Schmitz G, Kroeger D, Effenberg AO. *A Mobile Sonification System for Stroke Rehabilitation*. Georgia Institute of Technology (2014).
112. Kim J, Jung MY, Yoo, EY, Park JH, Kim SH, Lee J. Effects of rhythmic auditory stimulation during hemiplegic arm reaching in individuals with stroke: an exploratory study. *Hong Kong J Occup Ther.* (2014) 24:64–71. doi: 10.1016/j.hkjot.2014.11.002
113. Shahine EM, Shafshak TS. The effect of repetitive bilateral arm training with rhythmic auditory cueing on motor performance and central motor changes in patients with chronic stroke. *Egypt Rheumatol Rehabil* (2014) 41:8. doi: 10.4103/1110-161X.128128
114. Dispa D, Lejeune T, Thonnard JL. The effect of repetitive rhythmic precision grip task-oriented rehabilitation in chronic stroke patients: a pilot study. *Int J Rehabil Res.* (2013) 36:81–7. doi: 10.1097/MRR.0b013e32835acfd5
115. Whitall J, Waller SM, Sorkin JD, Forrester LW, Macko RF, Hanley DF, et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms a single-blinded randomized controlled trial. *Neurorehabil Neural Repair* (2011) 25:118–29. doi: 10.1177/1545968310380685
116. Chouhan S, Kumar S. Comparing the effects of rhythmic auditory cueing and visual cueing in acute hemiparetic stroke. *Int J Ther Rehabil.* (2012) 19. doi: 10.12968/ijtr.2012.19.6.344
117. Secoli R, Milot MH, Rosati G, Reinkensmeyer DJ. Effect of visual distraction and auditory feedback on patient effort during robot-assisted movement training after stroke. *J Neuroeng Rehabil.* (2011) 8:21. doi: 10.1186/1743-0003-8-21
118. Thielman G. Rehabilitation of reaching poststroke: a randomized pilot investigation of tactile versus auditory feedback for trunk control. *J Neurol Phys Ther.* (2010) 34:138–44. doi: 10.1097/NPT.0b013e3181efa1e8
119. Johannsen L, Wing AM, Pelton T, Kitaka K, Zietz D, Brittle N, et al. Seated bilateral leg exercise effects on hemiparetic lower extremity function in chronic stroke. *Neurorehabil Neural Repair* (2010) 24:243–53. doi: 10.1177/1545968309347679
120. Stoykov ME, Lewis GN, Corcos DM. Comparison of bilateral and unilateral training for upper extremity hemiparesis in stroke. *Neurorehabil Neural Repair* (2009) 23:945–53. doi: 10.1177/1545968309338190
121. Richards LG, Senesac CR, Davis SB, Woodbury ML, Nadeau SE. Bilateral arm training with rhythmic auditory cueing in chronic stroke: not always efficacious. *Neurorehabil Neural Repair* (2008) 22:180–4. doi: 10.1177/1545968307305355
122. Jeong S, Kim MT. Effects of a theory-driven music and movement program for stroke survivors in a community setting. *Appl Nurs Res.* (2007) 20:125–31. doi: 10.1016/j.apnr.2007.04.005
123. Waller SM, Whitall J. Hand dominance and side of stroke affect rehabilitation in chronic stroke. *Clin Rehabil* (2005) 19:544–51. doi: 10.1191/0269215505cr829oa
124. Thaut MH, Kenyon GP, Hurt CP, McIntosh GC, Hoemberg V. Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. *Neuropsychologia* (2002) 40:1073–81. doi: 10.1016/S0028-3932(01)00141-5
125. Maulucci RA, Eckhouse RH. Retraining reaching in chronic stroke with real-time auditory feedback. *Neurorehabilitation* (2001) 16:171–82. Available online at: https://content.iospress.com/articles/neurorehabilitation/nre00104
126. Whitall J, Waller SM, Silver KH, Macko RF. Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke* (2000) 31:2390–5. doi: 10.1161/01.STR.31.10.2390
127. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Austral J Physiother.* (2009) 55:129–33. doi: 10.1016/S0004-9514(09)70043-1
128. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther.* (2003) 83:713–21. doi: 10.1093/ptj/83.8.713
129. Borenstein M, Hedges LV, Higgins J, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* (2010) 1:97–111. doi: 10.1002/jrsm.12
130. Higgins JPT, Green S. (eds). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration (2011). Available online at: http://handbook.cochrane.org
131. Cumming G. *Understanding the New Statistics: Effect Sizes, Confidence Intervals, and Meta-Analysis*. New York, NY: Routledge (2013).
132. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L Erlbaum Associates (1988).
133. Bolier L, Haverman M, Westerhof GJ, Riper H, Smit F, Bohlmeijer E. Positive psychology interventions: a meta-analysis of randomized controlled studies. *BMC Public Health* (2013) 13:119. doi: 10.1186/1471-2458-13-119

134. Poole JL, Whitney SL. Assessments of motor function post stroke. *Phys Occup Ther Geriatr.* (2001) 19:1–22. doi: 10.1080/J148v19n02_01
135. Raghavan P. Upper limb motor impairment after stroke. *Phys Med Rehabil Clin N Am.* (2015) 26:599–610. doi: 10.1016/j.pmr.2015.06.008
136. Sullivan KJ, Tilson JK, Cen SY, Rose DK, Hershberg J, Correa A, et al. Fugl-Meyer assessment of sensorimotor function after stroke: standardized training procedure for clinical practice and clinical trials. *Stroke* (2011) 42:427–32. doi: 10.1161/STROKEAHA.110.592766
137. Duff SV, He J, Nelsen MA, Lane CJ, Rowe VT, Wolf SL, et al. Inter-rater reliability of the wolf motor function test-functional ability scale: why it matters. *Neurorehabil Neural Repair* (2015) 29:436–43. doi: 10.1177/1545968314553030
138. Nordin A, Alt Murphy M, Danielsson A. Intra-rater and inter-rater reliability at the item level of the Action Research Arm Test for patients with stroke. *J Rehabil Med.* (2014) 46:738–45. doi: 10.2340/16501977-1831
139. Ekstrand E, Lexell J, Brogårdh C. Test– retest reliability and convergent validity of three manual dexterity measures in persons with chronic stroke. *PM&R* (2016) 8:935–43. doi: 10.1016/j.pmrj.2016.02.014
140. Hallam S, Cross I, Thaut M. *Oxford Handbook of Music Psychology*. Oxford: Oxford University Press (2011).
141. Thaut MH. *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications.* New York, NY: Routledge (2005).
142. Ghai S, Ghai I, Schmitz G, Effenberg AO. Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. *Sci Rep.* (2018) 8:506. doi: 10.1038/s41598-017-16232-5
143. Fujioka T, Ween JE, Jamali S, Stuss DT, Ross B. Changes in neuromagnetic beta-band oscillation after music-supported stroke rehabilitation. *Ann NY Acad Sci.* (2012) 1252:294–304. doi: 10.1111/j.1749-6632.2011.06436.x
144. Keller PE, Novembre G, Hove MJ. Rhythm in joint action: psychological and neurophysiological mechanisms for real-time interpersonal coordination. *Philos Trans R Soc Lond B Biol Sci.* (2014) 369:20130394. doi: 10.1098/rstb.2013.0394
145. Cauraugh JH, Summers JJ. Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. *Prog Neurobiol.* (2005) 75:309–20. doi: 10.1016/j.pneurobio.2005.04.001
146. Reelick MF, van Iersel MB, Kessels RPC, Rikkert MO. The influence of fear of falling on gait and balance in older people. *Age Ageing* (2009) 38:435–40. doi: 10.1093/ageing/afp066
147. Schinkel-Ivy A, Inness EL, Mansfield A. Relationships between fear of falling, balance confidence, and control of balance, gait, and reactive stepping in individuals with sub-acute stroke. *Gait Posture* (2016) 43:154–9. doi: 10.1016/j.gaitpost.2015.09.015
148. Rizzo JR, Raghavan P, McCrery JR, Oh-Park M, Verghese J. Effects of emotionally charged auditory stimulation on gait performance in the elderly: a preliminary study. *Arch Phys Med Rehabil* 96 690–6. doi: 10.1016/j.apmr.2014.12.004
149. Choi W, Lee G, Lee S. Effect of the cognitive-motor dual-task using auditory cue on balance of surviviors with chronic stroke: a pilot study. *Clin Rehabil* (2015) 29:763–70. doi: 10.1177/0269215514556093
150. Hopkins K, Kass SJ, Blalock LD, Brill JC. Effectiveness of auditory and tactile crossmodal cues in a dual-task visual and auditory scenario. *Ergonomics* (2017) 60:692–700. doi: 10.1080/00140139.2016.1198495
151. Wickens CD. Multiple resources and mental workload. *Hum Factors* (2008) 50:449–55. doi: 10.1518/001872008X288394
152. Wickens C. Processing resources and attention. In: Parasuraman R, Davies R, editors. *Varieties of Attention*. New York, NY: Academic Press (1984).
153. Scerra VE, Brill JC. Effect of task modality on dual-task performance, response time, and ratings of operator workload. In: *Proceedings of the Human Factors and Ergonomics Society Annual Meeting.* Sage, CA; Los Angeles, CA: Sage Publications (2012) p. 1456–60.
154. Lu SA, Wickens CD, Prinet JC, Hutchins SD, Sarter N, Sebok A. Supporting interruption management and multimodal interface design: three meta-analyses of task performance as a function of interrupting task modality. *Hum Factors* (2013) 55:697–724. doi: 10.1177/0018720813476298
155. Sihvonen AJ, Särkämö T, Leo V, Tervaniemi M, Altenmüller E, Soinila S. Music-based interventions in neurological rehabilitation. *Lancet Neurol.* (2017) 16:648–60. doi: 10.1016/S1474-4422(17)30168-0
156. Särkämö T, Ripollés P, Vepsäläinen H, Autti T, Silvennoinen HM, Salli E, et al. Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: a voxel-based morphometry study. *Front Hum Neurosci* (2014) 8:245. doi: 10.3389/fnhum.2014.00245
157. Särkämö T, Altenmüller E, Rodríguez-Fornells A, Peretz I. Editorial: Music, brain, and rehabilitation: emerging therapeutic applications and potential neural mechanisms. *Front Hum Neurosci.* (2016) 10:103. doi: 10.3389/fnhum.2016.00103
158. Ghai S, Ghai I. Effenberg AO. "Low road" to rehabilitation: a perspective on subliminal sensory neuroprosthetics ? *Neuropsychiatr Dis Treat.* (2018) 14:301–7. doi: 10.2147/NDT.S153392
159. Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science* (1995) 269:1880. doi: 10.1126/science.7569931
160. Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. *Nature Rev Neurosci.* (2011) 12:739–51. doi: 10.1038/nrn3112
161. Rodger MWM, Craig CM. Beyond the metronome: auditory events and music may afford more than just interval durations as gait cues in Parkinson's disease. *Front Neurosci.* (2016) 10:272. doi: 10.3389/fnins.2016.00272
162. Young W, Rodger M, Craig CM. Perceiving and reenacting spatiotemporal characteristics of walking sounds. *J Exp Psych.* (2013) 39:464. doi: 10.1037/a0029402
163. Bamiou DE. Hearing disorders in stroke. In: *Handbook of Clinical Neurology.* Elsevier (2015) p. 633–47.
164. Ghai S, Ghai I, Effenberg AO. Effect of rhythmic auditory cueing on gait in cerebral palsy: a systematic review and meta-analysis. ?*Neuropsychiatr Dis Treat.* (2018) 14:43–59. doi: 10.2147/NDT.S148053
165. Young WR, Shreve L, Quinn EJ, Craig C, Bronte-Stewart H. Auditory cueing in Parkinson's patients with freezing of gait. What matters most: action-relevance or cue-continuity? *Neuropsychologia* (2016) 87:54–62. doi: 10.1016/j.neuropsychologia.2016.04.034
166. Young WR, Rodger MW, Craig CM. Auditory observation of stepping actions can cue both spatial and temporal components of gait in Parkinson? s disease patients. *Neuropsychologia* (2014) 57:140–53. doi: 10.1016/j.neuropsychologia.2014.03.009
167. Peng YC, Lu TW, Wang TH, Chen YL, Liao HF, Lin KH, et al. Immediate effects of therapeutic music on loaded sit-to-stand movement in children with spastic diplegia. *Gait Posture* (2011) 33:274–8. doi: 10.1016/j.gaitpost.2010.11.020
168. Tagliabue M, McIntyre J. A modular theory of multisensory integration for motor control. *Front Comput Neurosci.* (2014) 8:1. doi: 10.3389/fncom.2014.00001
169. Iacoboni M, Koski LM, Brass M, Bekkering H, Woods RP, Dubeau MC, et al. Reafferent copies of imitated actions in the right superior temporal cortex. *Proc Natl Acad Sci USA.* (2001) 98:13995–9. doi: 10.1073/pnas.241474598
170. Decety J, Grèzes J. Neural mechanisms subserving the perception of human actions. *Trends Cogn Sci.* (1999) 3:172–8. doi: 10.1016/S1364-6613(99)01312-1
171. Shams L, Seitz AR. Benefits of multisensory learning. *Trends Cogn Sci.* (2008) 12:411–7. doi: 10.1016/j.tics.2008.07.006
172. Lahav A, Saltzman E, Schlaug G. Action representation of sound: audiomotor recognition network while listening to newly acquired actions. *J Neurosci.* (2007) 27:308–14. doi: 10.1523/JNEUROSCI.4822-06.2007
173. Vinken PM, Kröger D, Fehse U, Schmitz G, Brock H, Effenberg AO. Auditory coding of human movement kinematics. *Multisens Res.* (2013) 26:533–52. doi: 10.1163/22134808-00002435
174. Inglis JT, Horak FB, Shupert CL, Jones-Rycewicz C. The importance of somatosensory information in triggering and scaling automatic postural responses in humans. *Exp Brain Res.* (1994) 101:159–64. doi: 10.1007/BF00243226
175. Thaut MH, McIntosh GC, Prassas SG, Rice RR. Effect of rhythmic auditory cuing on temporal stride parameters and EMG. Patterns in hemiparetic gait of stroke patients. *J Neurol Rehabil* (1993) 7:9–16. doi: 10.1177/136140969300700103
176. Thaut MH, McIntosh GC, Prassas SG, Rice RR. Effect of rhythmic auditory cuing on temporal stride parameters and EMG patterns in normal gait. *J Neurol Rehabil.* (1992) 6:185–90. doi: 10.1177/136140969200600403

177. Thaut M, Schleiffers S, Davis W. Analysis of EMG activity in biceps and triceps muscle in an upper extremity gross motor task under the influence of auditory rhythm. *J Music Ther*. (1991) 28:64–88. doi: 10.1093/jmt/28.2.64
178. Kaur P, Kwatra G, Kaur R, Pandian JD. Cost of stroke in low and middle income countries: a systematic review. *Int J Stroke* (2014) 9:678–82. doi: 10.1111/ijs.12322
179. Sharma S, Padma MV, Bhardwaj A, Sharma A, Sawal N, Thakur S. Telestroke in resource-poor developing country model. *Neurol India* (2016) 64:934–40. doi: 10.4103/0028-3886.190243
180. Lopez WO, Higuera CA, Fonoff ET, Souza Cde O, Albicker U, Martinez JA. Listenmee and Listenmee smartphone application: synchronizing walking to rhythmic auditory cues to improve gait in Parkinson's disease. *Hum Mov Sci.* (2014) 37:147–56. doi: 10.1016/j.humov.2014.08.001
181. Muto T, Herzberger B, Hermsdoerfer J, Miyake Y, Poeppel E. Interactive cueing with walk-mate for hemiparetic stroke rehabilitation. *J Neuroeng Rehabil.* (2012) 9:58. doi: 10.1186/1743-0003-9-58
182. Elia N, von Elm E, Chatagner A, Pöpping DM, Tramèr MR. How do authors of systematic reviews deal with research malpractice and misconduct in original studies? A cross-sectional analysis of systematic reviews and survey of their authors. *BMJ Open* (2016) 6:e010442. doi: 10.1136/bmjopen-2015-010442
183. Nascimento LR, de Oliveira CQ, Ada L, Michaelsen SM, Teixeira-Salmela LF. Walking training with cueing of cadence improves walking speed and stride length after stroke more than walking training alone: a systematic review. ?*J Physiother*. (2015) 61:10–5. doi: 10.1016/j.jphys.2014.11.015
184. Ghai S, Ghai I. Effects of rhythmic auditory cueing in gait rehabilitation for multiple sclerosis: a mini systematic review and meta-analysis. *Front Neurol.* (2018) 9. doi: 10.3389/fneur.2018.00386
185. Rocha PA, Porfírio GM, Ferraz HB, Trevisani VF. Effects of external cues on gait parameters of Parkinson's disease patients: a systematic review. *Clin Neurol Neurosurg.* (2014) 124:127–34. doi: 10.1016/j.clineuro.2014.06.026

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The Use of Rhythmic Auditory Stimulation to Optimize Treadmill Training for Stroke Patients: A Randomized Controlled Trial

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The use of functional music in gait training termed rhythmic auditory stimulation (RAS) and treadmill training (TT) have both been shown to be effective in stroke patients (SP). The combination of RAS and treadmill training (RAS-TT) has not been clinically evaluated to date. The aim of the study was to evaluate the efficacy of RAS-TT on functional gait in SP. The protocol followed the design of an explorative study with a rater-blinded three arm prospective randomized controlled parallel group design. Forty-five independently walking SP with a hemiparesis of the lower limb or an unsafe and asymmetrical walking pattern were recruited. RAS-TT was carried out over 4 weeks with TT and neurodevelopmental treatment based on Bobath approach (NDT) serving as control interventions. For RAS-TT functional music was adjusted individually while walking on the treadmill. Pre and post-assessments consisted of the fast gait speed test (FGS), a gait analysis with the locometre (LOC), 3 min walking time test (3MWT), and an instrumental evaluation of balance (IEB). Raters were blinded to group assignments. An analysis of covariance (ANCOVA) was performed with affiliated measures from pre-assessment and time between stroke and start of study as covariates. Thirty-five participants (mean age 63.6 ± 8.6 years, mean time between stroke and start of study 42.1 ± 23.7 days) completed the study (11 RAS-TT, 13 TT, 11 NDT). Significant group differences occurred in the FGS for adjusted post-measures in gait velocity [$F_{(2, 34)} = 3.864$, $p = 0.032$; partial $\eta^2 = 0.205$] and cadence [$F_{(2, 34)} = 7.656$, $p = 0.002$; partial $\eta^2 = 0.338$]. Group contrasts showed significantly higher values for RAS-TT. Stride length results did not vary between the groups. LOC, 3MWT, and IEB did not indicate group differences. One patient was withdrawn from TT because of pain in one arm. The study provides first evidence for a higher efficacy of RAS-TT in comparison to the standard approaches TT and NDT in restoring functional gait in SP. The results support the implementation of functional music in neurological gait rehabilitation and its use in combination with treadmill training.

Clinical Trial Registration: https://www.drks.de/drks_web/, identifier DRKS00014603

Keywords: stroke rehabilitation, exercise movement techniques, music therapy, music, gait

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INTRODUCTION

About 60% of all stroke patients (SP) have difficulties with walking (1). These are often caused by hemiparesis and/or sensory deficits of the lower extremity and/or trunk and are also due to uncoordinated movements. In addition to motor and sensory dysfunctions, symptoms such as spasticity, somatosensory neglect, and cognitive malfunctioning may further impede walking. Thus, the restoration of gait is often a key focus of rehabilitation efforts, enhancing not only physical activity but also autonomy and participation in everyday life (2, 3).

Treadmill training (TT) with and without body weight support has been shown to improve functional gait in stroke patients effectively. A meta-analysis comparing 44 trials ($n = 2{,}658$ patients) revealed clear therapeutic effects on gait velocity and walking endurance, the latter only for TT with body weight support (1). However, the improvements were identified only for independent walkers while patients who walked with assistance did not show an additional benefit from TT (1). Lee's work (4) provided evidence that TT with a high walking velocity at the beginning of training is more effective when compared to a stepwise increase in velocity.

Rhythmic-auditory stimulation (RAS) is defined as a therapeutic application of pulsed rhythmic or musical stimulation in order to improve gait or gait related aspects of movement (5). It has been demonstrated that SP are able to synchronize their gait pattern to auditory stimulation using music with an embedded metronome (6–8). This led to immediate improvements in stride time and stride length symmetry as well as weight bearing time on the paretic side, while EMG showed a more balanced muscular activation pattern between the paretic and non-paretic sides (6). Training effects of RAS for SP were confirmed in a meta-analysis comparing 7 randomized controlled studies ($n = 197$) that showed improvements in functional gait performance (velocity, cadence, and stride length) (9). This work also gave evidence, that a musical stimulation is more effective in improving gait velocity and cadence then the metronome (9). Hayden et al. found that RAS became more effective when it is implemented earlier in the rehabilitation program. This provides evidence that the variation in time of the RAS-training during the rehabilitation process may affect the success of the treatment (10). The application of RAS on the treadmill (RAS-TT) was evaluated over a 3-week training period by Park et al. In that study metronome stimulation was used for 9 patients with chronic stroke. The results were compared with a group of 10 patients performing over ground RAS walking training (11). The RAS-TT group experienced greater improvements in gait velocity (11).

While RAS and TT have proven to be effective for gait training in SP, the efficacy of its combination (RAS-TT) in the early course of rehabilitation in SP has not been investigated to date. Therefore, we hypothesized that RAS-TT in the early course of rehabilitation would improve the clinical efficacy of TT for SP. The purpose of the present study was to investigate the functional improvements of gait using a rehabilitation therapy combining RAS and TT in order to assess its clinical efficacy for patients suffering the aftermaths of a stroke.

MATERIALS AND METHODS

Design

The study protocol was approved by the state authorization association for medical issues in Brandenburg, that determined on the 21st of January 2010 that no formal ethics approval was required. Patients gave their informed consent according to the Helsinki declaration.

The study was designed as a prospective, single center three arm clinical study with parallel groups. We enrolled patients who performed either RAS on the treadmill (RAS-TT) or treadmill training alone (TT). A third group that received neurodevelopmental treatment following the Bobath approach (NDT) served as a control group. The patients were randomly assigned to the three training interventions by a person not involved in the study using a block randomization (software randlist). Allocations were placed in sealed sequentially numbered envelopes and were not opened until the actual study inclusion. Thus, the patients, the responsible doctor, the assessing physiotherapist, and study manager were not informed beforehand regarding the group assignment.

We included stroke patients with a hemiparesis of the lower limb (at least 1 muscle group with muscle strength grade <5 as defined by the British Medical Research Council) or with an unsafe and asymmetrical walking pattern (by assessment of a physiotherapist). The patients had to be able to walk independently with assistive devices if necessary for at least 3 min.

Criteria for exclusion were the following: significantly disturbed language perception (marked by either the Aachener Aphasietest or Token Test), cognitive impairment (Mini Mental Status Test <26), major depression or productive psychosis, adjustment disorder with a need for medical treatment, peripheral arterial occlusive disease with walking distance <100 m, and coronary heart disease (instable angina pectoris).

After having passed the diagnostics patients underwent a screening session on the treadmill. There they had to demonstrate a stable and sufficiently ergonomic gait. Candidates with insufficient quality of gait on the treadmill (multimodal neglect or spasticity as assessed by a physiotherapist) were postponed and re-screened every week (**Figure 1**).

Subjects

Patients were recruited in a clinical center for neurological rehabilitation in Beelitz-Heilstaetten/Germany. We included 45 stroke patients, of which ten were excluded during the intervention phase due to the following reasons: five for administrative reasons (funding of the in-patient rehabilitation was stopped) distributed over all three groups (RAS-TT: 2, TT: 1, NDT: 2); four patients developed acute medical complications that were unrelated to the movement therapies (occurring in group RAS-TT: 2 and group NDT: 2); one patient reported pain in the paretic arm following treadmill training (TT), which seemed to be associated with increasing spasticity. The data of 35 patients were used for data analysis (**Table 1**).

Training

The three interventions RAS-TT, TT and NDT were performed five times a week over of 4 weeks. All interventions were

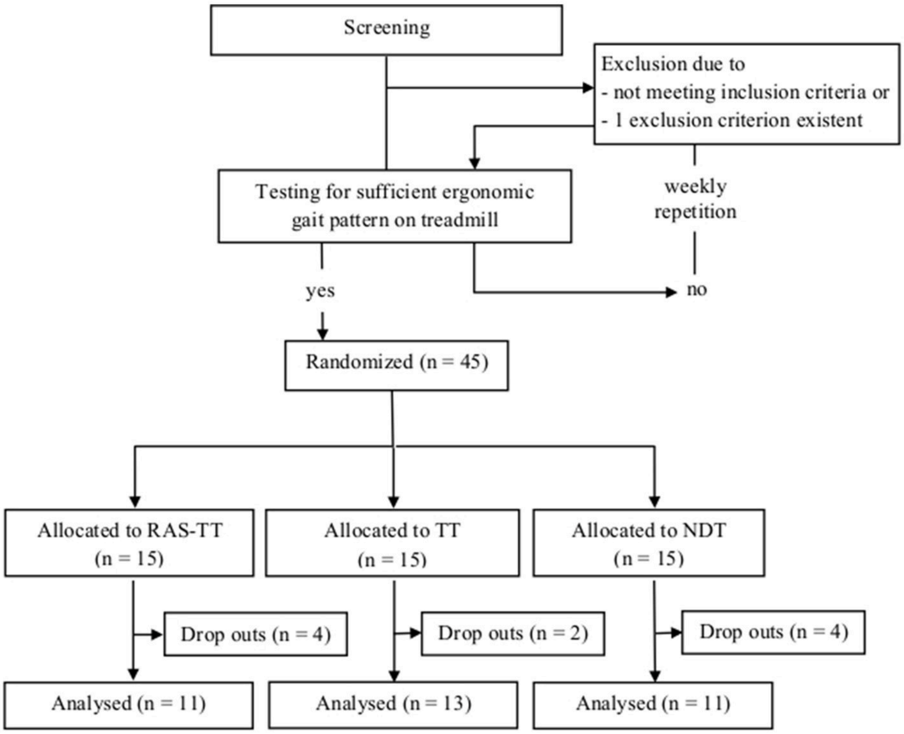

FIGURE 1 | Patient flow chart of study design. RAS-TT, rhythmic auditory stimulation on treadmill; TT, treadmill training; NDT, neurodevelopmental treatment.

carried out as a single therapy with individual instruction from a physiotherapist.

In the NDT patients practiced walking on an even surface, stair stepping, handling of a walking aid (if necessary) based on their actual walking disability for 30 min. During this treatment movements were directed toward an enhanced activation of the paretic side while inhibiting an immoderate co-activation of the non-affected side. NDT was applied by physiotherapists who had received an advanced training in the NDT for neurologically impaired adults.

No body weight support or inclination was used for the RAS-TT and the TT interventions. Patients walked on the treadmill (Loko S 70, Woodway, Waukesha/USA) holding themselves with at least one hand at the side bar. Therapists were instructed to keep the treadmill pace at a maximum level while striving for a normalized physiological gait pattern (e.g., limitation of compensational movements and reduction of pathological muscle tone). The training time was increased continually (15 min in week 1; 17 min in week 2; 20 min in weeks 3 and 4). Therapists were allowed to set breaks for the patient when needed.

For the RAS-TT intervention, patients listened to functional training music via ear plugs through an ordinary MP3 player while walking on the treadmill. The music was designed (software cubase 3 SE) according to the criteria described by Thaut et al. (5): clearly structured rhythm with strongly accentuated meter, adequate volume with no significant perturbations or qualitative changes in intensity, familiar melody, no lyrics, and a superimposed salient high-pitch bell sound to foster the metered walking pace additionally [(12), **Audio 1**]. The beat rate of the music was set to match the patients' cadence on the treadmill. Once audio-motor coupling was achieved, the musical tempo was slowed down a little in order to induce greater step lengths. The RAS-TT therapists were continually supervised by a certified neurologic music therapist. Therapists were assigned to one intervention type only to avoid a bias caused by preference for a certain intervention.

All patients were given extra conventional physiotherapy treatment either 30 or 60 min per week according to the level of impairment, which was constantly updated. All patients performed further training therapies according to their medical needs (e.g., occupational therapy, speech therapy, neuropsychological treatment, sports therapy, physical therapy applications, and others).

Assessment

Our primary outcome parameters were gait velocity, cadence and stride length. Secondary outcome parameters were gait symmetry, endurance and postural stability. Assessments were carried out by physiotherapists blinded for the group assignment. Pre-assessments were carried out at the beginning of the training period. Post-testing was performed on the day after completing the 4 weeks training.

We included a fast gait speed test (FGS), a gait analysis with the locometre (LOC), a 3-min walking test (3MWT), and an instrumental evaluation of balance (IEB).

TABLE 1 | Subject data with location of stroke and use of assistive device.

	RAS-TT	TT	NDT
Number	11	13	11
Age (years)	63.7 ± 8.8	65.5 ± 8.5	61.1 ± 8.6
Gender (F/M)	4/7	2/11	3/8
Time between stroke and start of study (days)	42.6 ± 30.1	46.9 ± 23.3	36.0 ± 16.7
Side of Lesion (L/R)	6/5	4/9	5/6
Location of stroke			
Middle cerebral artery	5	6	6
Brain stem	3	5	2
Basal ganglia/Thalamus	2	1	1
Internal capsule	–	1	1
Anterior cerebral artery	1	–	–
Posterior cerebral artery	–	–	1
Use of assistive device			
None	5	8	9
Walking aid	5	4	1
Ankle-foot orthosis + walking aid	1	1	1

RAS-TT, rhythmic auditory stimulation on treadmill; TT, treadmill training; NDT, neurodevelopmental treatment.

In the FGS, patients were asked to walk safely as fast as possible toward a goal, while starting 2 meters ahead of the start mark. The time was measured with a stop watch, and the heel strikes within a marked 10 meter walk way were counted. Patients were allowed walking aids when they needed them and were asked to use them again for the post-test. The test was performed twice. For the statistical analysis the data from the second trial were used. Stride length, gait velocity and cadence were calculated using the formula presented by Flansbjer et al. (13). The LOC represents an apparatus based analysis of walking performed with the locometre (SATEL, Blagnac, France) according to Bessou et al. (14). With this device, the longitudinal displacements of the feet are transmitted via threads to a pulley connected to an optical length-voltage transducer. Record analysis provides quantitative data to determine side related step length, cycle time and stance time, as well as walking velocity, cadence and stride length, recorded over a distance of 7 meters. The test was carried out twice at maximum walking speed. The data collected from the second trial were used for the statistical analysis.

In the 3MWT patients were asked to walk for 3 min as far as they could. The distance covered was measured in meters. The IEB was performed using a force platform (SATEL, Blagnac, France). In this test, postural balance was evaluated in a standing position on a firm surface with eyes open. The duration of recording was 51 s (sampling rate: 40 Hz). The length of sway, sway area and mean lateral displacement of the center of pressure were calculated (15).

Data Analysis

For the calculation of the sample size an ANOVA with repeated measures for the time effect was conducted (software G ∗ power 3.0.10) with an error probability of $\alpha = 0.05$, a given power of 0.8. The required sample size was 36 for the intended effect size $f = 0.25$.

Due to the applied power analysis we decided to enroll a total sample of 45. As some of the data were not normally distributed and there was no fitting non-parametric statistical method for the study design, an analysis of covariance (ANCOVA) was run (SPSS 11.5). Thus, post-intervention assessment measures were adjusted for the two covariates: (1) respective pre-intervention measure and (2) the time between the stroke and the start of training intervention. Significant pre-post-effects were followed up group-wise using Bonferoni corrected *t*-tests with a level of significance of $p = 0.0167$. The ANCOVA was calculated on the basis of the following comparisons of covariates and post-intervention measurements for each intervention type: the linear relationship between covariates and post-intervention measures, which was assessed by visual inspection of a scatterplot, the homogeneity of regression by determining the interaction term, the normal distribution of residuals using Shapiro-Wilk's test and the homoscedasticity and homogeneity of variances using visual inspection of a scatterplot and Levene's test of homogeneity of variance. Statistical outliers were detected by identifying cases with standardized residuals >±3. The assumptions for ANCOVA were met for all assessment parameters of the LOC, the FGS, and the 3MWT. One outlier in the standardized residuals (as defined by being greater than the standard deviation ±3) was found in the LOC parameter stride length. This outlier was kept for the analysis.

RESULTS

There were no significant differences between the groups with respect to baseline characteristics (i.e., age, gender), except for the use of assistive devices as these were notably less present in the NDT group. The groups differed also in time between stroke and study inclusion.

The results of the FGS showed significant time effects for the parameters gait velocity, cadence and stride length. For RAS-TT, we found significant pre-post-changes that corresponded with moderate to strong effect sizes (velocity: $p < 0.001$; cadence: $p = 0.001$; stride length: $p < 0.001$). For TT, there were significant changes in velocity ($p < 0.007$) and stride length ($p < 0.001$) while cadence did not improve significantly ($p = 0.283$). In the NDT group, no significant changes were observed (velocity: $p = 0.029$; cadence: $p = 0.93$; stride length: $p = 0.018$, **Table 2**). The ANCOVA showed statistically significant differences between groups for gait velocity [$F_{(2, 34)} = 3.864$, $p = 0.032$, partial $\eta^2 = 0.205$] and for cadence [$F_{(2, 34)} = 7.656$, $p = 0.002$, partial $\eta^2 = 0.338$]. The adjusted post-values compared by group contrasts were significantly higher in favor of RAS-TT (velocity: RAS-TT to TT $p = 0.031$, RAS-TT to NDT $p = 0.017$; cadence: RAS-TT to TT $p = 0.004$, RAS-TT to NDT $p = 0.001$) (**Figure 2**). The outcomes in the FGS stride length measures did not show any group differences.

The LOC allowed us to look at the lower extremities separately. Thereby, the RAS-TT patients improved significantly in 3 out of 6 spatial and temporal parameters, while TT patients

TABLE 2 | Pre and post-intervention measures and effect sizes for gait and postural balance parameters (means ± standard deviation with 95% confidence interval).

Parameter	RAS-TT (*N* = 11)			TT (*N* = 13)			*NDT (N = 11)*		
	Pre	Post	*d*	Pre	Post	*d*	Pre	Post	*d*
FAST GAIT SPEED TEST									
Velocity [m/s]†,	0.92 ± 0.46	1.27 ± 0.48*	0.75	0.85 ± 0.36	1.03 ± 0.35*	0.50	0.95 ± 0.37	1.12 ± 0.40	0.43
Cadence [steps/min]†	96.7 ± 22.8	116.5 ± 22.5*	0.87	98.0 ± 19.3	101.5 ± 16.8	0.19	101.4 ± 21.31	101.0 ± 16.9	−0.02
Stride length [m]†	1.09 ± 0.35	1.28 ± 0.32*	0.57	1.01 ± 0.28	1.19 ± 0.28*	0.66	1.10 ± 0.27	1.30 ± 0.34	0.65
LOCOMETRE GAIT ANALYSIS									
Velocity [m/s]†	0.84 ± 0.43	1.20 ± 0.47*	0.81	0.76 ± 0.29	0.97 ± 0.34*	0.69	0.84 ± 0.39	1.07 ± 0.36	0.60
Cadence [steps/min]†	96.6 ± 25.0	115.0 ± 23.4*	0.76	91.2 ± 19.6	102.7 ± 15.3*	0.65	98.4 ± 23.7	105.7 ± 17.7	0.35
Stride length [m]†	0.99 ± 0.31	1.22 ± 0.31*	0.76	0.96 ± 0.26	1.12 ± 0.29*	0.55	0.97 ± 0.29	1.18 ± 0.28*	0.74
3 MIN WALKING TIME TEST									
Distance [m]†	162.2 ± 69.4	216.8 ± 75.5*	0.75	146.5 ± 62.0	170.5 ± 53.7	0.41	180.3 ± 108.4	218.3 ± 119.9*	0.33
INSTRUMENTAL EVALUATION OF BALANCE									
Mean lateral COP displacement [mm]	11.2 ± 9.5	11.6 ± 9.3	0.05	15.9 ± 10.7	13.4 ± 10.6	−0.23	15.3 ± 9.9	13.0 ± 10.5	−0.23
Length of COP sway [mm]†	714.2 ± 393.5	702.5 ± 525.0	−0.03	938.6 ± 486.5	834.9 ± 410.9	−0.23	722.6 ± 274.7	632.6 ± 147.5	−0.41
Sway area of COP [mm^2]	485.6 ± 602.9	397.8 ± 364.9	−0.18	450.1 ± 245.1	351.5 ± 181.7	−0.48	326.6 ± 216.3	259.9 ± 147.5	−0.36

*†Statistically significant time effect ($p < 0.05$), *statistically significant differences between pre and post-intervention values ($p < 0.01\bar{6}$), d, effect size Cohen's; , strong effect; , moderate effect; , small effect; RAS-TT, rhythmic auditory stimulation on treadmill; TT, treadmill training; NDT, neurodevelopmental treatment; COP, center of pressure.*

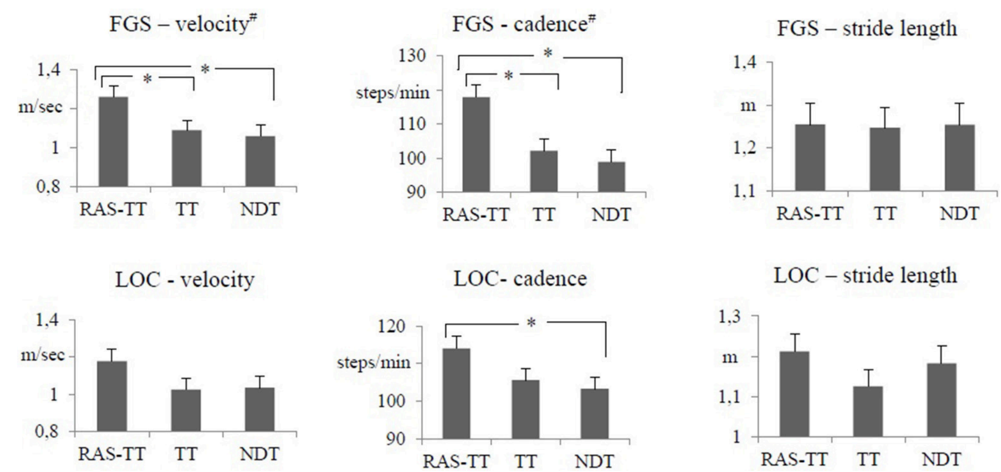

FIGURE 2 | Primary outcome measures: adjusted means of post intervention gait parameters with pre-intervention measures and time between stroke and study entrance as co-varieties. Error bars indicate the standard error. #Statistically significant group difference. *Statistically significant group contrast. ($p < 0.05$). RAS-TT, rhythmic auditory stimulation with treadmill training; TT, treadmill training; NDT, neurodevelopmental treatment; FGS, fast gait speed test; LOC, gait analysis with locometre.

showed significant changes in two parameters and NDT patients in no parameter. RAS-TT showed higher effect sizes representing moderate to strong effects throughout (**Table 3**). Also in the LOC measures for gait velocity, cadence, and stride length we observed statistically significant time effects. Looking at pre-post-effects in the three therapeutic interventions, significant changes were found for RAS-TT and TT throughout (velocity and stride length: $p < 0.001$, cadence for RAS-TT: $p = 0.001$, for TT $p = 0.002$) with moderate effect sizes. The results of NDT showed a significant improvement in stride length only ($p = 0.006$) while velocity ($p = 0.017$) and cadence changes ($p = 0.102$) did not reach the level of significance (**Table 2**).

There were no statistically significant differences in adjusted post-intervention gait parameters between the three groups [for velocity: $F_{(2, 34)} = 1.861$, $p = 0.173$, partial $\eta^2 = 0.11$; for stride length: $F_{(2, 34)} = 1.108$, $p = 0.343$, partial $\eta^2 = 0.069$]. The analysis for cadence fell short of the level of significance with $F_{(2, 34)} = 3.242$, $p = 0.053$, partial $\eta^2 = 0.178$. Group contrasts here revealed a significant difference between RAS-TT and NDT ($p = 0.023$) while the contrast RAS-TT to TT failed to show significance ($p = 0.06$) (**Figure 2**).

Walking endurance as assessed by the 3MWT improved significantly across all groups. The RAS-TT and NDT group experienced significant pre-post-changes (RAS-TT: $p < 0.001$, d = 0.75; NDT: $p = 0.001$, $d = 0.75$) while patients in the TT group did not improve significantly ($p = 0.046$) despite a small effect size of $d = 0.413$. The group comparison with the regression analysis showed no significance [$F_{(2, 34)} = 2.434$, $p = 0.104$, partial $\eta^2 = 0.136$] but revealed a significant group contrast between RAS-TT and TT ($p = 0.033$) (**Table 2** and **Figure 3**).

In the IEB, only the parameter length of sway showed a significant time effect ($p = 0.048$). No significant pre-post-improvements were present when looking separately at the three groups.

DISCUSSION

The objective of this study was to evaluate whether the focused use of functional music can make TT for SP more effective. In our study, this led to significantly improved gait velocity and cadence in the FGS. Single leg spatio-temporal parameters also showed higher effect sizes in this group. The latter can be stated as a hint for an optimized kinematic gait pattern, due to audio-motor coupling. The gains in velocity and cadence were not confirmed in the apparatus based gait analysis, where cadence only showed a tendency for higher values in favor of the RAS-TT group. The very high reliability of the FGS test for hemiparetic stroke patients has been proven with an intra-class-correlation of 0.97 (13, 16). For the apparatus based gait analysis LOC, there has been only limited evaluation of quality criteria assessing a small sample ($n = 12$) at comfortable walking speed (ICC 0.93) (17), but not for walking at maximum speed, which was assessed in our study. Nonetheless, we have included that assessment in order to evaluate kinematic changes for both lower extremities separately. It is possible that the patients felt disturbed by the straps attached to their feet when trying to reach maximum speed rather suddenly. In sum the results support our hypothesis that TT with auditory stimulation from functional music leads to greater improvement in functional gait. However, this was not reproduced in the gait endurance test, where all patients improved equally well.

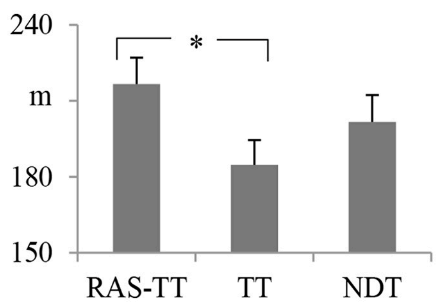

FIGURE 3 | Adjusted means of post intervention walking distance from the 3 min walking time test with pre-intervention measures and time between stroke and study entrance as co-variates. Error bars indicate the standard error. *Statistically significant group contrast. ($p < 0.05$). RAS-TT, rhythmic auditory stimulation with treadmill; TT, treadmill training; NDT, neurodevelopment treatment.

Our balance measures showed a significant time effect on the length of sway of COP. The fact, that this improvement was distributed equally across groups while gait improvement was not could indicate that balance functions improve unrelated to special training interventions due to general recovery from sensorimotor deficits. In order to deepen the understanding of the role of movement training in the improvement of balance functions in this clientele, further investigation using balance measures as an inclusion criteria should be carried out.

In conventional TT, the therapist mainly intervenes by adjusting the pace of the treadmill. Thus, the speed of gait can be regulated. The additional use of music enables the inherent correction of step frequency and gait pattern, by using auditory motor coupling. RAS has been used so far to increase cadence in gait training on the ground. Typically, cadence in TT with stroke patients is almost as high as in walking on the ground while stride length is short (18). This is attributed to negative psychological reactions such as anxiety and insecurity (18). In our RAS-TT approach, we used the music to induce bigger

TABLE 3 | Spatial and temporal parameters in pre and post-assessment and effect sizes for the impaired and the unimpaired lower extremity from gait analysis with locometre (means ± standard deviation with 95% confidence interval).

Parameter	RAS-TT ($N = 11$)			TT ($N = 13$)			NDT ($N = 11$)		
	Pre	Post	*d*	Pre	Post	*d*	Pre	Post	*d*
IMPAIRED LOWER EXTREMITY									
Step length [m]†	0.49 ± 0.19	0.60 ± 0.22	0.556	0.47 ± 0.15	0.54 ± 0.16	0.403	0.48 ± 0.19	0.59 ± 0.13	0.665
Cylce time [s] †	1.32 ± 0.33	1.08 ± 0.22*	−0.824	1.40 ± 0.43	1.20 ± 0.21	−0.623	1.30 ± 0.42	1.17 ± 0.27	−0.365
Stance phase portion [%] †	61.47 ± 4.47	59.16 ± 4.08	−0.538	59.92 ± 4.92	59.88 ± 3.66	−0.008	63.17 ± 8.04	58.76 ± 4.92	−0.662
UNIMPAIRED LOWER EXTREMITY									
Step length [m]†	0.50 ± 0.16	0.62 ± 0.21	0.647	0.49 ± 0.16	0.58 ± 0.15*	0.63	0.50 ± 0.17	0.60 ± 0.17	0.605
Cylce time [s]†	1.32 ± 0.33	1.08 ± 0.22*	−0.834	1.38 ± 0.37	1.20 ± 0.20*	−0.63	1.31 ± 0.43	1.18 ± 0.27	−0.378
Stance phase portion [%]†	65.63 ± 6.63	60.29 ± 5.94*	−0.848	64.57 ± 5.88	62.15 ± 5.55	−0.423	64.57 ± 7.21	61.76 ± 4.82	−0.458

*† Statistically significant time effect ($p < 0.05$), *statistically significant differences between pre and post-intervention values ($p < 0.01\overline{6}$), d, effect size Cohen's; [dark shading], strong effect; [medium shading], moderate effect; [light shading], small effect; RAS-TT, rhythmic auditory stimulation on treadmill; TT, treadmill training; NDT, neurodevelopmental treatment.*

steps by lowering the musical tempo in order to normalize the hemiparetic gait pattern and to reduce motoric and psychological stress. Presumably, the extra benefit of the RAS-TT patients can be attributed to an improved temporal stability that was induced via audio-motor entrainment through the adjusted music. It remains an open question whether a different manner of music adjustment would have led to different functional results.

In our study, there was one drop-out that was attributed to TT. In general, patients coped well with this form of apparatus based therapy while performing comparable to or better than when NDT was used. Even though we used computerized music, none of the patients would consider omitting the music. A few patients reported that they became bored with the long stereotype arrangement, but still felt the advantage for their gait training and wanted to carry on with it. According to our clinical observations, the severe motoric problems stroke patients experience call for the use of clear-cut and foreseeable music. This is especially important when training on the treadmill. Nonetheless, these considerations can be realized in a more refined and artistically ambitious manner. Ideally, patients will be able to choose their preferred musical genre in the future. This could lead to a still better compliance and to additional motivational effects.

Our study has some limitations. The power of the measured effects is limited by the small sample size. We were not able to follow up on patients. Therefore, it remains uncertain whether the effects would persist over a longer period of time. A weak point of our assessment battery can be seen in the absence of participation oriented assessments like the Barthel Index or functional ambulatory category.

Our data suggest, that RAS-TT can be considered a form of training that optimizes gait rehabilitation in stroke patients. The need for a larger study, preferably comparing TT, and RAS-TT, remains. Furthermore, it would be interesting to investigate, whether patients with either predominantly paretic or more sensory symptoms benefit most from the music intervention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

SM conceptualized and directed this study, performed data analysis, wrote the first draft of the manuscript. JW contributed to the conception and design of the study. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00755/full#supplementary-material

Audio 1 | Functional music used for rhythmic auditory stimulation on the treadmill at 77 bpm.

REFERENCES

1. Mehrholz J, Pohl M, Elsner B. Treadmill training and body weight support for walking after stroke. *Cochrane Lib.* (2014). doi: 10.1002/14651858.CD002840
2. World Health Organization. *ICF Browser* (2014). Available online at: http://apps.who.int/classifications/icfbrowser (Accessed May 19, 2015).
3. AWMF. *S3 Leitlinie Schlaganfall* (2012). Available online at: https://www.awmf.org/leitlinien/detail/ll/053-011.html (Accessed May 19, 2015).
4. Lee IH. Does the speed of the treadmill influence the training effect in people learning to walk after stroke? A double-blind randomized controlled trial. *Clin Rehabil.* (2015) 29:269–76.
5. Thaut CP, Rice RR. Rhythmic Auditory Stimulation (RAS). In: Thaut MH, Hoemberg V, editors. *Handbook of Neurologic Music Therapy.* Oxford, Oxford University Press (2014). p. 94–105.
6. Thaut MH, McIntosh GC, Rice RR, Prassas SG. Effect of rhythmic cuing on temporal stride parameters and EMG patterns in hemiparetic gait of stroke patients. *J Neurol Rehabil.* (1993) 7:9–16.
7. Cha Y, Kim Y, Chung Y. Immediate effects of rhythmic auditory stimulation with tempo changes on gait in stroke patients. *J Phys Ther Sci.* (2014) 26:479–82. doi: 10.1589/jpts.26.479
8. Ko BW, Lee HY, Song, WK. Rhythmic auditory stimulation using a portable smart device: short-term effects on gait in chronic hemiplegic stroke patients. *J Phys Ther Sci.* (2016) 28:1538–43. doi: 10.1589/jpts.28.1538
9. Yoo GE, Kim, SJ. Rhythmic Auditory cueing in motor rehabilitation for stroke patients: systematic review and meta-analysis. *J Mus Ther.* (2016) 53:149–77. doi: 10.1093/jmt/thw003
10. Hayden R, Clair AA, Johnson G, Otto D. The effect of rhythmic auditory stimulation (RAS) on physical therapy outcomes for patients in gait training following stroke: a feasibility study. *Int J Neurosci.* (2009) 12:2183–95. doi: 10.3109/00207450903152609
11. Park J, Park, SY, Kim YW, Woo Y. Comparison between treadmill training with rhythmic auditory stimulation and ground walking with rhythmic auditory stimulation on gait ability in chronic stroke patients: a pilot study. *NeuroRehabilitation* (2015) 37:193–202. doi: 10.3233/NRE-151252
12. Thaut MH, McIntosh GC, Rice RR. Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation. *J Neurol Sci.* (1997) 151:207–12.
13. Flansbjer U, Holmbäck A, Downham D, Patten, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. *J Rehabil.* (2005) 37:75–82. doi: 10.1080/16501970410017215

14. Bessou P, Dupui P, Montoya R, Pagès B. Simultaneous recording of longitudinal displacements of both feet during human walking. *J Physiol.* (1988) 83:102–10.
15. Missaoui B, Thoumie P. Balance training in ataxic neuropathies. Effects on balance and gait parameters. *Gait Posture* (2013) 38:471–6. doi: 10.1016/j.gaitpost.2013.01.017
16. Green J, Forster A, Young J. Reliability of gait speed measured by a timed walking test in patients one year after stroke. *Clin Rehabil.* (2002) 16:306–14. doi: 10.1191/0269215502cr495oa
17. Valentini FA, Granger B, Hennebelle DS, Eythrib N, Robain G. Repeatability and variability of baropdodometric and spatio-temporal gait parameters - Results in healthy subjects and in stroke patients. *Clin Neurophysiol.* (2011) 41:181–9. doi: 10.1016/j.neucli.2011.08.004
18. Steingrueber W. *Die Wirkung von Musik auf das Laufbandgehen Hemiparetischer Schlaganfallpatienten*. Berlin: Mensch & Buch (2000).

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PERSPECTIVE
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Role of Sonification and Rhythmic Auditory Cueing for Enhancing Gait Associated Deficits Induced by Neurotoxic Cancer Therapies: A Perspective on Auditory Neuroprosthetics

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Patients undergoing chemotherapy, radiotherapy, and immunotherapy experience neurotoxic changes in the central and peripheral nervous system. These neurotoxic changes adversely affect functioning in the sensory, motor, and cognitive domains. Thereby, considerably affecting autonomic activities like gait and posture. Recent evidence from a range of systematic reviews and meta-analyses have suggested the beneficial influence of music-based external auditory stimulations i.e., rhythmic auditory cueing and real-time auditory feedback (sonification) on gait and postural stability in population groups will balance disorders. This perspective explores the conjunct implications of auditory stimulations during cancer treatment to simultaneously reduce gait and posture related deficits. Underlying neurophysiological mechanisms by which auditory stimulations might influence motor performance have been discussed. Prompt recognition of this sensorimotor training strategy in future studies can have a widespread impact on patient care in all areas of oncology.

Keywords: cueing, chemotherapy, stability, rehabilitation, performance, balance, perception

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INTRODUCTION

Pharmacological treatment of cancer is varying dramatically with benefits for better patient outcomes and ease, but also with new toxicity profiles (1–3). Neurotoxicity is an unavoidable complication of life-saving cancer treatments, such as chemotherapy, radiotherapy, and immunotherapy (4, 5). Typically, treatment with immunotherapeutic agents involves activation of the body's own immune system for targeting malignant cells (6) (**Table 1**). During the treatment cross-adverse reactions with existing neural cells result in heightened neurotoxicity (7–9). Topp et al. (10) for instance, reported that approximately >50% of patients receiving Blinatumomab for acute B-lymphoblastic leukemia exhibited movement disorders, encephalopathic changes, cerebellar dysfunctions, and seizures. Similarly, chemotherapy acts by instigating damage to the structural composition of the DNA, and by also disrupting DNA repair and microtubule functioning. During its functioning the chemotherapeutic agents impart non-specific damage on the cells of the nervous system, thereby resulting in neurotoxicity (9) (**Table 1**). The most commonly

TABLE 1 | Pharmacological interventions for cancer treatment and associated neurotoxic effects.

Treatments	Drugs	Neurotoxic effects
Immunotherapy	Bispecific antibodies (Blinatumomab), Monoclonal antibodies (Trastuzumab, Brentuximab, Rituximab, Ramucirumab, Bevacizumab), Cellular treatments (Chimeric antigen receptor-T cells), Checkpoint inhibitors (Nivolumab Pembrolizumab, Ipilimumab), Tyrosine kinase inhibitors (Imatinib, Dasatinib, Ponatinib, Erlotinib, Pazopanib, Aflibercept, Idelalisib, Sorafenib, Sunitinib), Interferon alfa, Recombinant Interleukin 2	Peripheral nervous system: Gullian Barre syndrome, Myasthenia gravis, sensorimotor peripheral neuropathy, multifocal plexopathy/neuropathy, autonomic neuropathy, phrenic nerve palsy, cranial nerve palsy (optic, hypoglossal, facial nerve) Central nervous system: Aseptic meningitis, encephalitis, transverse myelitis, neurosarcoidosis, posterior reversible leukoencephalopathy syndrome, Vogt Harada Koyanagi syndrome, neurosarcoidosis, demyelination, vasculitis encephalopathy, generalized seizures, convulsions
Chemotherapy	Taxanes (Paclitaxel, Docetaxel), Epothilones (Ixabepilone), Platinum derived compounds (Cisplatin, Carboplatin, Oxaliplatin), Immunomodulatory drugs (Lenalidomide, Bortezomib, Thalidomide), Inhibitor of topoisomerase (Etoposide), Vinka alkaloids (Vincristine, Vindesine, Vinblastine, Vinorelbine), Metalloids (Arsenic), Alkylating agents (Procarbazine, Ifosfamide), Antimetabolites (5-Fluorouracil, Capecitabine, Gemcitabine, Fludarabine, Cytarabine), Farnesyltransferase inhibitors (Tipifarnib), Antiprotozoal and anthelmintic (Suramin)	Peripheral nervous system: Lhermitte's sign, (painful) sensory peripheral neuropathy, muscle cramps, post infusion parenthesias, sensorimotor peripheral neuropathy, mononeuroptherapy, cranial nerve palsy, autonomic neuropathy, myalgia, proximal motor weakness, lumbosacral radiculopathy, painful axonal peripheral neuropathy, ataxia, orthostatic hypotension, intrinsic hand muscle weakness, brachial plexopathy Central nervous system: Encephalopathy, headache, stroke, seizures, cortical blindness, ataxia, athetosis, parkinsonism, radiculomyeloencephalopathy, cerebellar dysfunctions, leukoencephalopathy, inflammatory leukoencephalopathy, stupor, somnolence, aseptic meningitis, myelopathy, ocular toxicity, blurred vision
Radiotherapy	-	Peripheral nervous system: Lumbosacral plexopathy and polyradiculopathy, brachial plexopathy, Lhermitte's sign, radiation myelopathy, dysthesia, motor neuron syndrome, muscle atrophy, fasciculations, areflexia Central nervous system: Encephalopathy, Bulbar palsy, cranial nerve injury, optic neuropathy, cochlear damage, radiation-induced central nervous system tumors (glioma, meningioma, vestibular schwannoma), diffused cerebral injury, stenosis/occlusion of extracranial or intracranial cerebral arteries, stroke-like migraine attack after radiation therapy (SMART syndrome), radiation necrosis

used class of chemotherapy drugs include Vinca alkaloids. This class of drugs has been reported to disrupt microtubule functioning, promote degeneration and axonal atrophy in dosages more than 2 mg/m^3 (11). Furthermore, radiotherapy inhibits cell division and promotes neurotoxicity by inducing vascular damage, hormonal disruption, alteration in cytokine expression, neural stem cell deletion, neural fibrosis (12, 13) (**Table 1**) [for a detailed review see (14)]. Several factors can influence the extent of neurotoxicity induced by radiation therapy i.e., volume of brain irradiated, fraction (>200cGy), cumulative radiation dosage (<5,000cGy), simultaneous administration of chemotherapy, administration of therapy in age groups <7 years old or more than 60 years old and pre-existence of stroke (15). Despite precarious planning to irradiate specific parts and minimize neuropathy, radiation-induced neurotoxicity is still prevalent in several parts of the neural axis (12).

There are several pathophysiological mechanisms by which neurotoxicity can be induced. For instance, therapeutic interventions can impart direct damage to the neuron, glia, and modify the cerebral microvasculature (8, 16–18). Moreover, pathological analysis has also suggested that onset of neural necrosis, axonal degeneration due to microtubular and secondary myelin disruptions (19), can result in central and peripheral nervous system neurotoxicity. Although, several sensory, motor, and cognitive deficits have been discussed in the published literature that can result due to neurotoxicity. In this present perspective our objectives are:

a) Outline the impact of cancer treatment-induced neurotoxicity on gait and posture.

b) Discuss the applicability of music-based external auditory stimulations for facilitating gait and postural recovery in cancer patients.

MOTOR DEFICITS (GAIT AND POSTURE)

Research has conclusively demonstrated that joint dysfunctions in sensory, motor and cognitive domains due to neurotoxicity can affect activities of daily living, such as gait (5, 20, 21), posture (22), and promote falls. Epidemiological evidence suggests that the majority of the diagnosed patients are geriatrics i.e., 60–70 years old (23, 24). Spoelstra et al. (25), for instance, reported that geriatric patients with a history of cancer were more likely to fall (33%) as compared to patients with no history of cancer (29%). This higher risk of fall can be due to joint additional neurological deficits imposed by drug-induced neurotoxicity and an age-associated neurological decline (2, 25). Studies analyzing the spatiotemporal gait parameters have also reported larger decrements in gait performance for cancer patients (2, 20, 26). Marshall et al. (2), reported a significantly reduced gait velocity, step length, and an increased duration in timed up and go test in patients with cancer as compared to their healthy counterparts (5, 27). Similarly, kinematic discrepancies during gait performance are also documented. Wright et al. (28) analyzed gait performance (3-D motion analysis, EMG) following treatment for acute lymphoblastic leukemia. The authors reported a significant reduction in peak hip extension, knee flexion during the loading phase, plantarflexion during pre-swing, dorsiflexion during initial heel contact, lower ankle moments, and power outputs. The authors also reported that the patients exhibited excessive co-activations and an atypical "out of phase" motor unit firing of gastrocnemius during the late swing and premature firing of tibialis anterior during terminal stance.

Monfort et al. (22) too in a longitudinal analysis reported a significant decrease in balance (center of pressure perturbations in medioateral direction) in breast cancer patients receiving taxane-based chemotherapy. The authors further correlated this decrease in balance with patient-reported outcomes i.e., EORTC QLQ-CIPN20 subscales (European Organization for Research and treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy) i.e., increased pain, fatigue, and disruption in physical functioning reported with the treatment progression.

COGNITIVE DEFICITS

In addition to the motor deficits, patients receiving cancer treatment also exhibit heightened cognitive deficits [see chemobrain or chemofog (29)]. These deficits can persist years after the treatment and can considerably affect a patient's quality of life (30). A wide range of cognitive disorders are manifested by patients i.e., disruptions in executive functions, multitasking, concentration, attentional allocation, even memory recall, visuospatial function, and more (29–31). The pathophysiological changes which account for such deficits include white matter abnormality, regional brain volume differences in superior and middle frontal gyri, parahippocampal gyrus, cingulate gyrus, and precuneus (32, 33). Silverman et al. (34), in a PET study, reported that breast cancer patients who received chemotherapy 5–10 years prior had differences in inferior frontal gyrus, contralateral posterior cerebellum, and left inferior frontal gyrus. The authors also implied the onset of cognitive overload by reporting a larger activation pattern of frontal cortical structures i.e., pre-frontal cortex during a memory task (34). This decline in cognitive performance due to adverse neurotoxic effects of oncologic therapy in our opinion might be amplified when coupled with an age-associated decline in cognition. This, then, might promote a major decline in cognitive performance, further affecting autonomic functions such as posture, gait (35). For instance, this reduced cognitive functioning might limit a patient's ability to effectively allocate attentional resources for instance in high-stress environments and instigate falls (36, 37).

SENSORY DEFICITS

A wide range of sensory deficits are accounted in patients due to neurotoxic effects on the nervous system (8). Evidence of optic neuropathy have been extensively documented due to radiotherapy, intra-arterial administration of drugs such as Carmustine, Oxaliplatin, Tamoxifen, and more (38, 39). Likewise, deficits in vestibular (40), and proprioceptive signaling (41), are also well reported. Vincent et al. (41) for instance, reported that administration of Oxaliplatin drug promoted the onset of movement disorders. The authors suggested that possibly neurotoxic changes impaired specific ionic current channels (NaPIC) on the sensory terminals of muscle proprioceptors further leading to a modified sensory encoding which could have affected motor functioning (41). Additionally, axonal degeneration of sensory neurons, which promotes receptor denervation, have also been associated with sensorimotor aberrations that affect motor execution (41–43). Bibi (44), for instance, reported that cancer therapy-induced neurotoxic changes can also promote pervasive deterioration in the autonomic mechanisms for sensory gating and sensory memory mechanisms. This contextual decline in the available state of sensory information might affect the state of a system to integrate sensorimotor information and develop internal models (45–47). Here, a mismatch incongruency of sensorimotor information or a decrease in the quality of perceptual information could promote sensorimotor deficits, further affecting motor planning, execution during gait, and postural performance (48, 49).

CONVENTIONAL REHABILITATION INTERVENTIONS

A few rehabilitation strategies have been discussed in the published literature that can enhance gait and balance dysfunctions in patients with cancer. These strategies include physiotherapy, physical exercises, virtual reality and more (21, 50, 51) (see **Table 2**). Moreover, to the best of our knowledge, only one recent systematic review has analyzed the influence of exercise rehabilitation interventions for managing deficits in gait and postural stability in cancer patients undergoing chemotherapy (21). Despite having a high prevalence for inducing fall-related morbidity and mortality (63), such a limited amount of research is a matter of concern for medical practitioners dealing with cancer patients. Therefore, the development of additional rehabilitation interventions that can be applied as an adjunct to conventional pharmacological interventions is strongly warranted.

PROSPECTIVE ROLE OF MUSIC-BASED THERAPIES: EXTERNAL AUDITORY STIMULATIONS

Music therapy has been extensively studied in cancer management [for detailed reviews see (64–66)]. This therapy has been reported to decrease pain, stress, anxiety associated

TABLE 2 | Conventional rehabilitation approaches for managing gait and postural deficits associated with neurotoxicity.

Disorders	Interventions
Gait	Physiotherapy (52)
	Physical exercise (53, 54)
	Virtual reality (obstacle crossing) (51)
	Sensorimotor balance training (55)
	Transcutaneous electrical stimulation (56)
	Joint stabilizers (56, 57)
Postural stability (static and dynamic)	Physiotherapy (58)
	Aerobic endurance training (55)
	Strength training (resistive TheraBand) (55, 59)
	Impact training (60)
	Home-based exercise programs (61)
	Virtual reality (obstacle crossing) (51)
	Closed kinematic chain exercises (62)
	Core stability ball exercises (62)
	Dynamic balance training (ankle point to point reach task) (51)
	Sensorimotor balance training (55)
	Transcutaneous electrical stimulation (56)
	Joint stabilizers (56, 57)

with cancer treatment and has also been documented to improve mood, relaxation, and quality of life (66). The studies predominantly deal with either active or passive types of music therapies (64–66). Here, the active therapy signifies playing musical instruments, improvisation, singing, and passive therapy signify listening to music, imagination (2, 3). Although the outcomes of these cumulative studies comprehend the beneficial psychological aspects of music therapy, the aim of this present study is to explore as to how motor rehabilitation might be facilitated by the application of music-based auditory stimulations?

Several studies have reported that a large component of motor (re)learning is dependent upon the extent of sensorimotor integration (67, 68). Here, amplification of sensorimotor representations by enhancing the salience of sensory afferent information while minimally engaging the deficit cognitive resources should be a major objective (69–71). This enhanced sensorimotor representations of body schematics and executed movements could facilitate the development of efficient internal models (46, 72). Thereby, enhancing the system's ability to acquire, process, and execute a skill in an efficient manner (73–75). In the published literature, movement sonification and rhythmic auditory cueing are two well-studied auditory stimulations that have been demonstrated to incur beneficial effects in motor performance by jointly targeting sensorimotor and cognitive deficits (76–83).

Rhythmic auditory cueing can be defined as a repetitive isosynchronous auditory stimulation applied with an aim to simultaneously synchronize motor execution (74, 84). Real-time kinematic auditory feedback (movement sonification) on the other hand is a comparatively new approach (85). Such type of an intervention involves mapping of movement parameters on the sound components, such as pitch, amplitude with a very minimal or no latency (72) [for differential effects of auditory cueing and sonification please see (82)]. Recent systematic reviews and meta-analyses have conclusively demonstrated the benefits of these auditory stimulations on gait and postural stability with aging (77), in neurological disorders such as stroke (82, 83, 86), parkinsonism (78), cerebral palsy (80), and multiple sclerosis (81). Findings from these reviews can have widespread implications for counteracting neurotoxicity related motor deficits in cancer patients.

For instance, rhythmic auditory cueing has been reported to enhance gait, and postural stability performance across all age groups (77). We have previously stated that the majority of the affected cancer population groups are geriatrics and that this factor according to several studies accounts for the majority of fall-related morbidity and mortality (25). Likewise, stroke, a common neurotoxic manifestation also account for widespread movement, cognitive disorders (2). Ghai (82) has demonstrated that both rhythmic and real-time auditory stimulations can benefit stroke patients in recovering their motor and cognitive performances. Additionally, we also presume that damage induced by white matter deficits, which are a prominent manifestation of neurotoxicity can also be supplemented by the application of auditory stimulations (32, 87). Ghai and Ghai (81) recently demonstrated the beneficial effects of auditory cueing on patients with multiple sclerosis (a multifocal white matter disease). The authors stated evidence which supports the possibility of white matter re-organization with auditory-motor training [see (88)].

Likewise, Ghai et al. (78), demonstrated the beneficial effects of auditory cueing on movement disorders exhibited during parkinsonism. Chemotherapy, for instance with Metoclopramide (dopamine receptor antagonist) has been associated with inhibition of D_2 receptors in putamen (89). This disruption has been reported to result in movement disorders which are identical to that exhibited by a patient in Parkinson's disease (90). Here, dysfunctions between the striatopallidal projections could affect the internal timing mechanism of a patient in a similar manner as of a patient with Parkinson's disease. In this instance, the application of external auditory stimulations could assist in movement execution by providing an external cue to time movements. The external cueing can effectively bypass the deficit internal cueing pathway (Cerebellum-putamen-thalamus-pre supplementary motor area-supplementary motor area-primary motor area) through an alternative preserved pathway between (cerebellum-thalamus-parietal cortex-premotor area-primary motor area) and facilitate motor activity (91) (**Figure 1**).

Furthermore, we presume that the auditory stimulations could counteract sensory-perceptual deficits i.e., hearing, visual loss by enhancing the salience of sensory afferent information and aiding in the development of sensorimotor representations. For instance, Schmitz et al. (92) in a neuroimaging study reported that observation of a convergent sensory feedback can enhance activations in frontoparietal networks, action

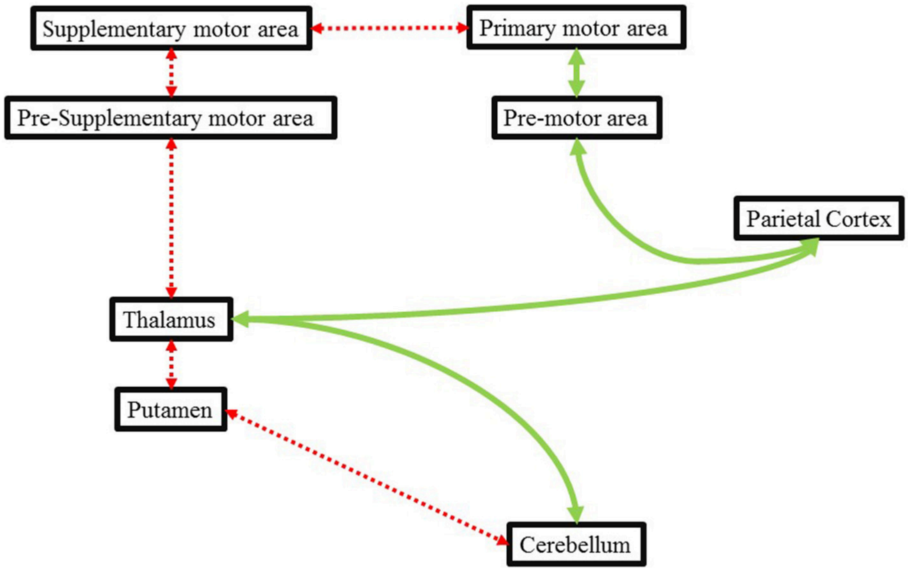

FIGURE 1 | Illustrating the deficit internal cueing pathways (dotted red line) and how external cueing might bypass this deficit pathway via an alternative route (green line). Adapted from Nombela et al. (91) and Ghai et al. (78).

observation system i.e., superior temporal sulcus, Broadman area 44, 6, insula, precentral gyrus, cerebellum, thalamus, and basal ganglia (92). The activations in these areas are associated with biological motion perception, thereby suggesting an enhancement in sensorimotor representation that might strengthen the perceptual analysis of a movement, ultimately resulting in efficient motor planning and execution (92).

Recent evidence has also demonstrated that auditory stimulations can even facilitate proprioceptive perceptions (93). Ghai et al. (94) demonstrated that concurrent auditory feedback can facilitate enhancements in knee-proprioception. Hasegawa et al. (95) too demonstrated that auditory biofeedback training resulted in enhanced spatiotemporal components of postural stability. Therefore, practical implications can be derived for cancer survivors, where deficits in proprioceptive perceptions are quite prominent (94, 96). According to Hasegawa et al. (95), auditory-motor training promoted a challenging environment that could have facilitated proprioceptive integration [for further insights on neuroimaging data see (97)]. Additional mechanisms by which auditory stimulations can facilitate motor performance are that they can provide explicit guidance to time/execute movements (94), reduce variability in musculoskeletal co-activation (98, 99), provide error feedback (100), enhance auditory-motor imagery (101, 102), allow cortical re-organization (103, 104), facilitate neural plasticity (105, 106), and even facilitate neural regeneration (107–109).

We would also like to draw the reader's attention toward literature suggesting how auditory stimulations might act by counteracting deficits in cognitive processing. Firstly, auditory stimulations have been suggested to strengthen attentional allocation (97). This might allow a patient to effectively switch between different tasks at hand without experiencing cognitive overload and/or movement failure. Secondly, enhanced cross-modal processing between auditory and proprioceptive signals can also circumvent cognitive overload and alleviate motor performance (94, 110). Thirdly, adjoining auditory stimulations with music can be an additional way to overcome cognitive deficits. For instance, coupling the auditory stimulations with musical mnemonics might facilitate synchronization of the oscillatory network in the prefrontal regions (111). Here, Thaut et al. (111) has reported that mnemonics might facilitate "deep encoding" during the acquisition phase of learning and might also amplify the internal timings of neural dynamics in the brain which are normally degraded by demyelination process in multiple sclerosis [also see (81)]. As demyelination is also a prominent neurotoxic manifestation of radiotherapy (8), transferrable beneficial effects on cognitive performance could be expected. Moreover, recent research also suggests that in addition to reducing cognitive overload in patients with stroke, the external auditory cueing via music might facilitate, reorganize deficit cortical structures (107–109). For instance, merging the external auditory stimuli with music can allow facilitation of neural network including prefrontal, and limbic cortex this, in turn, has been associated with cognitive and emotional recovery (109). Likewise, incorporating the component of music with external auditory stimulations might yield additional benefits in terms of reducing anxiety and stress (112). Studies have demonstrated that music therapy can allow a reduction in pain, fear-related stress [reduced salivary cortisol (113)], and anxiety outcomes (112). This can allow increased patient adherence toward medical procedures involved during cancer therapies and screening, for instance, screening mammography (114), sigmoidoscopy (115), colonoscopy (113), and even prostate biopsy (112, 116). Facilitation in the functioning of these mechanisms can have widespread influence on the regulation of cancer patient-related outcome and even the disease progression.

An additional outcome that can have important implications in management with auditory stimulations is the length of auditory-motor training duration. Here, interpretations can be drawn from neuroimaging research by Bangert and Altenmüller (117), and Ross et al. (106). Both the studies report that an auditory-motor training facilitates learning by acting on the rich neuroanatomical interconnectivity between the respective regions. The authors report a brief training duration lasting between 20 and 30 min to facilitate plasticity. Likewise, several of the published reviews and meta-analyses have also suggested a similar temporal course i.e., training session lasting for 25–40 min for auditory-motor training regimens (77, 78, 118). This training duration is relatively smaller as compared to conventional physiotherapy and physical exercise strategies discussed in the review by Duregon et al. (21). Therefore, beneficial implications in terms of cost-effectiveness and an enhanced prognosis in cancer survivors can be expected. Furthermore, we would also like to emphasize on the viability of the auditory stimulations, as a home-based intervention. Developing home-based interventions, are efficient for population groups in developing countries where lack of proper medical exposure accounts for widespread cancer-related morbidity and mortality (23). Wonders et al. (61) have also reported that home-based interventions can indeed impart beneficial effects in cancer survivors by reducing the peripheral neuropathic symptoms and enhancing the quality of life. We propose that in a home-based scenario patients can be taught by medical experts to utilize established smartphone rhythmic auditory cueing applications, such as Walkmate (119) to train gait effectively.

Finally, this perspective is a preliminary attempt to instigate scientific discussions for developing efficient rehabilitation protocols while using auditory neuroprosthetics based rehabilitation approach for enhancing motor recovery in patients with cancer. Incorporating these rehabilitation protocols with other sensory augmentation strategies such as virtual reality (120), joint prostheses (121–123), electrical stimulations (124) might have additional implications for enhancing the prognosis during cancer therapy. We have mentioned several mechanisms and findings from our previous review work, which could serve as the groundwork for future studies that could help design sensorimotor training regimens for the benefit of cancer population groups. Future studies are strongly recommended to analyze the effects of gait training with music-based auditory neuroprosthetics as a possible mechanism to counteract neurotoxic deficits because of cancer treatment.

AUTHOR CONTRIBUTIONS

SG conceptualized the perspective article. IG contributed in the formulation of the manuscript. Both authors approved the final draft.

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REFERENCES

1. Kroschinsky F, Stölzel F, von Bonin S, Beutel G, Kochanek M, Kiehl M, et al. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. *Critical Care* (2017) 21:89. doi: 10.1186/s13054-017-1678-1
2. Marshall TF, Zipp GP, Battaglia F, Moss R, Bryan S. Chemotherapy-induced-peripheral neuropathy, gait and fall risk in older adults following cancer treatment. *J Cancer Res Pract.* (2017) 4:134–8. doi: 10.1016/j.jcrpr.2017.03.005
3. Park SB, Goldstein D, Krishnan AV, Lin CSY, Friedlander ML, Cassidy J, et al. Chemotherapy-induced peripheral neurotoxicity: a critical analysis. *CA Cancer J.* (2013) 63:419–37. doi: 10.3322/caac.21204
4. Kolb NA, Smith A, Singleton JR, Beck SL, Stoddard GJ, Brown S, et al. The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling. *JAMA Neurol.* (2016) 73:860–6. doi: 10.1001/jamaneurol.2016.0383
5. Hojan K. Gait and balance disorders in cancer patients. *Pol Orthop Traumatol.* (2012) 77:1–4.
6. Rosenberg SA. Immunotherapy of cancer using interleukin 2: current status and future prospects. *Immunol Today* (1988) 9:58–62.
7. Gust J, Hay KA, Hanafi LA, Li D, Myerson D, Gonzalez-Cuyar LF, et al. Endothelial activation and blood–brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T cells. *Cancer Discov.* (2017) 7:1–16. doi: 10.1158/2159-8290.CD-17-0698
8. Stone JB, DeAngelis LM. Cancer-treatment-induced neurotoxicity—focus on newer treatments. *Nat Rev Clin Oncol.* (2016) 13:92. doi: 10.1038/nrclinonc.2015.152
9. Zhao C, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. *Cell* (2008) 132:645–60. doi: 10.1016/j.cell.2008.01.033
10. Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* (2015) 16:57–66. doi: 10.1016/S1470-2045(14)71170-2
11. Yarbro CH, Wujcik D, Gobel BH. *Cancer Nursing: Principles and Practice.* Jones & Bartlett Learning (2011).
12. Dropcho EJ. Neurotoxicity of radiation therapy. *Neurol Clin.* (2010) 28:217–34. doi: 10.1016/j.ncl.2009.09.008
13. Smart, D. Radiation Toxicity in the central nervous system: mechanisms and strategies for injury reduction. *Semin Radiat Oncol.* (2017) 27:332–9. doi: 10.1016/j.semradonc.2017.04.006
14. Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet* (2009) 374:1639–51. doi: 10.1016/S0140-6736(09)61299-X
15. Lee EQ. Neurotoxicity of radiation therapy and chemotherapy. *Neuro Oncol.* (2012) 223–230.
16. Plotkin SR, Wen PY. Neurologic complications of cancer therapy. *Neurol Clin.* (2003) 21:279–318. doi: 10.1016/S0733-8619(02)00034-8
17. Giglio P, Gilbert MR. Neurologic complications of cancer and its treatment. *Curr Oncol Rep.* (2010) 12:50–9. doi: 10.1007/s11912-009-0071-x
18. Belka C, Budach W, Kortmann R, Bamberg M. Radiation induced CNS toxicity–molecular and cellular mechanisms. *Br J Cancer* (2001) 85:1233. doi: 10.1054/bjoc.2001.2100
19. Toopchizadeh V, Barzegar M, Rezamand A, Feiz AH. Electrophysiological consequences of vincristine contained chemotherapy in children: a cohort study. *J Pediatr Neurol.* (2009) 7:351–6. doi: 10.3233/JPN-2009-0333
20. Pamoukdjian F, Paillaud E, Zelek L, Laurent M, Lévy V, Landre T, et al. Measurement of gait speed in older adults to identify complications

associated with frailty: a systematic review. *J Geriatr Oncol.* (2015) 6:484–96. doi: 10.1016/j.jgo.2015.08.006

21. Duregon F, Vendramin B, Bullo V, Gobbo S, Cugusi L, Di Blasio A, et al. Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: a systematic review. *Crit Rev Oncol Hematol.* (2018) 121:90–100. doi: 10.1016/j.critrevonc.2017.11.002
22. Monfort SM, Pan X, Patrick R, Ramaswamy B, Wesolowski R, Naughton MJ, et al.. Gait, balance, and patient-reported outcomes during taxane-based chemotherapy in early-stage breast cancer patients. *Breast Cancer Res Treat.* (2017) 164:69–77. doi: 10.1007/s10549-017-4230-8
23. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* (2016) 66:7–30. doi: 10.3322/caac.21332
24. Howlader N, Noone A, Krapcho M, Garshell J, Miller D, Altekruse S, et al. *SEER Cancer Statistics Review, 1975–2012.* Bethesda, MD: National Cancer Institute (2015).
25. Spoelstra SL, Given BA, Schutte DL, Sikorskii A, You M, Given CW. Do older adults with cancer fall more often? A comparative analysis of falls in those with and without cancer. *Oncol Nurs Forum* (2013) 40:E69–78. doi: 10.1188/13.ONF.E69-E78
26. Niederer D, Schmidt K, Vogt L, Egen J, Klingler J, Hübscher M, et al. Functional capacity and fear of falling in cancer patients undergoing chemotherapy. *Gait Post.* (2014) 39:865–9. doi: 10.1016/j.gaitpost.2013.11.014
27. Gilchrist L, Tanner L. Gait patterns in children with cancer and vincristine neuropathy. *Pediatr Phys Ther.* (2016) 28:16–22. doi: 10.1097/PEP.0000000000000208
28. Wright MJ, Twose DM, Gorter JW. Gait characteristics of children and youth with chemotherapy induced peripheral neuropathy following treatment for acute lymphoblastic leukemia. *Gait Post.* (2017) 58:139–45. doi: 10.1016/j.gaitpost.2017.05.004
29. Raffa R. Is a picture worth a thousand (forgotten) words?: neuroimaging evidence for the cognitive deficits in 'chemo-fog'/'chemo-brain'. *J Clin Pharmacy Therapeut.* (2010) 35:1–9. doi: 10.1111/j.1365-2710.2009.01044.x
30. Scherling CS, Smith A. Opening up the window into "chemobrain": a neuroimaging review. *Sensors* (2013) 13:3169–203. doi: 10.3390/s130303169
31. Raffa RB, Duong PV, Finney J, Garber DA, Lam LM, et al. Is 'chemo-fog'/'chemo-brain' caused by cancer chemotherapy? *J Clin Phar Therapeut.* (2006) 31:129–38. doi: 10.1111/j.1365-2710.2006.00726.x
32. Stemmer SM, Stears JC, Burton BS, Jones RB, Simon JH. White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *Am J Neuroradiol.* (1994) 15:1267–73.
33. Brown MS, Stemmer SM, Simon JH, Stears JC, Jones RB, Cagnoni PJ, et al. White matter disease induced by high-dose chemotherapy: longitudinal study with MR imaging and proton spectroscopy. *Am J Neuroradiol.* (1998) 19:217–21.
34. Silverman DH, Dy CJ, Castellon SA, Lai J, Pio BS, Abraham L, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5–10 years after chemotherapy. *Breast Cancer Res Treat.* (2007) 103:303–11. doi: 10.1007/s10549-006-9380-z
35. Rosso AL, Verghese J, Metti AL, Boudreau RM, Aizenstein HJ, Kritchevsky S, et al. Slowing gait and risk for cognitive impairment. The hippocampus as a shared neural substrate. *Neurology*. (2017) 89:336–42. doi: 10.1212/WNL.0000000000004153
36. Ghai S, Ghai I, Effenberg AO. Effects of dual tasks and dual-task training on postural stability: a systematic review and meta-analysis. *Clin Intervent Aging* (2017) 12:557–77. doi: 10.2147/CIA.S125201
37. Holtzer R, Wang C, Verghese J. The relationship between attention and gait in aging: facts and fallacies. *Motor Control* (2012) 16:64–80. doi: 10.1123/mcj.16.1.64
38. Reddy MA, Naeem Z, Duncan C, Robertson F, Herod J, Rennie A, et al. Reduction of severe visual loss and complications following intra-arterial chemotherapy (IAC) for refractory retinoblastoma. *Br J Ophthalmol.* (2017) 101:1704–8. doi: 10.1136/bjophthalmol-2017-310294
39. Omoti AE, Omoti CE. Ocular toxicity of systemic anticancer chemotherapy. *Pharm Pract.* (2006) 4:55-9.
40. Minor LB. Gentamicin-induced bilateral vestibular hypofunction. *JAMA* (1998) 279:541–4.
41. Vincent JA, Wieczerzak KB, Gabriel HM, Nardelli P, Rich MM, Cope TC. A novel path to chronic proprioceptive disability with oxaliplatin: distortion of sensory encoding. *Neurobiol Dis.* (2016) 95:54–65. doi: 10.1016/j.nbd.2016.07.004
42. Argyriou AA, Polychronopoulos P, Iconomou G, Chroni E, Kalofonos HP. A review on oxaliplatin-induced peripheral nerve damage. *Cancer Treat Rev.* (2008) 34:368–77. doi: 10.1016/j.ctrv.2008.01.003
43. Burakgazi AZ, Messersmith W, Vaidya D, Hauer P, Hoke A, Polydefkis M. Longitudinal assessment of oxaliplatin-induced neuropathy. *Neurology* (2011) 77:980–6. doi: 10.1212/WNL.0b013e31822cfc59
44. Bibi R. *Effects of Chemotherapy on Sensory Inhibition and Sensory Memory in Breast Cancer Survivor.* CUNY Academic Works (2013). Available online at: http://academicworks.cuny.edu/cc_etds_theses
45. Thaler DS. Design for an aging brain. *Neurobiol Aging* (2002) 23:13–15. doi: 10.1016/S0197-4580(01)00262-7
46. Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. *Nat Rev Neurosci.* (2011) 12:739–51. doi: 10.1038/nrn3112
47. Haggard P, Wolpert DM. Disorders of body scheme. In: Freund, HJ, Jeannerod M, Hallett M, and Leiguarda R, editors. *Higher-Order Motor Disorders*. Oxford: Citeseer (2005).
48. Skoura X, Papaxanthis C, Vinter A, Pozzo T. Mentally represented motor actions in normal aging: I. Age effects on the temporal features of overt and covert execution of actions. *Behav Brain Res.* (2005) 165:229–39. doi: 10.1016/j.bbr.2005.07.023
49. Boisgontier MP, Nougier V. Ageing of internal models: from a continuous to an intermittent proprioceptive control of movement. *Age* (2013) 35:1339–55. doi: 10.1007/s11357-012-9436-4
50. Ospina PA, McComb A, Wiart LE, Eisenstat DD, McNeely ML. Physical therapy interventions, other than general physical exercise interventions, in children and adolescents before, during and following treatment for cancer. *Cochrane Database Syst Rev.* (2018) CD012924. doi: 10.1002/14651858.CD012924
51. Schwenk M, Grewal GS, Holloway D, Muchna A, Garland L, Najafi B. Interactive Sensor-based balance training in older cancer patients with chemotherapy-induced peripheral neuropathy: a randomized controlled trial. *Gerontology* (2016) 62:553–63. doi: 10.1159/000442253
52. Rizzo A. The role of exercise and rehabilitation in the cancer care plan. *J Advanc Practit Oncol.* (2016) 7:339. doi: 10.6004/jadpro.2016.7.3.20
53. Andersen C, Rørth M, Ejlertsen B, Stage M, Møller T, Midtgaard J, et al. The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue. *Eur J Oncol Nurs.* (2013) 17:331–9. doi: 10.1016/j.ejon.2012.09.003
54. Dalzell M, Smirnow N, Sateren W, Sintharaphone A, Ibrahim M, Mastroianni L, et al. Rehabilitation and exercise oncology program: translating research into a model of care. *Curr Oncol.* (2017) 24: e191–8. doi: 10.3747/co.24.3498
55. Streckmann F, Kneis S, Leifert J, Baumann F, Kleber M, Ihorst G, et al. Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Ann Oncol.* (2014) 25:493–99. doi: 10.1093/annonc/mdt568
56. Kumar SP. Cancer pain: a critical review of mechanism-based classification and physical therapy management in palliative care. *Indian J Palliat Care* (2011) 17:116–26. doi: 10.4103/0973-1075.84532
57. Paice JA. Mechanisms and management of neuropathic pain in cancer. *J Support Oncol.* (2003) 1:107–20.
58. Angin S, Karadibak D, Yavuzşen T, Demirbüken I. Unilateral upper extremity lymphedema deteriorates the postural stability in breast cancer survivors. *Contem Oncol.* (2014) 18:279–84. doi: 10.5114/wo.2014.44120
59. Mizrahi D, Broderick C, Friedlander M, Ryan M, Harrison M, Pumpa K, et al. An exercise intervention during chemotherapy for women with recurrent ovarian cancer: a feasibility study. *Int J Gynecol Cancer* (2015) 25:985–92. doi: 10.1097/IGC.0000000000000460
60. Winters-Stone K, Dobek J, Nail L, Bennett J, Leo M, Torgrimson-Ojerio B, et al. Impact+ resistance training improves bone health and body composition in prematurely menopausal breast cancer survivors: a randomized controlled trial. *Osteop Int.* (2013) 24:1637–46. doi: 10.1007/s00198-012-2143-2

61. Wonders KY, Whisler G, Loy H, Holt B, Bohachek K, Wise R. Ten weeks of home-based exercise attenuates symptoms of chemotherapy-induced peripheral neuropathy in breast cancer patients. *Health Psychol Res.* (2013) 1:e28. doi: 10.4081/hpr.2013.e28
62. Fernandes J, Kumar S. Effect of lower limb closed kinematic chain exercises on balance in patients with chemotherapy-induced peripheral neuropathy: a pilot study. *Int J Rehabil Res.* (2016) 39:368–71. doi: 10.1097/MRR.0000000000000196
63. Huang MH, Shilling T, Miller KA, Smith K, LaVictoire K. History of falls, gait, balance, fall risks in older cancer survivors living in the community. *Clin Intervent Aging* (2015) 10:1497. doi: 10.2147/CIA.S89067
64. Boyde C, Linden U, Boehm K, Ostermann T. The use of music therapy during the treatment of cancer patients: a collection of evidence. *Glob Adv Health Med.* (2012) 1:24–9. doi: 10.7453/gahmj.2012.1.5.009
65. Archie P, Bruera E, Cohen L. Music-based interventions in palliative cancer care: a review of quantitative studies and neurobiological literature. *Support Care Cancer* (2013) 21:2609–24. doi: 10.1007/s00520-013-1841-4
66. Stanczyk MM. Music therapy in supportive cancer care. *Rep Pract Oncol Radiother.* (2011) 16:170–2. doi: 10.1016/j.rpor.2011.04.005
67. Bolognini N, Russo C, Edwards DJ. The sensory side of post-stroke motor rehabilitation. *Restor Neurol Neurosci.* (2016) 34:571–86. doi: 10.3233/RNN-150606
68. Ghai S, Schmitz G, Hwang T-H, Effenberg AO. Training proprioception with sound: effects of real-time auditory feedback on intermodal learning. *Ann NY Acad Sci.* (2018). doi: 10.1111/nyas.13967. [Epub ahead of print].
69. Prinz W. Why don't we perceive our brain states? *Eur J Cogn Psychol.* (1992) 4:1–20.
70. Prinz W. Perception and action planning. *Eur J Cogn Psychol.* (1997) 9:129–54.
71. Effenberg AO, Schmitz G. Acceleration and deceleration at constant speed: systematic modulation of motion perception by kinematic sonification. *Ann NY Acad Sci.* (2018) 1425:56–9. doi: 10.1111/nyas.13693
72. Effenberg AO, Fehse U, Schmitz G, Krueger B, Mechling H. Movement sonification: effects on motor learning beyond rhythmic adjustments. *Front Neurosci.* (2016) 10:67. doi: 10.3389/fnins.2016.00219
73. Wolpert DM, Ghahramani Z, Jordan MI. An internal model for sensorimotor integration. *Science* (1995) 269:1880. doi: 10.1126/science.7569931
74. Schaefer RS. Auditory rhythmic cueing in movement rehabilitation: findings and possible mechanisms. *Philos Trans R Soc B Biol Sci.* (2014) 369:20130402. doi: 10.1098/rstb.2013.0402
75. Thaut MH, Abiru M. Rhythmic auditory stimulation in rehabilitation of movement disorders: a review of current research. *Music Percept.* (2010) 27:263–9. doi: 10.1525/mp.2010.27.4.263
76. Thaut MH. *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications.* New York, NY: Routledge (2005).
77. Ghai S, Ghai I, Effenberg AO. Effect of rhythmic auditory cueing on aging gait: a systematic review and meta-analysis. *Aging Dis.* (2017) 9:901–23. doi: 10.14336/AD.2017.1031
78. Ghai S, Ghai I, Schmitz G, Effenberg AO. Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. *Sci Rep.* (2018) 8:506. doi: 10.1038/s41598-017-16232-5
79. Ghai S, Ghai I, Effenberg AO. "Low road" to rehabilitation: a perspective on subliminal sensory neuroprosthetics. *Neuropsychiat Dis Treat.* (2018) 14:301–7. doi: 10.2147/NDT.S153392
80. Ghai S, Ghai I, Effenberg AO. Effect of rhythmic auditory cueing on gait in cerebral palsy: a systematic review and meta-analysis. *Neuropsyc Dis Treat.* (2018) 14:43–59. doi: 10.2147/NDT.S148053
81. Ghai S, Ghai I. Effects of rhythmic auditory cueing in gait rehabilitation for multiple sclerosis: a mini systematic review and meta-analysis. *Front Neurol.* (2018) 9:386. doi: 10.3389/fneur.2018.00386
82. Ghai S. Effects of real-time (sonification) and rhythmic auditory stimuli on recovering arm function post stroke: a systematic review & meta-analysis. *Front Neurol.* (2018) 9:488. doi: 10.3389/fneur.2018.00488
83. Yoo GE, Kim SJ. Rhythmic auditory cueing in motor rehabilitation for stroke patients: systematic review and meta-analysis. *J Music Therapy* (2016) 53:149–77. doi: 10.1093/jmt/thw003
84. Thaut MH, Hoemberg V. *Handbook of Neurologic Music Therapy.* Oxford: Oxford University Press (2014).
85. Höner O, Hunt A, Pauletto S, Röber N, Hermann T, Effenberg AO. Aiding movement with sonification in "exercise, play and sport". In: Hermann T, Hunt A, Neuhoff JG, editors. *The Sonification Handbook.* Berlin: Logos (2011). p. 525–553.
86. Ghai S, Ghai I. Effects of (music-based) rhythmic auditory cueing training on gait & posture post-stroke: a systematic review & dose response meta-analysis. *Sci Rep.* (in press). doi: 10.1038/s41598-019-38723-3
87. Correa D, Wang Y, West J, Peck K, Root J, Baser R, et al. Prospective assessment of white matter integrity in adult stem cell transplant recipients. *Brain Imaging Behav.* (2016) 10:486–96. doi: 10.1007/s11682-015-9423-3
88. Bengtsson SL, Nagy Z, Skare S, Forsman L, Forssberg H, Ullén F. Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci.* (2005) 8:1148–50. doi: 10.1038/nn1516
89. Fernández-Seara MA, Aznárez-Sanado M, Mengual E, Irigoyen J, Heukamp F, et al. Effects on resting cerebral blood flow and functional connectivity induced by metoclopramide: a perfusion MRI study in healthy volunteers. *Br J Pharmacol.* (2011) 163:1639–52. doi: 10.1111/j.1476-5381.2010.01161.x
90. Feng DD, Cai W, Chen X. The associations between Parkinson's disease and cancer: the plot thickens. *Trans Neurodegen.* (2015) 4:20. doi: 10.1186/s40035-015-0043-z
91. Nombela C, Hughes LE, Owen AM, Grahn JA. Into the groove: can rhythm influence Parkinson's disease? *Neurosci Biobehav Rev.* (2013) 37:2564–70. doi: 10.1016/j.neubiorev.2013.08.003
92. Schmitz G, Mohammadi B, Hammer A, Heldmann M, Samii A, Münte TF, et al. Observation of sonified movements engages a basal ganglia frontocortical network. *BMC Neurosci.* (2013) 14:32. doi: 10.1186/1471-2202-14-32
93. Effenberg AO, Hwang T-H, Ghai S, Schmitz G. Auditory modulation of multisensory representations. In: Aramaki M, Davis M, Kronland-Martinet R, Ystad S. editors. *Music Technology WITH SWING. CMMR. 2017. Lecture Notes in Computer Science,* Vol. 11265. Cham: Springer (2018). doi: 10.1007/978-3-030-01692-0_20
94. Ghai S, Schmitz G, T.-Hwang H, Effenberg AO. Auditory proprioceptive integration: Effects of real-time kinematic auditory feedback on knee proprioception. *Front Neurosci.* (2018) 12:142. doi: 10.3389/fnins.2018.00142
95. Hasegawa N, Takeda K, Sakuma M, Mani H, Maejima H, Asaka T. Learning effects of dynamic postural control by auditory biofeedback versus visual biofeedback training. *Gait Post.* (2017) 58:188–93. doi: 10.1016/j.gaitpost.2017.08.001
96. Danna J, Velay JL. On the auditory-proprioception substitution hypothesis: movement sonification in two deafferented subjects learning to write new characters. *Front Neurosci.* (2017) 11:137. doi: 10.3389/fnins.2017.00137
97. Ronsse R, Puttemans V, Coxon JP, Goble DJ, Wagemans J, Wenderoth N, Swinnen SP. Motor learning with augmented feedback: modality-dependent behavioral and neural consequences. *Cereb Cortex* (2011) 21:1283–94. doi: 10.1093/cercor/bhq209
98. Thaut MH, McIntosh GC, Hoemberg V. Neurobiological foundations of neurologic music therapy: rhythmic entrainment and the motor system. *Front Psychol.* (2014) 5:1185. doi: 10.3389/fpsyg.2014.01185
99. Thaut M, Schleiffers S, Davis W. Analysis of EMG activity in biceps and triceps muscle in an upper extremity gross motor task under the influence of auditory rhythm. *J Music Therapy* (1991) 28:64–88. doi: 10.1093/jmt/28.2.64
100. van Vugt FT, Tillmann B. Auditory feedback in error-based learning of motor regularity. *Brain Res.* (2015) 1606:54–67. doi: 10.1016/j.brainres.2015.02.026
101. Heremans E, Nieuwboer A, Spildooren J, De Bondt S, D'hooge AM, Helsen W, et al. Cued motor imagery in patients with multiple sclerosis. *Neuroscience* (2012) 206:115–21. doi: 10.1016/j.neuroscience.2011.12.060
102. Heremans E, Helsen WF, De Poel HJ, Alaerts K, Meyns P, Feys P. Facilitation of motor imagery through movement-related cueing. *Brain Res.* (2009) 1278:50–8. doi: 10.1016/j.brainres.2009.04.041
103. Whitall J, McCombe Waller S, Sorkin JD, Forrester LW, Macko RF, Hanley DF, et al. Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: a single-blinded randomized controlled trial. *Neurorehabil Neural Repair* (2011) 25:118–29. doi: 10.1177/1545968310380685
104. Luft AR, McCombe-Waller S, Whitall J, Forrester LW, Macko R, Sorkin JD, et al. Repetitive bilateral arm training and motor cortex activation in

chronic stroke: a randomized controlled trial. *J Am Med Associat.* (2004) 292:1853–61. doi: 10.1001/jama.292.15.1853
105. Fujioka T, Ween JE, Jamali S, Stuss DT, Ross B. Changes in neuromagnetic beta-band oscillation after music-supported stroke rehabilitation. *Ann NY Acad Sci.* (2012) 1252:294–304. doi: 10.1111/j.1749-6632.2011.06436.x
106. Ross B, Barat M, Fujioka T. Sound-making actions lead to immediate plastic changes of neuromagnetic evoked responses and induced beta-band oscillations during perception. *J Neurosci.* (2017) 37:5948–59. doi: 10.1523/JNEUROSCI.3613-16.2017
107. Särkämö T, Ripollés P, Vepsäläinen H, Autti T, Silvennoinen HM, Salli E, et al. Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: a voxel-based morphometry study. *Front Hum Neurosci.* (2014) 8:245. doi: 10.3389/fnhum.2014.00245
108. Särkämö T, Altenmüller E, Rodríguez-Fornells A, Peretz I. Editorial: music, brain, and rehabilitation: emerging therapeutic applications and potential neural mechanisms. *Front Hum Neurosci.* (2016) 10:103. doi: 10.3389/fnhum.2016.00103
109. Sihvonen AJ, Särkämö T, Leo V, Tervaniemi M, Altenmüller E, Soinila S. Music-based interventions in neurological rehabilitation. *Lancet Neurol.* (2017) 16:648–60. doi: 10.1016/S1474-4422(17)30168-0
110. Hopkins K, Kass SJ, Blalock LD, Brill JC. Effectiveness of auditory and tactile crossmodal cues in a dual-task visual and auditory scenario. *Ergonomics* (2017) 60:692–700. doi: 10.1080/00140139.2016.1198495
111. Thaut MH, Peterson DA, McIntosh GC, Hoemberg V. Music mnemonics aid verbal memory and induce learning – related brain plasticity in multiple sclerosis. *Front Hum Neurosci.* (2014) 8:395. doi: 10.3389/fnhum.2014.00395
112. Pichler A, Pichler M. Music therapy in cancer patients: fact or fiction? *Fut Oncol.* (2014) 10:2409–11. doi: 10.2217/fon.14.181
113. Uedo N, Ishikawa H, Morimoto K, Ishihara R, Narahara H, Akedo I, et al. Reduction in salivary cortisol level by music therapy during colonoscopic examination. *Hepatogastroenterology* (2004) 51:451–3.
114. Zavotsky KE, Adrienne Banavage M, Patricia James R, Kathy Easter M, Pontieri-Lewis V, et al. The effects of music on pain and anxiety during screening mammography. *Clin J Oncol Nurs.* (2014) 18:E45. doi: 10.1188/14.CJON.E45-E49
115. Chlan L, Evans D, Greenleaf M, Walker J. Effects of a single music therapy intervention on anxiety, discomfort, satisfaction, and compliance with screening guidelines in outpatients undergoing flexible sigmoidoscopy. *Gastroenterol Nurs.* (2000) 23:148–56. doi: 10.1097/00001610-200007000-00003
116. Tsivian M, Qi P, Kimura M, Chen VH, Chen SH, Gan TJ, et al. The effect of noise-cancelling headphones or music on pain perception and anxiety in men undergoing transrectal prostate biopsy. *Urology* (2012) 79:32–6. doi: 10.1016/j.urology.2011.09.037
117. Bangert M, Altenmüller EO. Mapping perception to action in piano practice: a longitudinal DC-EEG study. *BMC Neurosci.* (2003) 4:26. doi: 10.1186/1471-2202-4-26
118. Nascimento LR, de Oliveira CQ, Ada L, Michaelsen SM, Teixeira-Salmela LF. Walking training with cueing of cadence improves walking speed and stride length after stroke more than walking training alone: a systematic review. *J Physiother.* (2015) 61:10–5. doi: 10.1016/j.jphys.2014.11.015
119. Hove MJ, Suzuki K, Uchitomi H, Orimo S, Miyake Y. Interactive rhythmic auditory stimulation reinstates natural 1/f timing in gait of Parkinson's patients. *PLoS ONE* (2012) 7:e32600. doi: 10.1371/journal.pone.0032600
120. Ghai S, Ghai I. Virtual reality enhances gait recovery in cerebral palsy: a training dose-response meta-analysis. *Front Neurol.* (2019).
121. Ghai S, Driller MW, Masters RSW. The influence of below-knee compression garments on knee-joint proprioception. *Gait Posture* (2018) 60:258-61. doi: 10.1016/j.gaitpost.2016.08.008
122. Ghai S, Driller M, Ghai I. Effects of joint stabilizers on proprioception and stability: a systematic review and meta-analysis. *Phys Ther Sport* (2017) 25:65-75. doi: 10.1016/j.ptsp.2016.05.006
123. Ghai S. *Proprioception and Performance: The Role of Below-Knee Compression Garments and Secondary Tasks*. Hamilton: University of Waikato (2016). Available online at: https://hdl.handle.net/10289/10575
124. Windholz T, Swanson T, Vanderbyl BL, Jagoe RT. The feasibility and acceptability of neuromuscular electrical stimulation to improve exercise performance in patients with advanced cancer: a pilot study. *BMC Palliat Care* (2014) 13:23. doi: 10.1186/1472-684X-13-23

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Motor Synchronization to Rhythmic Auditory Stimulation (RAS) Attenuates Dopaminergic Responses in Ventral Striatum in Young Healthy Adults: [^{11}C]-(+)-PHNO PET Study

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Auditory-motor entrainment using rhythmic auditory stimulation (RAS) has been shown to improve motor control in healthy persons and persons with neurologic motor disorders such as Parkinson's disease and stroke. Neuroimaging studies have shown the modulation of corticostriatal activity in response to RAS. However, the underlying neurochemical mechanisms for auditory-motor entrainment are unknown. The current study aimed to investigate RAS-induced dopamine (DA) responses in basal ganglia (BG) during finger tapping tasks combined with [^{11}C]-(+)-PHNO-PET in eight right-handed young healthy participants. Each participant underwent two PET scans with and without RAS. Binding potential relative to the non-displaceable compartment (BP_{ND}) values were derived using the simplified reference tissue method. The task performance was measured using absolute tapping period error and its standard deviation. We found that the presence of RAS significantly improved the task performance compared to the absence of RAS, demonstrated by reductions in the absolute tapping period error ($p = 0.007$) and its variability ($p = 0.006$). We also found that (1) the presence of RAS reduced the BG BP_{ND} variability ($p = 0.013$) and (2) the absence of RAS resulted in a greater DA response in the left ventral striatum (VS) compared to the presence of RAS ($p = 0.003$), These suggest that the absence of external cueing may require more DA response in the left VS associated with more motivational and sustained attentional efforts to perform the task. Additionally, we demonstrated significant age effects on D2/3 R availability in BG: increasing age was associated with reduced D2/3 R availability in the left putamen without RAS ($p = 0.026$) as well as in the right VS with RAS ($p = 0.02$).

This is the first study to demonstrate the relationships among RAS, DA response/D2/3 R availability, motor responses and age, providing the groundwork for future studies to explore mechanisms for auditory-motor entrainment in healthy elderly and patients with dopamine-based movement disorders.

Keywords: finger tapping, rhythmic auditory stimulation, D2/3 receptors, dopamine, PET, [^{11}C]-(+)-PHNO, auditory-motor entrainment, basal ganglia

INTRODUCTION

Rhythmic auditory stimulation (RAS) – presented either as single auditory beats or metronome clicks embedded in instrumental music – has shown to improve motor control in healthy persons and persons with neurologic motor disorders such as Parkinson's disease (PD) and stroke (Miller et al., 1996; Thaut et al., 1996, 2002; McIntosh et al., 1997; Massie et al., 2009). Reduction in variability of motor timing, electromyography recruitment, and movement kinematics as well as increases in speed are among the positive effects demonstrated.

These benefits result from rhythmic auditory entrainment. Entrainment refers to the frequency locking of two oscillating bodies that can move in stable periodic cycles (Thaut, 2015). The rhythmic frequency provides the brain (already equipped with internal time keeper mechanism) with an additional externally triggered time keeper, which generates a precise temporal interval as a continuous time reference (Thaut, 2015). Importantly, the auditory system is more precise and faster to detect temporal patterns than other sensory systems such as visual and tactile systems (Shelton and Kumar, 2010).

Auditory rhythm can prime and time muscle activation by providing precise anticipatory time cues for motor planning and execution (Paltsev and E-lner, 1967; Rossignol and Jones, 1976), which increases the readiness to move and improves subsequent response quality (Thaut, 2015). Once auditory-motor entrainment occurs, movements stays locked to the auditory rhythm presented even when subtle tempo changes occur in the auditory stimuli that are not consciously perceived (Thaut et al., 1998a,b; Large et al., 2002).

The auditory and the motor systems are connected through widely distributed and hierarchically organized neural networks from cortical to subcortical, brain stem, and cerebellar regions (Thaut, 2003; Schmahmann and Pandya, 2006; Felix et al., 2011; Konoike et al., 2012). Functional MRI studies have shown that listening to regular auditory rhythm modulated activities in premotor (Chen et al., 2006, 2008), cortico-basal ganglia (BG) including putamen, caudate, and pallidum (Grahn and Brett, 2007; Grahn and Rowe, 2009, 2013), and cortico-cerebellar (Thaut et al., 2009; Konoike et al., 2012) networks. It also led to the rapid and precise brain wave entrainment, mainly in beta oscillation bands in the motor areas such as supplementary motor area (SMA) and cerebellum (Fujioka et al., 2012; Crasta et al., 2018). In addition to auditory rhythm, music generally modulates activity in widely distributed brain areas, particularly in the limbic regions including the nucleus accumbens/ventral striatum (VS) (Blood and Zatorre, 2001; Menon and Levitin, 2005; Salimpoor et al., 2011, 2013; Koelsch, 2014; Mueller et al., 2015). Furthermore, anatomical (Hackett, 2015) and resting functional MRI (Helmich et al., 2010) studies demonstrated connectivity between superior temporal gyrus and striatum (i.e., putamen and caudate). These suggest a close link between auditory areas and BG.

However, it is not well understood how dopamine (DA) in BG is involved in auditory-motor entrainment due to a paucity of research. Neuroimaging studies can investigate the neural mechanisms by employing a synchronization paradigm (Thaut et al., 1998a,b), in which finger tapping is synchronized to external auditory cueing that is thought to occur through entrainment (Braunlich et al., 2018). This can be contrasted to a continuation task (i.e., finger tapping without external auditory cueing) to elucidate the role of external auditory cueing in motor timing (Koshimori and Thaut, 2018; Teghil et al., 2018). To our knowledge, all of the studies using the synchronization/continuation task design employed fMRI and showed that cortical motor areas and cerebellum were activated during auditory-motor entrainment (Rao et al., 1997; Jäncke et al., 2000; Toyomura et al., 2012), but whose activation was similar to that during the continuation task. However, activation of the putamen and SMA was absent during the synchronization task (Rao et al., 1997; Lewis et al., 2004; Toyomura et al., 2012). These suggest that external auditory cueing may not have an extra role in brain activation in motor areas or that external auditory cueing may not require cortico-basal ganglia activity in young healthy adults. On the other hand, one PET study in PD suggested the association between dopaminergic function measured by baseline striatal dopaminergic denervation and auditory-motor synchronization performance (Miller et al., 2013). In addition, pharmacological studies in PD (McIntosh et al., 1997; Rochester et al., 2010) suggested that DA may play a partial role in auditory-motor entrainment or that intact dopaminergic system may be required for auditory-motor entrainment (Koshimori and Thaut, 2018).

To date there have been no studies investigating the role of BG DA in auditory-motor entrainment using the synchronization/continuation paradigm. Studying dopaminergic responses may be of particular importance to understand how PD benefits from RAS, since BG is an important subcortical structure for timing perception, which is crucial for movements and is negatively affected by dopamine depletion, yet persons with PD have significantly improved motor control with RAS, especially in gait performance (Ghai et al., 2018). The current study is therefore intended to investigate neurochemical mechanisms underlying the effect of RAS through dopamine responses in young healthy adults, serving as a baseline response to which later studies with healthy elderly and patients with dopamine-deficient movement disorders can be compared.

For this purpose, we employed [11C]-(+)-PHNO-PET to measure dopaminergic function during auditory-motor entrainment. Compared to the commonly used D2/3 R radioligand, [11C]-racropride, it shows higher sensitivity in detecting D3 receptors (Narendran et al., 2006), which allows for better quantification of the regions with greater expression of D3 receptors such as the ventral striatum (VS) and globus pallidus (GP) (Narendran et al., 2006; Willeit et al., 2006). In addition, being an agonist radioligand, it is more sensitive to competition with endogenous DA *in vivo* compared to an antagonist radioligand, [11C]-racropride (Caravaggio et al., 2014, 2016), which is more advantageous in a functional study. It has been employed in the studies that investigated task-induced functional changes (Mizrahi et al., 2014) and task-induced functional changes associated with reward and motivation (Caravaggio et al., 2018).

We hypothesized that (1) finger tapping performance would be better with RAS compared to No-RAS, (2) the PET outcome measure, BP_{ND} values would be significantly different between the task conditions in BG and its regions, and (3) finger tapping performance would be associated with BP_{ND} values.

MATERIALS AND METHODS

Participants

Twelve right-handed healthy participants (seven women and five men) aged from 18 to 35 years enrolled in this study. The participants were recruited through self-referral in response to advertisements. Inclusion criteria were: no history of neurologic/psychiatric disorders or major medical conditions, no hearing issues, no contradictions for PET and MRI scans (e.g., metal implants, claustrophobia, pacemaker, or pregnancy), no alcohol, medication or drug dependency or abuse, right-handedness confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971), no current depression assessed by Beck Depression Inventory II (BDI II). The study was carried out in accordance with the recommendations of the Ethical Committee of the Centre for Addiction and Mental Health. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethical Committee of the Centre for Addiction and Mental Health.

Study Design

Each participant underwent two [11C]-(+)-PHNO PET and one MRI scans. During one scan, a participant was performing a finger-tapping task with RAS (RAS condition) and during the other scan, a finger-tapping task without RAS (No-RAS condition). A finger tapping task started upon the radioligand injection to be consistent across the participants (**Figure 1**). During each scan, there were three task blocks with 10-min rests in between. One block consists of six tapping sessions with each lasting for 2 min followed by a 1-min rest. The total time of one task block lasted for 17 min. After completion of three task blocks, a participant rested until the PET scan was completed. The order of the two PET scans was counterbalanced across participants.

Finger Tapping Task

Rhythmic auditory stimulation was programmed using Psychophysics Toolbox Version 3 (Brainard, 1997; Pelli, 1997; Kleiner et al., 2007) and run on Matlab (R2016a). It was

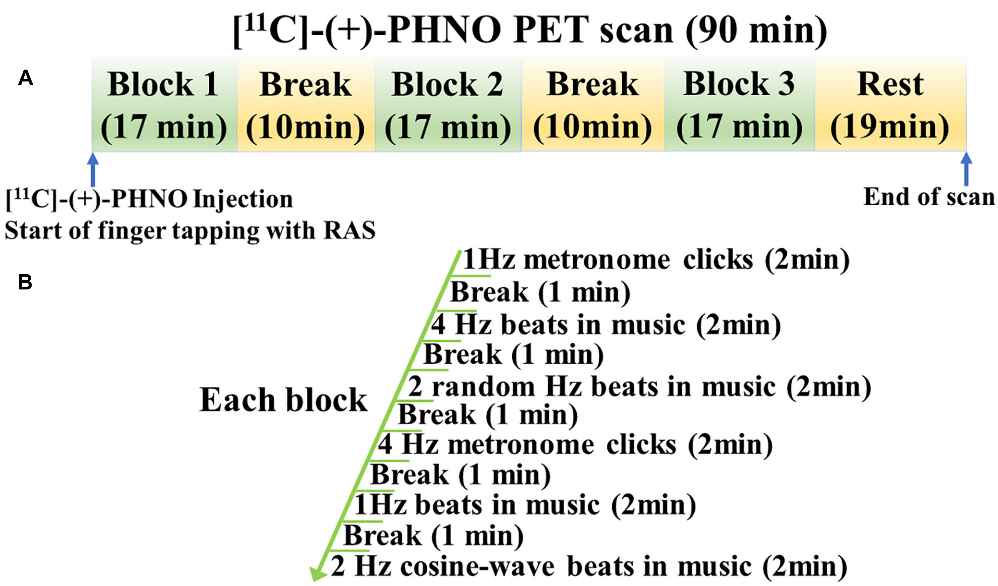

FIGURE 1 | Study design for finger tapping task during PET scan. **(A)** PET scan consisted of three task blocks with two breaks in between followed by resting. **(B)** Each task block consisted of six tapping sessions with breaks in between, starting with 1 Hz metronome clicks. RAS was presented in the entire task block in the RAS condition whereas it was faded after six beats/clicks in the No-RAS condition.

presented through speakers above the participant's head located outside of the scanner. The loudness of RAS was tested after the participant laid down on the scanner bed. It was set at a comfortable listening level determined by each participant. In addition, a keyboard on which the participant tapped was stabilized at a comfortable location. Participants performed the task briefly before the radioligand injection. Beep sounds indicated the start and the end of each tapping session. In the RAS condition, a participant was asked to tap his/her right index finger to six different rhythmic cues including (1) 1 Hz beats embedded in music (Capricho Catalán by Isaac Albéniz), (2) 4 Hz metronome clicks, (3) 2 Hz beats with random tempo changes below the threshold of conscious perception (4% of interbeat interval) embedded in music (Allegro Robusto by Bela Bartok), (4) 4 Hz beats embedded in music (Rondo a Capriccio "Rage Over My Lost Penny" by Ludwig von Beethoven), (5) 1 Hz metronome clicks, and (6) 2 Hz with tempo changes continuously modulated on a cosine function below the threshold of conscious perception (4% of interbeat interval) embedded in music (Allegro Robusto by Bela Bartok). Our choice of the auditory stimuli regarding the frequency and presentation mode was based on extensive research in synchronization paradigms using auditory rhythm and finger tapping in the past 50 years in healthy persons and persons with movement disorders: the most pronounced entrainment effects have been demonstrated ranging between 1 and 4 Hz (e.g., Michon and van der Valk, 1967; Rao et al., 1997; Thaut et al., 1998a,b; Stephan et al., 2002; Thaut and Kenyon, 2003; Molinari et al., 2005; Repp, 2005; Thaut et al., 2008; Braunlich et al., 2018). The current study aimed to investigate DA responses across the typical frequency range of entrainment. In order to enhance beat perception, a musical context via melody and harmony components was added to half of the rhythm presentation (Thaut et al., 1997; Nozaradan et al., 2011). The choice of the order and mode of presentation of RAS was also intended to reduce fatigue of the participants and boredom of the task. The RAS was presented in the same order across the participants. In the No-RAS condition, a participant was asked to tap his/her right index finger to the six cue-in beats/clicks following the same rhythm presentation and order as in the RAS condition. After six beats/clicks, the cue was faded, and participants continued to tap without the external cuing. Participants practiced each finger tapping task outside of the scanner on the scan day. The finger tapping performance was recorded on Matlab (R2016a) and measured using the absolute tapping period error and its standard deviation. The absolute tapping period error was the absolute differences between interstimulus intervals and interresponse intervals. The absolute tapping period errors that were 50% longer or shorter than the target intervals were excluded as outliers from the analysis. In addition, the first six taps were excluded from the analysis.

MRI Acquisition

Each participant underwent one structural MRI scan acquired with a General Electric Discovery MR 750 3T scanner with 8-channel head coil (General Electric, Milwaukee, WI, United States). Proton density-weighted MRIs (oblique plane, 84 slices; matrix of 256 × 192; 22 cm field of view; 2 cm slice thickness; echo time = Min Full; repetition time = 6000 ms; flip angle = 8°) were used for co-registration to PET images for region of interest (ROI) delineation.

PET Acquisition

Each participant underwent two $[^{11}C]$-(+)-PHNO scans acquired with a high resolution PET/CT Siemens-Biograph HiRez XVI (Siemens Molecular Imaging, Knoxville, TN, United States), operating in 3D mode with an in-plane resolution of approximately 4.6 mm full width at half-maximum. The radiosynthesis of $[^{11}C]$-(+)-PHNO ($[^{11}C]$-(+)-4-propyl-9-hydroxynaphthoxazine) has been described in detail elsewhere (Wilson et al., 2005). Briefly, $[^{11}C]$-propionyl chloride was reacted with 9-hydroxynaphthoxazine to generate a $[^{11}C]$-amide, which is subsequently reduced by lithium aluminum hydride. Purification by HPLC and formulation give radiochemically pure $[^{11}C]$-(+)-PHNO as a sterile, pyrogen-free solution suitable for human studies.

Prior to the PET scan, a low dose (0.2 mSv) CT scan was performed and used for attenuation correction. In order to prevent head movement during the PET scan, a thermoplastic facemask was custom-fitted to each participant and attached to a head-fixation system (Tru-Scan Imaging, Annapolis). For each scan, ∼10 mCi $[^{11}C]$-(+)-PHNO was injected as a bolus into an intravenous line placed in an antecubital vein. The emission data were acquired over 90 min. For each 3D sinogram, data were normalized with attenuation and scatter corrected before applying fourier rebinning to convert the 3D sinograms into 2D sinograms. The 2D sinograms were then reconstructed into image space using a 2D filtered back projection algorithm, with a ramp filter at Nyquist cutoff frequency. After reconstruction, a Gaussian filter with a 5 mm FWHM was applied and the images calibrated to nCi/cc. The spatial resolution of the reconstructed images was 2 mm × 2 mm × 2 mm.

PET Image Processing

$[^{11}C]$-(+)-PHNO images were processed using in-house software ROMI platform (Rusjan et al., 2006). The preprocessing steps included (1) motion correction if necessary, (2) transformation of a standard brain template with a set of predefined ROIs to match individual high-resolution MR images, (3) refinement of the ROIs from the transformed template based on the gray matter probability of voxels in the individual MR images (segmentation step), (4) coregistration of the individual MR images to the PET images to transform the individual refined ROIs to the PET image space, and (5) extraction of time activity curves of the ROIs. We chose ROI analysis over voxel-based analysis due to poor spatial resolution of PET imaging. Our ROIs included the entire BG and its regions (i.e., putamen, caudate, VS, and GP). Binding potential relative to the non-displaceable compartment (BP_{ND}) were extracted bilaterally in the ROIs using the simplified reference tissue model with the cerebellum (excluding the vermis) as a reference region using PMOD (version 3.6).

Statistical Analysis

The normality was tested on the behavioral and $[^{11}C]$-(+)-PHNO PET outcome measures using a Shapiro–Wilk test. Correlation analyses were performed between age and music experience, and BP_{ND} values. Depending on the results of these tests, appropriate statistical analyses were used to test differences in BP_{ND} values between conditions as well as correlations (1) between BP_{ND} values and task performance for each condition and (2) between percentage changes in BP_{ND} value and percentage changes in task performance. The statistical analyses were conducted using SPSS (version 20). The significance level for the statistical analyses was set at $p < 0.05$ (Bonferroni corrected).

RESULTS

Participants

Among 12 participants who enrolled in this study, one participant withdrew from the study because of a schedule conflict. Two participants were excluded because their behavioral data were not recorded due to a technical failure. In addition, one participant did not perform the finger tapping task in the No-RAS condition as practiced. Therefore, a total of eight participants (four women and four men) were included in the analyses. Among them, five participants had their PET scans with RAS-condition first. The demographic characteristics and their PET scan parameters were presented in **Table 1**. Music experiences varied from none ($N = 2$), to 1 year ($N = 1$), 5 years ($N = 5$), 9 years ($N = 1$), and 10 years ($N = 1$). The PET parameters including the amount injected, specific activity, and mass inject were not significantly different between conditions.

Normality of Outcome Measures

The Shapiro–Wilk test did not show any significant results in normality of BP_{ND} values. Therefore, the statistical analyses were conducted using parametric tests.

TABLE 1 | Demographics and PET scan parameters of eight right-handed young healthy participants.

Demographics		
Age	27.25 ± 4.65	
Sex (men: women)	4:4	
Years of music experience	4.38 ± 3.9	
Beck depression inventory	3.75 ± 5.09	
PET scan parameters		
		***p*-value**
Amount injected (mCi)		
No-RAS condition	9.27 ± 1.04	$p = 0.601$
RAS condition	9.80 ± 0.58	
Specific activity (mCi/μmol)		
No-RAS condition	1323.54 ± 425.62	$p = 0.732$
RAS condition	1315.65 ± 254.56	
Mas injected (μg)		
No-RAS condition	1.85 ± 0.45	$p = 0.616$
RAS condition	1.89 ± 0.31	

Data are presented in mean and standard deviation.

Finger Tapping Performance

Rhythmic auditory stimulation significantly improved the finger tapping task performance in young healthy individuals (**Figure 2**). Two-sided paired t-tests revealed that the absolute tapping period error was significantly reduced with RAS compared to without RAS (0.027 ± 0.009 vs. 0.036 ± 0.014, $t(7) = 3.8$, $p = 0.007$). Similarly, the variability of the absolute tapping period error was significantly reduced with RAS compared to without RAS (0.038 ± 0.015 vs. 0.052 ± 0.018, $t(7) = 3.9$, $p = 0.006$). The better finger tapping performance in the RAS-condition was consistently found across the participants regardless of the scan order. The number of outliers did not significantly differ between conditions, indicating that the participants engaged equally in both tasks and that the number of taps did not affect the BP_{ND} differences (Wessel et al., 1997). The outliers accounted for approximately 2% of the finger tapping performance on average in each condition.

BP_{ND} Values

A two-sided paired t-test did not reveal a significant difference in the BG BP_{ND} value between the task conditions. However, the BP_{ND} value was significantly higher in the RAS condition compared to in the No-RAS condition in the left VS (2.942 ± 0.407 vs. 2.625 ± 0.541; $t(7) = 4.515$, $p = 0.003$), indicating less DA responses in the RAS condition compared to in the No-RAS condition in this region (**Figure 3**). The higher BP_{ND} values in the left VS in the RAS-condition was also consistently found across the participants regardless of the scan order. There were no significant differences in any other ROIs. Because RAS significantly reduced behavioral variability, we also explored whether the variability in BP_{ND} value in the entire BG (measured by the standard deviation across the participants and regions) also differed between conditions. Similar to the behavioral result, the RAS condition resulted in significantly less variability in BP_{ND} value in the entire BG compared to the No-RAS condition (0.3 vs. 0.42, $t(7) = 3.289$, $p = 0.013$) (**Figure 4**).

Correlations Between BP_{ND} Values in the Left Ventral Striatum and Finger Tapping Performance

To further investigate the DA responses in the left VS, we first performed a Pearson correlation analysis to investigate the confounding effects of age and music experience on finger tapping performance and BP_{ND} values in the BG regions. Age showed significant negative correlations with the BP_{ND} values in the left putamen in the No-RAS condition ($r = -0.77$, $p = 0.026$) and in the right VS in the RAS-condition ($r = -0.789$, $p = 0.02$). Because there were no confounding effects on the BP_{ND} values in the left VS, we used a bivariate correlation to test (1) between BP_{ND} values in the left VS and finger tapping performance for each condition and (2) between the percentage change of the BP_{ND} values in the left VS and of finger tapping performance between conditions. No significant correlations were found.

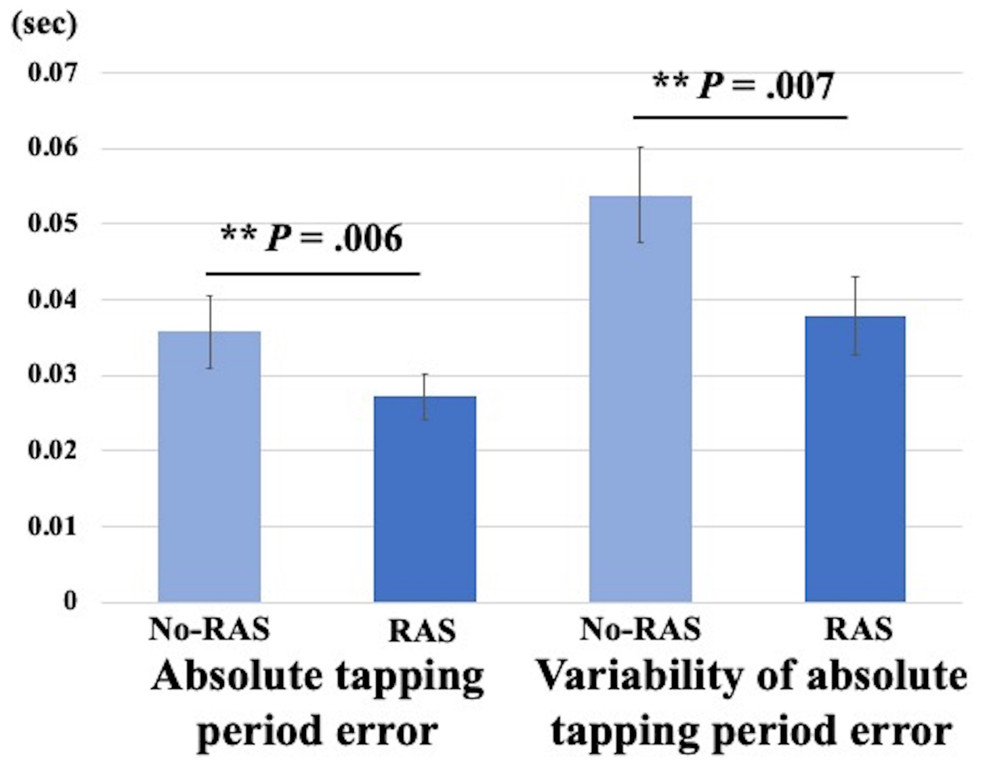

FIGURE 2 | Mean differences in finger tapping performance between No-RAS and RAS conditions. In the RAS condition, both absolute tapping period error and its variability were significantly reduced compared to in the No-RAS condition. Error bars represent standard deviation.

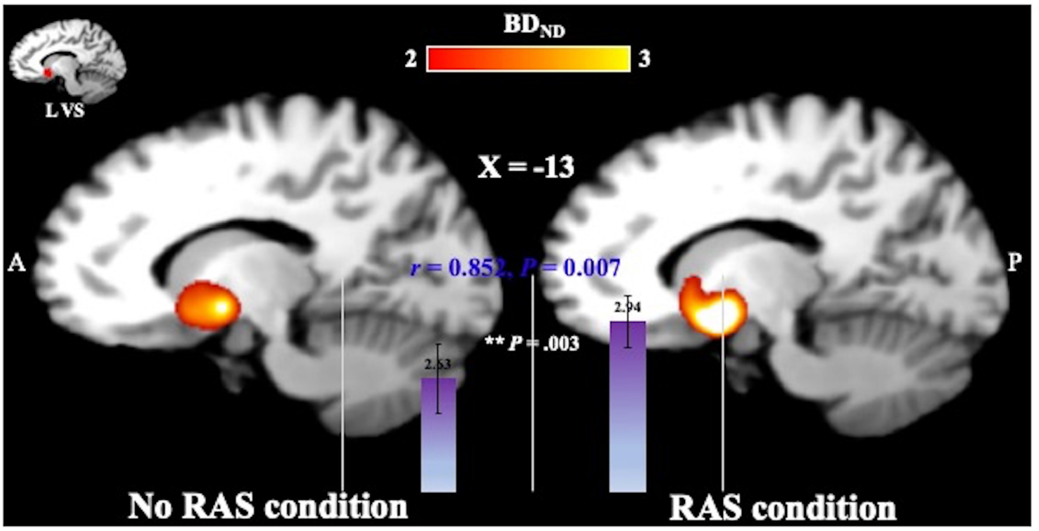

FIGURE 3 | Mean BP_{ND} images in the left ventral striatum (L VS) in MNI space for each condition generated using SPM for visualization. The ROI mask was shown in the image in the upper left corner. In the RAS condition, BP_{ND} was significantly higher compared to in the No-RAS condition, suggesting that RAS was associated with less DA responses. Error bars represent standard error of the mean.

DISCUSSION

This is the first study to investigate DA responses with [^{11}C]-(+)-PHNO PET during auditory-motor entrainment using RAS in young healthy adults. Our major findings include that the presentation of RAS significantly improved finger tapping task performance and that the presentation of RAS led to significantly reduced DA responses in the left VS. In addition, increasing

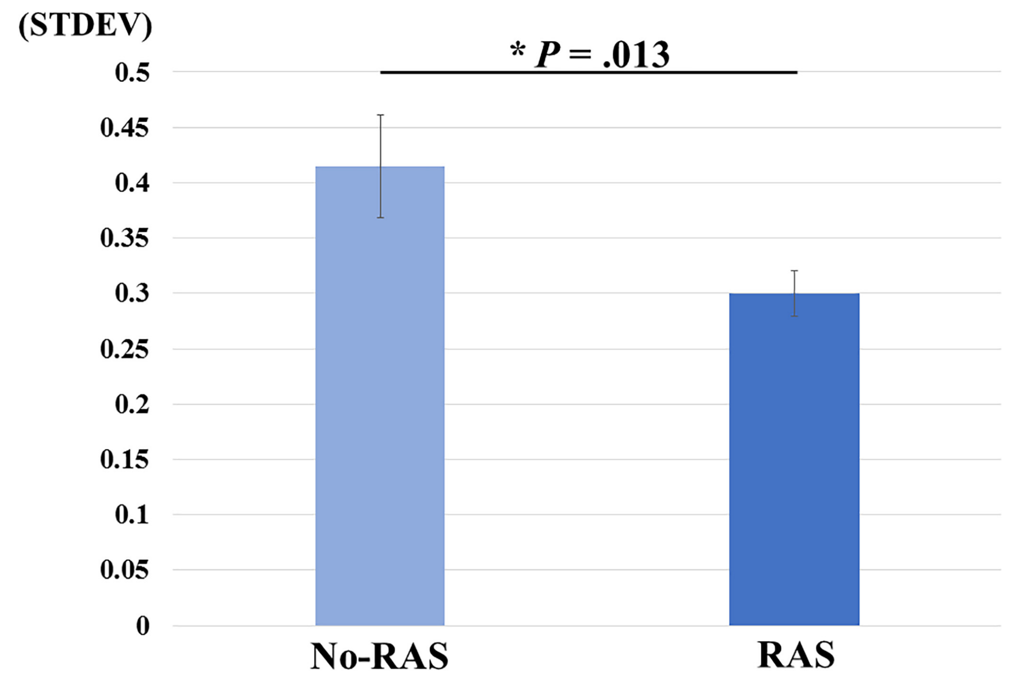

FIGURE 4 | Mean differences in BP_{ND} variability changes between No-RAS and RAS conditions across the participants and regions of interest. In the RAS condition, the variability was significantly reduced compared to in the No-RAS condition. Error bars represent standard error of the mean. STDEV: standard deviation.

age was associated with reduced D2/3 R availability in the right VS in the RAS-condition and in the left putamen in the No-RAS condition.

As we hypothesized, the presentation of RAS improved finger tapping task performance in young healthy adults as indicated by reductions of absolute tapping period error and its variability measured using the standard deviations. This is consistent with previous literature (Rao et al., 1997; Jantzen et al., 2005) and corroborated the positive effects of RAS on motor behaviors (Ghai et al., 2018). Consistent with our hypothesis, BP_{ND} values would significantly different between conditions in BG. More specifically, the absence of RAS resulted in a significantly greater DA response in the left VS. The VS is part of the mesolimbic dopamine pathway and is implicated to play an important role in reward and motivational processing (Richard et al., 2013; Berridge and Kringelbach, 2015; Saga et al., 2017). The significant finding in the left laterization in the VS may be associated with its functional connectivity with the default mode network (DMN) (Zhang et al., 2017). DMN becomes activated in the thought process in which attention is internally directed such as episodic memory retrieval and planning (Spreng, 2012). Therefore, the absence of RAS may have reflected more motivational/attentional efforts directed toward the internal control of motor timing without auditory rhythmic cueing. Contrary to our hypothesis, finger tapping performance was not associated with dopaminergic function. This may be because the motor responses are more associated with cortical motor areas or cortico-subcortical connectivity.

In addition to these major findings, less D2/3 R availability in the left putamen was associated with increasing age in the No-RAS condition. The striatal D2/3 R availability is highly age-sensitive, as demonstrated in younger healthy adults (Yang et al., 2003). Furthermore, young healthy adults who display the D2R polymorphism associated with reduced D2 R availability (Jönsson et al., 1999) showed increased striatal activation during a perceptual timing task (Wiener et al., 2014). Therefore, less D2/3 R availability in the No-RAS condition observed in our data may be an age associated compensatory response for a more challenging/effortful task condition. These suggest that individual variance in D2/3 R availability due to age and the polymorphism needs to account for in the future studies.

Increasing age was also associated with less D2/3 R availability in the right VS in the RAS condition. Music modulates brain activity in the NAc/VS (Menon and Levitin, 2005; Salimpoor et al., 2011). The right laterization may be associated with rightward processing of music (Menon and Levitin, 2005; Zatorre et al., 2007), musical pleasure (Menon and Levitin, 2005; Salimpoor et al., 2011), reward (Martin-Soelch et al., 2011), and/or emotion (Molochnikov and Cohen, 2014). It is unknown why increased age was associated with less D2/3 R availability in the right VS in the RAS condition as there is no literature to support this finding. DA changes in the mesocorticolimbic system associated with reward and motivation may partially contribute to some of the age-related motor performance (Seidler et al., 2010). Further investigations are needed including a larger number of participants as well as including self-reports on emotion and valence concerned with RAS.

The current study has shed light on the roles of DA in auditory-motor entrainment using RAS in a small sample size of young healthy adults. The initial findings warrant future studies to confirm and further elucidate the current findings with a larger sample size of younger and older healthy adults as well as persons with dopamine-based movement disorders such as PD. If RAS can modulate DA responses in PD, it is of particular interest because the dopaminergic role in the enhancement of motor control in PD with RAS is unknown. The knowledge of baseline D2/3 R availability will allow to determine whether or not the tasks induce significant DA release and will also help to interpret the significant reduction in the variability of DA responses in BG with RAS. It was interesting to find that both neural and behavioral variability measures decreased in the RAS condition although a direct correlational analysis could not be done due to the different metric calculations. A future study can address whether the presence of RAS would modulate individual DA functions to behave similarly. In addition, the knowledge of genetic variations in the D2/3 R subtypes will be of use. As a significant difference in DA response was observed in the VS that is associated with musical pleasure, reward, and motivation, the administration of associated self-reports regarding RAS may be able to further clarify the interpretations of the current findings.

AUTHOR CONTRIBUTIONS

YK, AS, S-sC, and MT conceived and designed the study. YK, MV, and VS acquired the data. YK analyzed the data. YK and MT interpreted the data. YK drafted the manuscript. AS, MV, VS, S-sC, SH, and MT critically reviewed the manuscript.

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REFERENCES

Berridge, K. C., and Kringelbach, M. L. (2015). Pleasure systems in the brain. *Neuron* 86, 646–664. doi: 10.1016/j.neuron.2015.02.018

Blood, A. J., and Zatorre, R. J. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc. Natl. Acad. Sci.* 98, 11818–11823. doi: 10.1073/pnas.191355898

Brainard, D. H. (1997). The psychophysics toolbox. *Spa.Vis.* 10, 433–436. doi: 10.1163/156856897X00357

Braunlich, K., Seger, C. A., Jentink, K. G., Bauard, I., Kuger, B. M., and Thaut, M. H. (2018). Rhythmic auditory cues shape neural network recruitment in parkinson's disease during repetitive motor behavior. *Eur. J. Neurosci.* [Epub ahead of print]. doi: 10.1111/ejn.14227,

Caravaggio, F., Fervaha, G., Browne, C. J., Gerretsen, P., Remington, G., and Graff-Guerrero, A. (2018). Reward motivation in humans and its relationship to dopamine D2/3receptor availability: A pilot study with dual [11C]-raclopride and [11C]-(+)-PHNO imaging. *J. Psychopharmacol.* 32, 357–366. doi: 10.1177/0269881118756059

Caravaggio, F., Kegeles, L. S., Wilson, A. A., Remington, G., Borlido, C., Mamo, D. C., et al. (2016). Estimating the effect of endogenous dopamine on baseline [11C]-(+)-PHNO binding in the human brain. *Synapse* 70, 453–460. doi: 10.1002/syn.21920

Caravaggio, F., Nakajima, S., Borlido, C., Remington, G., Gerretsen, P., Wilson, A., et al. (2014). Estimating endogenous dopamine levels at D 2 and D 3 receptors in humans using the agonist radiotracer 11 C-(+)-PHNO. *Neuropsychopharmacology* 39, 2769–2776. doi: 10.1038/npp.2014.125

Chen, J., Nakamura, M., Kawamura, T., Takahashi, T., and Nakahara, D. (2006). Roles of pedunculopontine tegmental cholinergic receptors in brain stimulation reward in the rat. *Psychopharmacology* 184, 514–522. doi: 10.1007/s00213-005-0252-8

Chen, J. L., Penhune, V. B., and Zatorre, R. J. (2008). Listening to musical rhythms recruits motor regions of the brain. *Cereb. Cortex* 18, 2844–2854. doi: 10.1093/cercor/bhn042

Crasta, J. E., Thaut, M. H., Anderson, C. W., Davies, P. L., and Gavin, W. J. (2018). Auditory priming improves neural synchronization in auditory-motor entrainment. *Neuropsychologia* 117, 102–112. doi: 10.1016/j.neuropsychologia.2018.05.017

Felix, R. A., Fridberger, A., Leijon, S., Berrebi, A. S., and Magnusson, A. K. (2011). Sound rhythms are encoded by postinhibitory rebound spiking in the superior paraolivary nucleus. *J. Neurosci.* 31, 12566–12578. doi: 10.1523/JNEUROSCI.2450-11.2011

Fujioka, T., Trainor, L. J., Large, E. W., and Ross, B. (2012). Internalized timing of isochronous sounds is represented in neuromagnetic beta oscillations. *J. Neurosci.* 32, 1791–1802. doi: 10.1523/JNEUROSCI.4107-11.2012

Ghai, S., Ghai, I., Schmitz, G., and Effenberg, A. O. (2018). Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. *Sci. Rep.* 8, 1–19. doi: 10.1038/s41598-017-16232-5

Grahn, J. A., and Brett, M. (2007). Rhythm and beat perception in motor areas of the brain. *J. Cogn. Neurosci.* 19, 893–906. doi: 10.1162/jocn.2007.19.5.893

Grahn, J. A., and Rowe, J. B. (2009). Feeling the beat: Premotor and striatal interactions in musicians and nonmusicians during beat perception. *J. Neurosci.* 29, 7540–7548. doi: 10.1523/JNEUROSCI.2018-08.2009

Grahn, J. A., and Rowe, J. B. (2013). Finding and feeling the musical beat: striatal dissociations between detection and prediction of regularity. *Cereb. Cortex* 23, 913–921. doi: 10.1093/cercor/bhs083

Hackett, T. A. (2015). "Anatomic organization of the auditory cortex," in *Handbook of Clinical Neurology*, eds G. G. Celesia and G. Hickok (Amsterdam: Elsevier).

Helmich, R. C., Derikx, L. C., Bakker, M., Scheeringa, R., Bloem, B. R., and Toni, L. (2010). Spatial remapping of cortico-striatal connectivity in parkinson's disease. *Cereb. Cortex.* 20, 1175–1186. doi: 10.1093/cercor/bhp178

Jäncke, L., Loose, R., Lutz, K., Specht, K., and Shah, N. J. (2000). Cortical activations during paced finger-tapping applying visual and auditory pacing stimuli. *Cogn. Brain Res.* 10, 51–66. doi: 10.1016/S0926-6410(00)00022-7

Jantzen, K. J., Steinberg, F. L., and Kelso, J. A. S. (2005). Functional MRI reveals the existence of modality and coordination-dependent timing networks. *Neuroimage* 25, 1031–1042. doi: 10.1016/j.neuroimage.2004.12.029

Jönsson, E. G., Nöthen, M. M., Grünhage, F., Farde, L., Nakashima, Y., Propping, P., et al. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol. Psychiatr.* 4, 290–296. doi: 10.1038/sj.mp.4000532

Kleiner, M., Brainard, D., Pelli, D., Ingling, A., Murray, R., and Broussard, C. (2007). What's new in psychtoolbox-3. *Perception* 36, 1–16.

Koelsch, S. (2014). Brain correlates of music-evoked emotions. *Nat. Rev. Neurosci.* 15, 170–180. doi: 10.1038/nrn3666

Konoike, N., Kotozaki, Y., Miyachi, S., Miyauchi, C. M., Yomogida, Y., Akimoto, Y., et al. (2012). Rhythm information represented in the fronto-parieto-cerebellar motor system. *Neuroimage* 63, 328–338. doi: 10.1016/j.neuroimage.2012.07.002

Koshimori, Y., and Thaut, M. (2018). Future perspectives on neural mechanisms underlying rhythm and music based neurorehabilitation in Parkinson's disease. *Ageing Res. Rev.* 47, 133–139. doi: 10.1016/j.arr.2018.07.001

Large, E. W., Fink, P., and Kelso, J. A. S. (2002). Tracking simple and complex sequences. *Psychol. Res.* 66, 3–17. doi: 10.1007/s004260100069

Lewis, P. A., Wing, A. M., Pope, P. A., Praamstra, P., and Mirall, R. C. (2004). Brain activity correlates differently with increasing temporal complexity of thythms during initialisation, synchronisation, and continuation phases of paced finger tapping. *Neuropsychologia* 42, 1301–1312. doi: 10.1016/j.neuropsychologia.2004.03.001

Martin-Soelch, C., Szczepanik, J., Nugent, A., Barhaghi, K., Rallis, D., Herscovitch, P., et al. (2011). Lateralization and gender differences in the dopaminergic response to unpredictable reward in the human ventral striatum. *Eur. J. Neurosci.* 33, 1706–1715. doi: 10.1111/j.1460-9568.2011.07642.x

Massie, C., Malcolm, M. P., Greene, D., and Thaut, M. (2009). The effects of constraint-induced therapy on kinematic outcomes and compensatory movement patterns: an exploratory study. *Arch. Phys. Med. Rehabil.* 90, 571–579. doi: 10.1016/j.apmr.2008.09.574

McIntosh, G. C., Brown, S. H., Rice, R. R., and Thaut, M. H. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with parkinson's disease. *J. Neurol. Neurosurg. Psychiatr.* 62, 22–26. doi: 10.1136/jnnp.62.1.22

Menon, V., and Levitin, D. J. (2005). The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage* 28, 175–184. doi: 10.1016/j.neuroimage.2005.05.053

Michon, J. A., and van der Valk, N. J. (1967). A dynamic model of timing behavior. *Acta Psychol.* 27, 204–212. doi: 10.1016/0001-6918(67)90061-3

Miller, N., Kwak, Y., Bohnen, N., Müller, M. L., Dayalu, P., and Seidler, R. D. (2013). The pattern of striatal dopaminergic denervation explains sensorimotor synchronization accuracy in parkinson's disease. *Behav. Brain Res.* 257, 100–110. doi: 10.1016/j.bbr.2013.09.032

Miller, R. A., Thaut, M. H., McIntosh, G. C., and Rice, R. R. (1996). Components of EMG symmetry and variability in parkinsonian and healthy elderly gait. *Electroencephalogr. Clin. Neurophysiol. Electromyogr. Mot. Control* 101, 1–7. doi: 10.1016/0013-4694(95)00209-X

Mizrahi, R., Kenk, M., Suridjan, I., Boileau, I., George, T. P., McKenzie, K., et al. (2014). Stress-induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. *Neuropsychopharmacology* 39, 1479–1489. doi: 10.1038/npp.2013.347

Molinari, M., Leggio, M. G., Filippini, V., Gioia, M. C., Cerasa, A., and Thaut, M. H. (2005). Sensorimotor transduction of time information is preserved in subjects with cerebellar damage. *Brain Res. Bull.* 67, 448–458. doi: 10.1016/j.brainresbull.2005.07.014

Molochnikov, I., and Cohen, D. (2014). Hemispheric differences in the mesostriatal dopaminergic system. *Front. Syst. Neurosci.* 8:110. doi: 10.3389/fnsys.2014.00110

Mueller, K., Fritz, T., Mildner, T., Richter, M., Schulze, K., Lepsien, J., et al. (2015). Investigating the dynamics of the brain response to music: a central role of the ventral striatum/nucleus accumbens. *Neuroimage* 116, 68–79. doi: 10.1016/j.neuroimage.2015.05.006

Narendran, R., Slifstein, M., Guillin, O., Hwang, Y., Hwang, D. R., Scher, E., et al. (2006). Dopamine (D2/3) receptor agonist positron emission tomography radiotracer [11C]-(+)-PHNO is a D3 receptor preferring agonist in vivo. *Synapse* 60, 485–495. doi: 10.1002/syn.20325

Nozaradan, S., Peretz, I., Missal, M., and Mouraux, A. (2011). Tagging the neuronal entrainment to beat and meter. *J. Neurosci.* 31, 10234–10240. doi: 10.1523/JNEUROSCI.0411-11.2011

Oldfield, R. C. (1971). The assessment and analysis of handedness: the edinburgh inventory. *Neuropsychologia* 9, 97–113. doi: 10.1016/0028-3932(71)90067-4

Paltsev, E. I., and E-lner, A. M. (1967). Change in the functional state of the segmental apparatus of the spinal cord under the influence of acoustic stimuli and its role in bringing about an arbitray movement. *Biofizika* 12, 1064–1070.

Pelli, D. G. (1997). The videotoolbox software for visual psychophysics: tranforming numbers into movies. *Spa. Vis.* 10, 437–442. doi: 10.1163/156856897X00366

Rao, S. M., Harrington, D. L., Haaland, K. Y., Bobholz, J. A., Cox, R. W., and Binder, J. R. (1997). Distributed neural systems underlying the timing of movements. *J. Neurosci.* 17, 5528–5535. doi: 10.1523/JNEUROSCI.17-14-05528.1997

Repp, B. H. (2005). Sensorimotor synchronization: a review of the tapping literature. *Psychon. Bull. Rev.* 12, 969–992. doi: 10.3758/BF03206433

Richard, J. M., Castro, D. C., DiFeliceantonio, A. G., Robinson, M. J. F., and Berridge, K. C. (2013). Mapping brain circuits of reward and motivation: In the footsteps of ann kelley. *Neurosci. Biobehav. Rev.* 37, 1919–1931. doi: 10.1016/j.neubiorev.2012.12.008

Rochester, L., Rafferty, D., Dotchin, C., Msuya, O., Minde, V., and Walker, R. W. (2010). The effect of cueing therapy on single and dual-task gait in a drug naïve population of people with parkinson's disease in northern tanzania. *Mov. Disord.* 25, 906–911. doi: 10.1002/mds.22978

Rossignol, S., and Jones, G. M. (1976). Audio-spinal influence in man studied by the H-reflex and its possible role on rhythmic movements synchronized to sound. *Electroencephalogr. Clin. Neurophysiol.* 41, 83–92. doi: 10.1016/0013-4694(76)90217-0

Rusjan, P., Mamo, D., Ginovart, N., Hussey, D., Vitcu, I., Yasuno, F., et al. (2006). An automated method for the extraction of regional data from PET images. *Psychiatr. Res. Neuroimag.* 147, 79–89. doi: 10.1016/j.pscychresns.2006.01.011

Saga, Y., Hoshi, E., and Tremblay, L. (2017). Roles of multiple globus pallidus territories of monkeys and humans in motivation, cognition and action: an anatomical, physiological and pathophysiological review. *Front. Neuroanat.* 11:30. doi: 10.3389/fnana.2017.00030

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., and Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat. Neurosci.* 14, 257–262. doi: 10.1038/nn.2726

Salimpoor, V. N., van den Bosch, I., Kovacevic, N., McIntosh, A. R., and Dagher, A. Z. R. (2013). Interactions between the nucleus accumbens and auditory cortices predict music reward value. *Science* 340, 216–219. doi: 10.1126/science.1231059

Schmahmann, J., and Pandya, D. (2006). *Fiber Pathways of the Brain*. Oxford: Oxford University Press. doi: 10.1093/acprof:oso/9780195104233.001.0001

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., et al. (2010). Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci. Biobehav. Rev.* 34, 721–733. doi: 10.1016/j.neurobiorev.2009.10.005

Shelton, J., and Kumar, G. P. (2010). Comparison between auditory and visual simple reaction times. *Neurosci. Med.* 01, 30–32. doi: 10.4236/nm.2010.11004

Spreng, N. R. (2012). The fallacy of a "task-negative" network. *Front. Psychol.* 3:145. doi: 10.3389/fpsyg.2012.00145

Stephan, K. M., Thaut, M. H., Wunderlich, G., Schicks, W., Tian, B., Tellmann, L., et al. (2002). Conscious and subconscious sensorimotor synchronization–prefrontal cortex and the influence of awareness. *Neuroimage* 15, 345–352. doi: 10.1006/nimg.2001.0929

Teghil, A., Boccia, M., D'Antonio, F., Di Vita, A., de Lena, C., and Guariglia, C. (2018). Neural substrates of internally-based and externally-cued timging: an activation likelihood estimation (ALE) meta-analysis of fMRI studies. *Neurosci. Biobehav. Rev.* 96, 197–209. doi: 10.1016/j.neubiorev.2018.10.003

Thaut, M. (2003). Neural basis of rhythmic timing networks in the human brain. *Ann. N. Y. Acad. Sci.* 999, 364–373. doi: 10.1196/annals.1284.044

Thaut, M. H. (2015). The discovery of human auditory-motor entrainment and its role in the development of neurologic music therapy. *Prog. Brain Res.* 217, 253–266. doi: 10.1016/bs.pbr.2014.11.030

Thaut, M. H., Demartin, M., and Sanes, J. N. (2008). Brain networks for integrative rhythm formation. *PloS One* 3:e2312. doi: 10.1371/journal.pone.0002312

Thaut, M. H., and Kenyon, G. P. (2003). Rapid motor adaptations to subliminal frequency shifts during syncopated rhythmic sensorimotor synchronization. *Hum. Mov. Sci.* 22, 321–338. doi: 10.1016/S0167-9457(03)00048-4

Thaut, M. H., Kenyon, G. P., Hurt, C. P., McIntosh, G. C., and Hoemberg, V. (2002). Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. *Neuropsychologia* 40, 1073–1081. doi: 10.1016/S0028-3932(01)00141-145

Thaut, M. H., McIntosh, G. C., and Rice, R. R. (1997). Rhthmic facilitation of gait training in hemiparetic stroke rehabilitation. *J. Neurol. Sci.* 151, 207–212. doi: 10.1016/S0022-510X(97)00146-9

Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., and Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for parkinson's disease patients. *Mov. Disord.* 11, 193–200. doi: 10.1002/mds.870110213

Thaut, M. H., Miller, R. A., and Schauer, L. M. (1998a). Multiple synchronization strategies in rhythmic sensorimotor tasks: phase vs period correction. *Biol. Cybern.* 79, 241–250. doi: 10.1007/s004220050474

Thaut, M. H., Tian, B., and Azimi-Sadjadi, M. R. (1998b). Rhythmic finger tapping to cosine-wave modulated metronome sequences: evidence of subliminal entrainment. *Hum. Mov. Sci.* 17, 839–863. doi: 10.1016/S0167-9457(98)00031-31

Thaut, M. H., Stephan, K. M., Wunderlich, G., Schicks, W., Tellmann, L., Herzog, H., et al. (2009). Distinct cortico-cerebellar activations in rhythmic auditory motor synchronization. *Cortex* 45, 44–53. doi: 10.1016/j.cortex.2007.09.009

Toyomura, A., Shibata, M., and Kuriki, S. (2012). Self-paced and externally triggered rhythmical lower limb movements: a functional MRI study. *Neurosci. Lett.* 516, 39–44. doi: 10.1016/j.neulet.2012.03.049

Wessel, K., Zeffiro, T., Toro, C., and Hallett, M. (1997). Self-paced versus metronome-paced finger movements. *J. Neuroimaging* 7, 145–151. doi: 10.1111/jon199773145

Wiener, M., Lee, Y. S., Lohoff, F. W., and Coslett, H. B. (2014). Individual differences in the morphometry and activation of time perception networks are influenced by dopamine genotype. *Neuroimage* 89, 10–22. doi: 10.1016/j.neuroimage.2013.11.019

Willeit, M., Ginovart, N., Kapur, S., Houle, S., Hussey, D., Seeman, P., et al. (2006). High-affinity states of human brain dopamine D2/3 receptors imaged by the agonist [11C]-(+)-PHNO. *Biol. Psychiatr.* 59, 389–394. doi: 10.1016/j.biopsych.2005.09.017

Wilson, A. A., McCormick, P., Kapur, S., Willeit, M., Garcia, A., Hussey, D., et al. (2005). Radiosynthesis and evaluation of [11C]-(+)-4-propyl-3,4,4a,5,6, 10b-hexahydro-2H-naphtho[1,2-b][1,4]oxazin-9-ol as a potential radiotracer for in vivo imaging of the dopamine D2 high-affinity state with positron emission tomography. *J. Med. Chem.* 48, 4153–4160. doi: 10.1021/jm050155n

Yang, Y. K., Chiu, N. T., Chen, C. C., Chen, M., Yeh, T., and Lee, I. H. (2003). Correlation between fine motor activity and striatal dopamine D2 receptor density in patients with schizophrenia and healthy controls. *Psychiatr. Res. Neuroimag.* 123, 191–197. doi: 10.1016/S0925-4927(03)00066-0

Zatorre, R. J., Chen, J. L., and Penhune, V. B. (2007). When the brain plays music: auditory–motor interactions in music perception and production. *Nat. Rev. Neurosci.* 8, 547–558. doi: 10.1038/nrn2152

Zhang, S., Hu, S., Chao, H. H., and Li, C. R. (2017). Hemispheric lateralization of resting-state functional connectivity of the ventral striatum: an exploratory study. *Brain Struct. Funct.* 222, 2573–2583. doi: 10.1007/s00429-016-1358-y

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Preliminary Neurophysiological Evidence of Altered Cortical Activity and Connectivity With Neurologic Music Therapy in Parkinson's Disease

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Neurologic Music Therapy (NMT) is a novel impairment-focused behavioral intervention system whose techniques are based on the clinical neuroscience of music perception, cognition, and production. Auditory Stimulation (RAS) is one of the NMT techniques, which aims to develop and maintain a physiological rhythmic motor activity through rhythmic auditory cues. In a series of breakthrough studies beginning in the mid-nineties, we discovered that RAS durably improves gait velocity, stride length, and cadence in Parkinson's disease (PD). No study to date reports the neurophysiological evidence of auditory-motor frequency entrainment after a NMT intervention in the Parkinson's community. We hypothesized that NMT-related motor improvements in PD are due to entrainment-related coupling between auditory and motor activity resulting from an increased functional communication between the auditory and the motor cortices. Spectral analysis in the primary motor and auditory cortices during a cued finger tapping task showed a simultaneous increase in evoked power in the beta-range along with an increased functional connectivity after a course of NMT in a small sample of three older adults with PD. This case study provides preliminary evidence that NMT-based motor rehabilitation may enhance cortical activation in the auditory and motor areas in a synergic manner. With a lack of both control subjects and control conditions, this neuroimaging case-proof of concept series of visible changes suggests potential mechanisms and offers further education on the clinical applications of musical interventions for motor impairments.

Keywords: auditory-motor, entrainment, therapy, fine motor, rehabilitation

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BACKGROUND

Neurologic Music Therapy (NMT) is a novel impairment-focused behavioral intervention system whose techniques are based on the clinical neuroscience of music perception, cognition, and production (Thaut, 2014). One of the perceptual and neural mechanisms underlying NMT applications is "rhythmic entrainment" where one system's motion or signal frequency entrains the frequency of another system. In the brain, firing rates of auditory neurons, triggered by auditory rhythms and music, entrain the firing patterns of motor neurons, thus driving the motor system into different frequency levels (Thaut, 2015). Rhythmic Auditory Stimulation (RAS) is one of the NMT techniques, which aims to develop and maintain a physiological rhythmic motor activity through rhythmic auditory cues. Psychophysics studies show auditory cues function as a timekeeper entraining the motor response into a very rapid and temporally precise state of synchronization to the rhythmic cue frequency (Thaut et al., 1999). In cortical sensory areas, auditory-evoked oscillatory rhythms in the beta (15–30 Hz) and gamma (40–80 Hz) frequency range are direct measures of rhythm perception and possibly reflect auditory-motor interactions (Snyder and Large, 2005; Fujioka et al., 2009). Therefore, they are useful to investigating the entrainment-related coupling between auditory and motor activity. Beta oscillations have been holding a crucial role in directional auditory-to-motor coupling during piano playing of non-PD professional pianists (Jäncke, 2012).

Parkinson's disease (PD) is a neurodegenerative illness defined by characteristic motor symptoms including slow and small movements as well as difficulty with movement initiation and disruptions in timing. Several explanations for the underlying pathophysiology include beta and gamma impairments in subcortical structures such as the basal ganglia (BG) (Doyle et al., 2005) as well as in the cortical motor areas (Heinrichs-Graham et al., 2014; Stegemöller et al., 2016). Deep brain stimulation or dopamine replacement therapy restore normal BG beta oscillations (Jenkinson and Brown, 2011) as well as cortical motor networks dynamic (Michely et al., 2015). This suggests that interventions targeting motor symptoms have the ability to influence oscillatory rhythms in the brain or vice-versa.

In a series of breakthrough studies beginning in the mid-nineties we have discovered that auditory rhythmic cues durably improve gait velocity, stride length, and cadence in PD (Thaut et al., 1996; McIntosh et al., 1997). RAS is now recognized as state of the art for mobility treatment for PD (Hove and Keller, 2015), and may occur via a shift from basal ganglia-thalamocortical to other pathways involving possibly the cerebellum (Cunnington et al., 2001; Debaere et al., 2003) or through an effective cognitive strategy (Manly et al., 2004; Rochester et al., 2007) although recent studies suggest that auditory-motor entrainment may be compromised in PD (Praamstra and Pope, 2007; Grahn and Brett, 2009; te Woerd et al., 2014, 2015). In healthy controls, auditory-motor entrainment (Thaut et al., 2014) relies on diverse brain areas such as the auditory cortex, the inferior parietal lobule, and frontal areas such as the supplementary motor area (SMA) and premotor cortex (PMC) (Todd and Lee, 2015). Interestingly, those regions appear to be unaffected by PD pathophysiology. Therefore, it may be possible to use NMT methodology to strengthen the aforementioned networks as a compensatory mechanism to improve motor function in PD.

We know that (1) auditory rhythm very rapidly creates stable internal reference intervals to guide the timing of motor responses and that (2) the dominant synchronization strategy is based on frequency entrainment. Entrainment of distant brain regions most likely relies on synchronization at specific frequencies that can be recorded via whole brain neuroimaging modalities such as magnetoencephalography (MEG).

No study to date reports the neurophysiological evidence of auditory-motor frequency entrainment after a NMT intervention in the Parkinson's community. We wanted to share a neuroimaging case-proof of concept series of visible changes that suggest potential mechanisms and provide further education on the clinical applications of musical interventions for motor impairments. We hypothesized that NMT-related motor improvements in PD are due to entrainment-related coupling between auditory and motor activity resulting from an increased functional connectivity between the auditory cortex and the motor cortex.

METHODS

Three right-handed PD participants were recruited from the University of Colorado Hospital Movement Disorders clinic and signed informed consents to participate in the study approved by the Colorado Multiple Institution Review Board. Inclusion criteria included a diagnosis of probable PD according to the UK Brain Bank Criteria (Hughes et al., 1992). All study visits were performed in the PD subjects' best dopaminergic "On" state. Participants' characteristics can be found in the **Supplementary Table 1**.

Neurologic Music Therapy Intervention

Fifteen sessions of somatosensory-related NMT techniques were administered 3 times per week for 5 consecutive weeks by one of the NMT-certified music therapists from Rehabilitative Rhythms, Aurora, CO. Each session consisted on bimanual exercises using a keyboard, castanets and miscellaneous objects to strengthen fine motor muscles. Each finger movement was cued by either a metronome or beats produced by the therapist playing a musical instrument.

Motor Assessments

Fine motor-related changes were assessed and quantified before and after NMT within 2 days from the first and last NMT session. We chose three different assessments to cover overall motor function, fine motor coordination and bradykinesia as well as PD-specific dexterity in order to capture the expected benefits on those symptoms:

1. The Unified Parkinson's Disease Rating Scale (UPDRS, Fahn et al., 1987) Section 3 (Motor Examination). The UPDRS is an overall marker for Parkinson's disease progression, symptoms severity and a validated measure of treatment-related benefits.
2. The Grooved Pegboard Test, which is a manipulative dexterity test consisting of 25 holes with randomly positioned slots (Trites, 1989) commonly used as a test of fine motor performance (Bryden and Roy, 2005) and general slowing due to medication or disease progression. In PD, the GPT has also been used extensively as a motor outcome of clinical trials (Haas et al., 2006).
3. The Finger-Thumb Opposition Task is one item from the Neurological Evaluation Scale (Buchanan and Heinrichs, 1989), which assesses different sensory and motor functions. Participants were asked to perform bilateral finger-thumb

appositions during a 2-min lag to quantify fine motor coordination and bradykinesia.

Magnetoencephalography Data Acquisition, Preprocessing, and Coregistration With Structural MRI

Neuromagnetic data was acquired using a Magnes 3,600 whole head MEG device with an array of 248 sensors (4D Neuroimaging, San Diego, CA) in a magnetically shielded room (ETS-Lindgren, Cedar Park, TX, USA). Participants were asked to tap with their right index finger with an acoustic burst stimuli (30 ms duration at 2,000 Hz, intensity of 70 dB above subjective threshold) delivered in their right ear every second. A quick practice session was performed prior to the MEG recording session. A total of 6 sequences of 30 s separated by a 5-s rest period were presented. Data was acquired continuously at 678 Hz with an acquisition bandwidth of 0.1–200 Hz. Scalp shape and location was determined with a 3-D digitizer to allow for comparison across subjects in a common coordinate system and for co-localization with an averaged MRI brain atlas. Data was divided into 800 ms epochs. Preprocessing included 3–70 Hz band pass filtering, noise reduction, and rejection of epochs with significant artifact. Independent component analysis was used to remove eye blink and other common artifacts (Jung et al., 2000). Epochs were baseline corrected using 800 ms baseline epochs that were extracted within the inter-block trials rest periods to prevent contamination with extended motor signals. A mean of 229 ± 18 (before NMT) and 215 ± 49 (after) epochs were subjected to further analysis. Participants' response occurred on average between 31.6 ms before (anticipatory response) and 123.7 ms after the stimulus. Stimulus-locked spectral analysis was performed over a 0–400 ms time period (0 being tone onset) in order to fully capture entrainment-related coupling between auditory and motor activity. Each participant's MEG data were co-registered with structural T1-weighted magnetic resonance imaging (MRI, **Supplementary Materials**) data prior to source space analyses using common landmarks from the MEG digitization procedure and MRI scan data via SPM12 software (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) (Friston, 2007).

MEG Source Analysis and Source Space Statistics

Source analysis was performed in Matlab (2010b; MathWorks, Inc., Natick, MA, USA) using the SPM12 toolbox. Following co-registration of the MEG fiducials with each participant's MRI, leadfields were computed using a single shell volume conductor model. Source localization was then performed using a cortically constrained group minimum norm inversion with multiple sparse priors (Litvak et al., 2011), on all subjects' data pooled together from the three participants, which resulted in common source space images across subjects. The cortical surface used was a standard MNI space surface with 20,484 vertices supplied within SPM12. Source analysis was performed on the 15–80 Hz passband between 0 and 400 ms. Source space images were submitted to GLM-based statistical analysis using a one-sample t-test across all subjects to confirm the involvement of auditory and motor cortices as well to extract peak MNI coordinates in areas that survived multiple comparison correction, using a family wise error (FWE) of $p < 0.05$.

Source Waveforms, Spectral Analyses, and Functional Connectivity

Regional time-courses were created via source-space projection (Tesche et al., 1995) from dipoles within both regions of interest: left auditory and primary motor cortices. Using the peak MNI coordinates obtained in the previous step (left auditory: −52 −35 15, left motor: −7 −25 73), the lead field and its pseudoinverse were computed and the following current source waveform (Ross et al., 2000) was created. Time-frequency transformations were then obtained using a Morlet wavelet decomposition with wave number linearly increasing from 3 to 12 across the frequency range of 15–80 Hz, on the epochs from 0 to 400 ms. Evoked power relative to the rest period baseline was calculated and averaged across subjects. In order to evaluate directional functional connectivity between our regions of interest in the frequency domain, we computed frequency domain coherence using the Fieldtrip connectivity analysis functions (Oostenveld et al., 2011), which first involved an autoregressive model fit to the data using the bsmart matlab toolbox (Cui et al., 2008). For these analyses, we downsampled the data to 250 Hz for better model order estimation and submit the data to detrenting, differencing, and pre-whitening. Then, we estimated the model order to be 16 using ARfit toolbox for Matlab (Schneider and Neumaier, 2001).

RESULTS AND DISCUSSION

Five weeks of NMT had beneficial effects on fine motor function in our cohort of three patients with PD (**Supplementary Figure 1**). PD-specific overall motor assessments showed clinically significant improvements after NMT (A). Score improvements were more mitigated for the Grooved Pegboard test, for which the dominant hand from two out of three subjects exhibited higher proficiency at picking and placing the pegs into their designated holes (B). Lastly, finger-thumb opposition test scores were greatly improved after NMT sessions, here again for two out of three participants, regardless of the hand tested (C). While fine motor assessments did not show consistent improvements among all participants, each one benefited in one or more areas of fine motor function, including the dominant hand or both hands. Interestingly, we found that finger tapping before the cue (anticipatory response) during the MEG recording occurred 73.72% before NMT whereas after NMT 90.31% of the trials were anticipatory, suggesting that NMT may enhance anticipatory motor behavior. These results are in agreement with other behavioral interventions in the PD community (Alves Da Rocha et al., 2015). In addition, this extends the benefits of NMT from gross motor to fine motor skills.

Spectral analysis in the primary motor and auditory cortices during a cued finger tapping task showed a possible coinciding

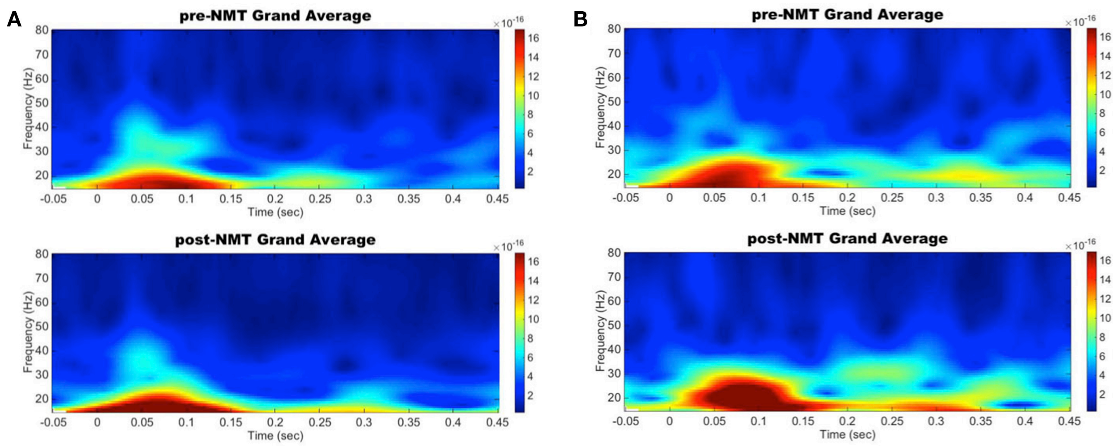

FIGURE 1 | Left primary auditory and motor areas evoked power time-frequency results. Grand average evoked power in the beta range increased simultaneously in the auditory **(A)** and motor **(B)** cortices between pre-NMT (top) and post-NMT (bottom) during a cued right hand finger tapping.

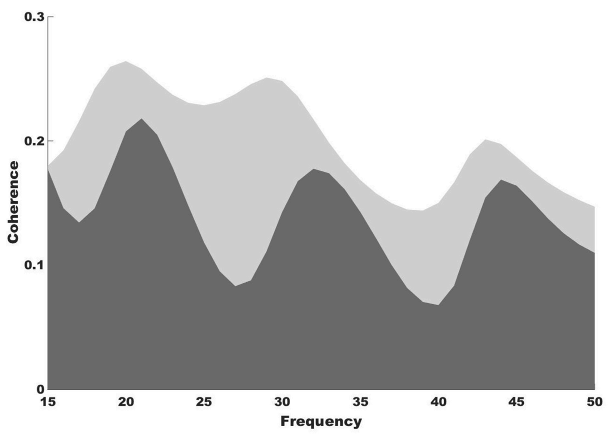

FIGURE 2 | Coherence results. Coherence spectra show increased functional connectivity between the auditory and motor cortices after (light gray shade) compared to before NMT (dark gray shade).

increase in evoked power in the beta-range suggesting an activity coupling in those two areas most likely due to their simultaneous activation (**Figure 1**). While this case report lacks a control group and statistical analysis, we demonstrate here NMT-related changes in cortical beta activity, an oscillation that is definitely challenged in PD. Other interventions, especially physical therapies, have been shown to modify sensorimotor alpha and beta rhythms (Mierau et al., 2009). Our results therefore suggest that musical interventions may also hold potential to influence cortical activity. Regardless of the specific pathways underlying this phenomenon, it appears that information related to the beat is simultaneously perceived by the auditory and the motor cortices, both regions we postulated would be more highly connected after NMT training.

Stronger functional connectivity between the auditory and motor cortices was observed after NMT (**Figure 2**). It is highly possible that the NMT-related increased connectivity between the auditory and motor cortices explains the simultaneous beta power increase in auditory and motor areas. Increased auditory-motor functional connectivity is indeed observed during synchronization to rhythm (Chen et al., 2006), which suggests a relationship between brain connectivity and rhythmic entrainment. While beat perception has been attributed to the putamen, the outermost portion of the BG, it is possible that NMT uses alternative relays to drive impaired areas via intact ones in PD. The use of brain imaging techniques with subcortical resolution will help investigating this idea.

CONCLUSION

This case study provides very preliminary evidence that NMT-based motor rehabilitation may enhance cortical activation in the auditory and motor areas in a synergic manner. Our connectivity findings and the existing literature both suggest that auditory-motor connections may be improved and strengthened by training, even in the PD population. With a lack of both control subjects and control conditions, future controlled trials are warranted to further explore the effects of NMT therapy in those vulnerable patients, especially looking at symptom-specific groups given the heterogeneity of the motor symptoms found in patients with PD.

AUTHOR CONTRIBUTIONS

IB and MT: conceived and designed the experiments; IB: performed the experiments; IB and WD: analyzed the data; IB wrote the paper; IB, WD, MT, and BK: reviewed and revised the manuscript and approved the final manuscript as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.00105/full#supplementary-material

Supplementary Figure 1 | Fine motor assessments scores for both dominant and non-dominant hands before (pre) and after (post) a 5-week session of Neurologic Music Therapy. **(A)** Overall motor score, section 3 of the UPDRS; **(B)** Time to complete the pegboard, as part of the GPT (Grooved Pegboard Test); **(C)** Number of finger-to-thumb oppositions, as part of the NES (Neurological Evaluation Scale).

Supplementary Table 1 | Participants' demographics and baseline characteristics. UPDRS, Unified Parkinson's disease rating scale, an overall marker for Parkinson's disease progression and symptoms severity.

REFERENCES

Alves Da Rocha, P., McClelland, J., and Morris, M. E. (2015). Complementary physical therapies for movement disorders in parkinson's disease: a systematic review. *Eur. J. Phys. Rehabil. Med.* 51, 693–704.

Bryden, P. J., and Roy, E. A. (2005). A new method of administering the grooved pegboard test: performance as a function of handedness and sex. *Brain Cogn.* 58, 258–268. doi: 10.1016/j.bandc.2004.12.004‘

Buchanan, R. W., and Heinrichs, D. W. (1989). The neurological evaluation scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res.* 27, 335–350. doi: 10.1016/0165-1781(89)90148-0

Chen, J. L., Zatorre, R. J., and Penhune, V. B. (2006). Interactions between auditory and dorsal premotor cortex during synchronization to musical rhythms. *Neuroimage* 32, 1771–1781. doi: 10.1016/j.neuroimage.2006.04.207

Cui, J., Xu, L., Bressler, S. L., Ding, M., and Liang, H. (2008). BSMART: a matlab/C toolbox for analysis of multichannel neural time series. *Neural Netw.* 21, 1094–1104. doi: 10.1016/j.neunet.2008.05.007

Cunnington, R., Lalouschek, W., Dirnberger, G., Walla, P., Lindinger, G., Asenbaum, S., et al. (2001). A medial to lateral shift in pre-movement cortical activity in hemi-parkinson's disease. *Clin. Neurophysiol.* 112, 608–618. doi: 10.1016/S1388-2457(01)00467-9

Debaere, F., Wenderoth, N., Sunaert, S., Van Hecke, P., and Swinnen, S. P. (2003). Internal vs. external generation of movements: differential neural pathways involved in bimanual coordination performed in the presence or absence of augmented visual feedback. *Neuroimage* 19, 764–776. doi: 10.1016/S1053-8119(03)00148-4

Doyle, L. M., Kühn, A. A., Hariz, M., Kupsch, A., Schneider, G. H., and Brown, P. (2005). Levodopa-induced modulation of subthalamic beta oscillations during self-paced movements in patients with parkinson's disease. *Eur. J. Neurosci.* 21, 1403–1412. doi: 10.1111/j.1460-9568.2005.03969.x

Fahn, S. M. C.,Calne, D. B., and Goldstein M. (1987). *Unified Parkinson Disease Rating Scale. Recent developments in Parkinson's Disease*. New York, NY: Macmillan 2, 153–163.

Friston, K. J. (2007). *Statistical parametric mapping: the analysis of funtional brain images, 1st Edn*. Amsterdam; Boston: Elsevier/Academic Press. doi: 10.1016/B978-012372560-8/50002-4

Fujioka, T., Trainor, L. J., Large, E. W., and Ross, B. (2009). Beta and gamma rhythms in human auditory cortex during musical beat processing. *Ann. N. Y. Acad. Sci.* 1169, 89–92. doi: 10.1111/j.1749-6632.2009.04779.x

Grahn, J. A., and Brett, M. (2009). Impairment of beat-based rhythm discrimination in parkinson's disease. *Cortex* 45, 54–61. doi: 10.1016/j.cortex.2008.01.005

Haas, C. T., Turbanski, S., Kessler, K., and Schmidtbleicher, D. (2006). The effects of random whole-body-vibration on motor symptoms in parkinson's disease. *NeuroRehabilitation* 21, 29–36. doi: 10.1007/3-540-36741-1_8

Heinrichs-Graham, E., Wilson, T. W., Santamaria, P. M., Heithoff, S. K., Torres-Russotto, D., Hutter-Saunders, J. A., et al. (2014). Neuromagnetic evidence of abnormal movement-related beta desynchronization in parkinson's disease. *Cereb. Cortex* 24, 2669–2678. doi: 10.1093/cercor/bht121

Hove, M. J., and Keller, P. E. (2015). Impaired movement timing in neurological disorders: rehabilitation and treatment strategies. *Ann. N. Y. Acad. Sci.* 1337, 111–117. doi: 10.1111/nyas.12615

Hughes, A. J., Daniel, S. E., Kilford, L., and Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatr.* 55, 181–184. doi: 10.1136/jnnp.55.3.181

Jäncke, L. (2012). The dynamic audio-motor system in pianists. *Ann. N. Y. Acad. Sci.* 1252, 246–252. doi: 10.1111/j.1749-6632.2011.06416.x

Jenkinson, N., and Brown, P. (2011). New insights into the relationship between dopamine, beta oscillations and motor function. *Trends Neurosci.* 34, 611–618. doi: 10.1016/j.tins.2011.09.003

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., et al. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology* 37, 163–178. doi: 10.1111/1469-8986.3720163

Litvak, V., Mattout, J., Kiebel, S., Phillips, C., Henson, R., Kilner, J., et al. (2011). EEG and MEG data analysis in SPM8. *Comput. Intell. Neurosci.* 201:852961. doi: 10.1155/2011/852961

Manly, T., H. J., Davidson, B., Gaynord, B., Greenfield, E., Parr, A., et al. (2004). An electronic knot in the handkerchief: "Content free cueing" and the maintenance of attentive control. *Neuropsychol. Rehabil.* 14, 89–116. doi: 10.1080/09602010343000110

McIntosh, G. C., Brown, S. H., Rice, R. R., and Thaut, M. H. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with parkinson's disease. *J. Neurol. Neurosurg. Psychiatr.* 62, 22–26. doi: 10.1136/jnnp.62.1.22

Michely, J., Volz, L. J., Barbe, M. T., Hoffstaedter, F., Viswanathan, S., Timmermann, L., et al. (2015). Dopaminergic modulation of motor network dynamics in parkinson's disease. *Brain* 138, 664–678. doi: 10.1093/brain/awu381

Mierau, A., Schneider, S., Abel, T., Askew, C., Werner, S., and Strüder, H. K. (2009). Improved sensorimotor adaptation after exhaustive exercise is accompanied by altered brain activity. *Physiol. Behav.* 96, 115–121. doi: 10.1016/j.physbeh.2008.09.002

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J. M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput. Intell. Neurosci.* 2011:156869. doi: 10.1155/2011/156869

Praamstra, P., and Pope, P. (2007). Slow brain potential and oscillatory EEG manifestations of impaired temporal preparation in parkinson's disease. *J. Neurophysiol.* 98, 2848–2857. doi: 10.1152/jn.00224.2007

Rochester, L., Nieuwboer, A., Baker, K., Hetherington, V., Willems, A. M., Chavret, F., et al. (2007). The attentional cost of external rhythmical cues and their impact on gait in parkinson's disease: effect of cue modality and task complexity. *J. Neural Transm.* 114, 1243–1248. doi: 10.1007/s00702-007-0756-y

Ross, B., Borgmann, C., Draganova, R., Roberts, L. E., and Pantev, C. (2000). A high-precision magnetoencephalographic study of human auditory steady-state responses to amplitude-modulated tones. *J. Acoust. Soc. Am.* 108, 679–691. doi: 10.1121/1.429600

Schneider, T., and Neumaier, A. (2001). Algorithm 808: ARfit - A matlab package for the estimation of parameters and eigenmodes of multivariate autoregressive models. *ACM Trans. Math. Softw.* 27, 58–65. doi: 10.1145/382043.382316

Snyder, J. S., and Large, E. W. (2005). Gamma-band activity reflects the metric structure of rhythmic tone sequences. *Brain Res. Cogn. Brain Res.* 24, 117–126. doi: 10.1016/j.cogbrainres.2004.12.014

Stegemöller, E. L., Allen, D. P., Simuni, T., and MacKinnon, C. D. (2016). Motor cortical oscillations are abnormally suppressed during repetitive movement in patients with parkinson's disease. *Clin. Neurophysiol.* 127, 664–674. doi: 10.1016/j.clinph.2015.05.014

te Woerd, E. S., Oostenveld, R., Bloem, B. R., de Lange, F. P., and Praamstra, P. (2015). Effects of rhythmic stimulus presentation on oscillatory brain activity: the physiology of cueing in parkinson's disease. *Neuroimage Clin.* 9, 300–309. doi: 10.1016/j.nicl.2015.08.018

te Woerd, E. S., Oostenveld, R., de Lange, F. P., and Praamstra, P. (2014). A shift from prospective to reactive modulation of beta-band oscillations in parkinson's disease. *Neuroimage* 100, 507–519. doi: 10.1016/j.neuroimage.2014.06.039

Tesche, C. D., Uusitalo, M. A., Ilmoniemi, R. J., Huotilainen, M., Kajola, M., and Salonen, O. (1995). Signal-space projections of MEG data characterize both distributed and well-localized neuronal sources. *Electroencephalogr. Clin. Neurophysiol.* 95, 189–200. doi: 10.1016/0013-4694(95)00064-6

Thaut, M. H. (2015). The discovery of human auditory-motor entrainment and its role in the development of neurologic music therapy. *Prog. Brain Res.* 217, 253–266. doi: 10.1016/bs.pbr.2014.11.030

Thaut, M. H., Kenyon, G. P., Schauer, M. L., and McIntosh, G. C. (1999). The connection between rhythmicity and brain function. *IEEE Eng. Med. Biol. Mag.* 18, 101–108. doi: 10.1109/51.752991

Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., and Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for parkinson's disease patients. *Mov. Disord.* 11, 193–200. doi: 10.1002/mds.870110213

Thaut, M. H., Trimarchi, P. D., and Parsons, L. M. (2014). Human brain basis of musical rhythm perception: common and distinct neural substrates for meter, tempo, and pattern. *Brain Sci.* 4, 428–452. doi: 10.3390/brainsci4020428

Thaut, M. H. V. (2014). *Oxford Handbook of Neurologic Music Therapy*. New York, NY: Oxford University Press.

Todd, N. P., and Lee, C. S. (2015). The sensory-motor theory of rhythm and beat induction 20 years on: a new synthesis and future perspectives. *Front. Hum. Neurosci.* 9:444. doi: 10.3389/fnhum.2015.00444

Trites, R. (1989). *Grooved Pegboard Test.* Lafayette, IN: Lafayette Instruments.

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Music and Visual Art Training Modulate Brain Activity in Older Adults

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Cognitive decline is an unavoidable aspect of aging that impacts important behavioral and cognitive skills. Training programs can improve cognition, yet precise characterization of the psychological and neural underpinnings supporting different training programs is lacking. Here, we assessed the effect and maintenance (3-month follow-up) of 3-month music and visual art training programs on neuroelectric brain activity in older adults using a partially randomized intervention design. During the pre-, post-, and follow-up test sessions, participants completed a brief neuropsychological assessment. High-density EEG was measured while participants were presented with auditory oddball paradigms (piano tones, vowels) and during a visual GoNoGo task. Neither training program significantly impacted psychometric measures, compared to a non-active control group. However, participants enrolled in the music and visual art training programs showed enhancement of auditory evoked responses to piano tones that persisted for up to 3 months after training ended, suggesting robust and long-lasting neuroplastic effects. Both music and visual art training also modulated visual processing during the GoNoGo task, although these training effects were relatively short-lived and disappeared by the 3-month follow-up. Notably, participants enrolled in the visual art training showed greater changes in visual evoked response (i.e., N1 wave) amplitude distribution than those from the music or control group. Conversely, those enrolled in music showed greater response associated with inhibitory control over the right frontal scalp areas than those in the visual art group. Our findings reveal a causal relationship between art training (music and visual art) and neuroplastic changes in sensory systems, with some of the neuroplastic changes being specific to the training regimen.

Keywords: aging, music training, art training, brain plasticity, executive functions, ERPs

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INTRODUCTION

Aging is associated with structural and functional changes in prefrontal, parietal, and medial temporal regions, which has been linked to enhanced sensory evoked responses in auditory and visual areas as well as deficits in attention, memory and executive functions (Dempster, 1992; Alain and Woods, 1999; West and Alain, 2000; Bugaiska et al., 2007; Kropotov et al., 2016; Aljondi et al., 2018). Some theories emphasize age-related declines in inhibitory processes

(Hasher and Zacks, 1988; Knight, 1994; West, 1996), which involve the ability to regulate incoming sensory input and behavior so as to override internal predispositions or external lures to accomplish more appropriate actions or behaviors (Diamond, 2013). Age-related declines in attentional regulation and inhibitory control (May et al., 1999; Erber, 2013) result in negative consequences for perceptual and cognitive skills (Gazzaley et al., 2007; Lustig et al., 2007), which may be reflected in the overall responsiveness (amplitude) of sensory evoked responses (Bidelman et al., 2017). Age-related declines in inhibitory control may also be associated with impairments in language comprehension (Pichora-Fuller et al., 1995, 2017) and can lead to an increase in socially inappropriate behavior. Given the rapid expansion of the aging population in modern society, there is increasing need to identify and develop effective interventions that reduce, halt, or even reverse declines in inhibitory control to preserve daily cognitive abilities in older adults.

Recent studies have shown that lifelong engagement in musical activities might help maintain the brain in a younger state (Rogenmoser et al., 2018), slow cognitive declines (Hanna-Pladdy and Gajewski, 2012; Parbery-Clark et al., 2012; Zendel and Alain, 2012; Bidelman and Alain, 2015), and preserve or even enhance neural functioning in old age (Parbery-Clark et al., 2011; Bidelman et al., 2014; Zendel and Alain, 2014). For example, older musicians show improved performance compared to non-musicians in several cognitive areas including spatial memory, processing speed, and cognitive flexibility (Parbery-Clark et al., 2011), as well as inhibitory control (Moreno et al., 2014; Moussard et al., 2016). A positive relationship between years of musical engagement and cognitive performance further implied experience-dependent changes in older adults' behavioral skills (Parbery-Clark et al., 2011, 2012; Bidelman and Alain, 2015).

Several developmental studies have been conducted investigating the effect of learning how to sing or to play a musical instrument over a period of time. Using expert and intervention designs, results have shown benefits on different types of cognitive processes such as verbal processing (Moreno et al., 2009; Seither-Preisler et al., 2014), intelligence (Schellenberg, 2004), reading (Moreno et al., 2011), inhibitory processing (Moreno et al., 2011), auditory processing (Moreno and Farzan, 2015; Tierney and Kraus, 2015) and on general brain development (Hyde et al., 2009). However, evidence to date demonstrating benefits of musical training in older adults has often been correlational, not causal. Very few studies have investigated, in longitudinal designs, whether engagement in musical activity can improve cognitive functions. Although evidence suggests that short-term musical training (e.g., piano lessons) can improve executive functioning and working memory (Bugos et al., 2007; Seinfeld et al., 2013), prior studies often suffer from methodological limitations (e.g., lack of an active control group, lack of randomization for group assignment), and have not measured the effects of the intervention on brain activity. Thus, it remains unclear whether engagement in musical activities would yield neuroplastic changes in brain activity, and whether these changes could be long-lasting. Examining neural activity prior to, and after short-term music training and comparing it with that of another artistic activity would allow for a greater understanding of brain plasticity and potential transfer mechanisms in the aged brain.

A cognitively demanding form of training that could be considered equally as engaging as musical activity is visual art. Evidence from neuroimaging studies suggests that activity elicited during visual art engagement, including both visual object learning (Op de Beeck and Baker, 2010) and hand-related motor activities (Draganski et al., 2004), induces neuroplastic changes in brain areas associated with spatial-reasoning skills (Pollmann and von Cramon, 2000). Visual art training has also been associated with structural differences in areas of the brain pertaining to fine motor control and procedural memory between artists and non-artists (Chamberlain et al., 2014). Therefore, there is reason to believe that visual art training, like musical training, may promote cognitive improvements in older adults. Importantly, visual art training provides a means to assess whether neuroplastic changes associated with music training are specific to music training itself or whether they reflect non-training specific effects associated with engagement in art programs in general.

In this study, we investigated the short-term (3-month) impact of two forms of engaging training – music and visual art instruction – on older adults' perceptual and cognitive functions using a three group intervention design (music, visual art and a no-contact control). We also measured maintenance of the effects with a follow-up testing 3 months after the cessation of training. All participants completed a brief neuropsychological assessment to ensure that our groups were comparable before training. We used the same battery after training and at follow-up to explore whether music and visual art training impacted cognitive functioning as measured with neuropsychological tests. We anticipated that participants in the music group would show higher cognitive functioning than those in the active (visual art) and passive control groups. We anticipated that participants in the music group would show higher cognitive functioning after training than those in the control group. We also expected potential improvements following visual art training, as an exploratory hypothesis.

In addition, we recorded neuroelectric event-related potentials (ERPs) using auditory oddball paradigms and during a visual GoNoGo task at each session (pre, post, and follow-up), to evaluate training-related neuroplastic changes in sensory processing and executive functions. These paradigms were chosen because prior studies have shown neuroplastic changes associated with music training on these tasks (e.g., Shahin et al., 2003; Zendel and Alain, 2009; Moussard et al., 2016). We hypothesized that each form of art training would impact sensory processing in the trained modality paralleling training-related benefits reported in children (e.g., Fujioka et al., 2006; Moreno et al., 2011, 2014). That is, music training was expected to impact the N1 and P2 waves of the auditory ERPs as previously found in younger populations (e.g., Tremblay et al., 2001; Reinke et al., 2003; Alain et al., 2010). We also anticipated that music training would improve listeners' ability to notice changes in auditory stimuli as indexed by the mismatch negativity (MMN), which has also been observed in young adults (Tervaniemi et al., 1997; Nikjeh et al., 2009). We also hypothesized that visual art training would have greater impact than music training on visual sensory evoked responses such as the N1 and P2 waves at parietal-occipital sites.

Furthermore, we expected to observe neuroplastic enhancements in brain mechanisms subserving inhibitory control in the music group relative to the visual art group and age-matched no-training controls. Following music training, changes were expected in the N2, and P3 complex of the ERPs during the visual GoNoGo task as previously found in younger (Brydges et al., 2014; Moreno et al., 2014) and older (Moussard et al., 2016) populations. As shown in previous studies in young adults, music training induced enhancements in right hemisphere activity (Moreno et al., 2014). Thus, we hypothesized that the music group would show an increase in ERP amplitude over the right hemisphere after training. Prior research has also shown long lasting benefits of music training that persist years after the training has ended (White-Schwoch et al., 2013). Hence, we expected brain and behavioral enhancements to persist at 3-month follow-up. This finding would establish that relatively engaging art training could produce lasting effects in neural and behavioral function in older adults well after the cessation of instruction.

MATERIALS AND METHODS

Participants

Sixty healthy older adults with limited prior musical or visual art training were recruited from the Greater Toronto Area. For pre- and post-training phases, five participants were lost to attrition, and two due to technical problems during EEG recording, resulting in 17 participants in the music group (three males), 19 in the visual art group (two males), and 17 in the no-contact control group (three males). The groups did not differ in age ($p = 0.82$; music: $M = 67.7$, $SD = 5.8$ years; visual art: $M = 68.9$, $SD = 6$ years; control, $M = 68.5$, $SD = 6$ years), years of formal education ($p = 0.55$; music: $M = 16.4$, $SD = 2.6$ years; visual art: $M = 17.2$, $SD = 2.3$ years; control: $M = 16.9$, $SD = 1.5$ years), or intelligence on the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II FSIQ4; $p = 0.51$; music: $M = 114.2$, $SD = 10.5$; visual art: $M = 115.8$, $SD = 11$; control: $M = 111.8$, $SD = 13.9$). Participants were screened for amusia and other auditory or musical deficits that could have interfered with the study using the Musical Ear Test (MET, Wallentin et al., 2010). All three groups showed similar scores at baseline psychometric assessment (all p-values > 0.1). After 3 months, 15 participants from the music group and 14 participants from the visual art group returned for follow-up testing. These two subgroups remained similar in age ($p = 0.57$), education ($p = 0.31$), and had comparable intelligence on WASI-II FSIQ4 ($p = 0.39$) at pre-test. The study received approval from the Baycrest Research Ethics Committee, and all participants provided written informed consent.

Study Design

This longitudinal study consisted of four phases: pre-test, 3-month training, post-test, and 3-month follow-up test (**Figure 1**). During the 3 months between post-test and follow-up, participants did not engage in formal music or visual arts activities. At pre-test, post-test, and follow-up sessions, participants were tested individually and were blind to our hypotheses. After the pre-test, participants were assigned to either music or visual art training in a pseudorandom manner to equate pre-training differences between groups on intelligence scores and background demographic measures (gender, age, and years of education). An additional passive control group was further recruited in order to collect data to distinguish potential training effects from test–retest effects.

Training Curricula

The trained participants received group classroom instruction and activities in their respective training by a professional teacher (i.e., two teachers: a music and a visual art teacher) at the Royal Conservatory of Music in Toronto for 3 months (36 1-h sessions, three times per week). The music group was engaged in music making using body percussion, voice, and non-pitched musical instruments. They also learned basic music theory as well as

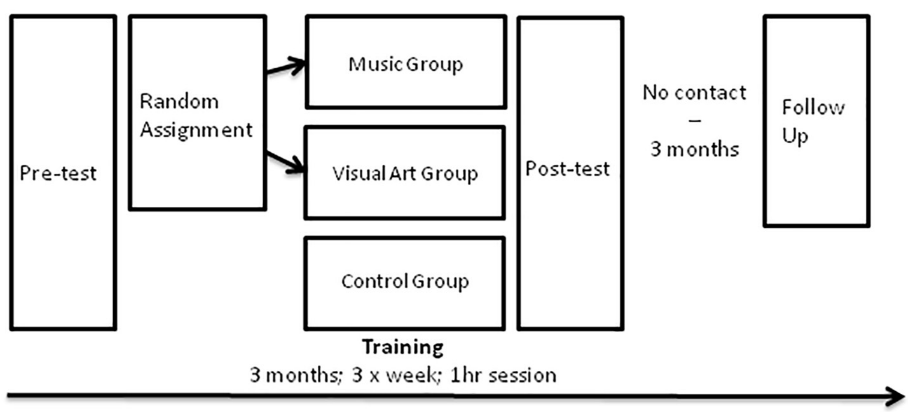

FIGURE 1 | Schematic of the study design.

melody and harmony concepts through the singing of simple canons. The visual art group learned basic drawing and painting techniques, analyzed work of famous artists, and created original paintings of landscape, still-life, and self-portrait. All materials were provided for them (i.e., instruments for music lesson and all the material for drawing and painting in the visual art lesson).

Procedure

Testing (EEG and psychometric tests) took place in the laboratory on two different days and lasted approximately 1.5–2 h per session. For EEG testing, recordings took place in an acoustically and electrically shielded room.

Psychometric Assessment

Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)

WASI-II assesses intelligence using four different subtests including measures of verbal comprehension: (1) Vocabulary and (2) Similarities; and measures of perceptual reasoning: (3) Block Design and (4) Matrix Reasoning. A composite score (FSIQ4) was then calculated to reflect global IQ.

Forward and Backward Word Span

The Word Span task measured verbal working memory, with one *forward* and one *backward* condition. The experimenter read sequences of words with a 1-s pause between words. Word lists were organized into sequence lengths (*spans*) of two to eight. There were two versions of the test that were counterbalanced across testing sessions. Each sequence had two trials. Testing continued until the experimenter recorded all recalled words from each list. A total span score was calculated for each condition as the total number of correctly recalled items across all trials (maximum *word span* score = 70).

Stroop Test

A paper version with three subtests of the Stroop test was used to measure cognitive inhibition and processing speed (Stroop, 1935). Subtest 1 involved reading color words printed in black font while subtest 2 included naming the color of squares. Subtest 3 required naming the color in which the word was printed while the written color name differed (i.e., incongruent condition). Response time was measured for each subtest. The interference score was calculated by subtracting response time on subtest 3 from that of subtest 2. The interference effect was also reflected by the number of mistakes at subtest 3.

Computerized Peabody Picture Vocabulary Test (PPVT)

The Peabody Picture Vocabulary Test (PPVT) was used to measure receptive vocabulary (Dunn and Dunn, 2007). In this test, participants saw four pictures on the screen while the computer said a word. Their task was to click on the picture that best characterized the meaning of the word. We used the number of correct responses in the analysis.

Digit symbol (subtest of the WAIS-R)

Participants were given 2 min to copy symbols below numbers according to a coding key where a number corresponded to a specific symbol. The test was scored as the number of correctly completed symbols.

EEG Recording and Data Analysis

To probe training-related changes in brain activity supporting perceptual and executive control processes, we measured neuroelectric activity (electroencephalogram, EEG) using auditory oddball paradigms and during a visual GoNoGo task. The same stimuli were used at each of the three testing sessions (pre, post, follow-up) while the order of trials was randomized across participants and sessions.

Auditory oddball paradigms

Auditory processing was assessed via the N1, P2 and mismatch negativity (MMN) recorded before and after training using two oddball sequences consisting of a either music or speech sound contrast. For the music condition, two synthesized piano tones, Eb4 (F0 = 314 Hz) and D4 (F0 = 294 Hz) served as the standard and deviant tokens, respectively. The two notes differed only in pitch and were otherwise matched in acoustic characteristics including overall amplitude and duration (500 ms). For the speech condition, two French vowels as produced by a native female speaker, /u/ and /ou/, functioned as the standard and deviant stimulus, respectively. The two speech tokens had similar duration (280 ms), mean voice fundamental frequency (F0: ∼240 Hz), amplitude, and first/third formant frequencies; only their second formant differed to yield the two distinct vowel timbres (/u/: ∼1,850 Hz; /ou/: ∼750 Hz). Presentation order was pseudorandom such that at least one standard stimulus preceded a deviant. Stimuli were presented with a stimulus onset asynchrony of 750 ms and delivered binaurally via ER-3 insert earphones (Etymotic Research) at an intensity of 80 dB sound pressure level. A total of 510 standards and 90 deviants (i.e., 85/15% ratio) were collected for both the speech and music conditions.

Visual GoNoGo task

Participants were presented with white or purple geometric triangle or squares at the center of the screen located at about 1 m from the participant. Before each trial, a white fixation cross appeared on a black background for a variable duration (500–1,000 ms), then a geometric shape appeared in the center of the screen for 500 ms. Participants were instructed to press the right mouse button in response to white shapes (80% probability) and to withhold responding to purple shapes (20% probability). The experiment consisted of 200 trials (160 Go and 40 NoGo trials). A practice block of 20 trials was used to familiarize participants with the task. During the task, participants did not receive feedback on their performance. Accuracy rates were recorded for Go and NoGo trials, and reaction times were recorded for Go trials.

EEG recording and data processing

EEG was recorded from 66 scalp electrodes using a BioSemi Active Two acquisition system (BioSemi V.O.F., Amsterdam, Netherlands). The electrode montage was according to the BioSemi electrode cap based on the 10/20 system and included a common mode sense active electrode and driven right leg passive electrode serving as ground. Ten additional electrodes were placed below the hair line (both mastoid, both pre-auricular points, outer canthus of each eye, inferior orbit of each eye, two facial electrodes) to monitor eye movements and to cover the whole scalp evenly. The latter is important because we used an average reference (i.e., the average of all scalp EEG channels as the reference for each EEG channel) for ERP analyses. Neuroelectric activity was digitized continuously at rate of 512 Hz with a bandpass of DC-100 Hz, and stored for offline analysis. Offline analyses were performed using Brain Electrical Source Analysis software (BESA, version 6.1; MEGIS GmbH, Gräfelfing, Germany).

Continuous EEGs were first digitally filtered with 0.5 Hz high-pass (forward, 6 dB/octave) and 40 Hz low-pass filters (zero phase, 24 dB/octave). For the auditory evoked potentials, the analysis epoch consisted of 100 ms of pre-stimulus activity and 500 ms of post-stimulus activity time-locked to sound onset. For the GoNoGo, the analysis epoch consisted of 200 ms of pre-stimulus activity and 1,000 ms of post-stimulus activity time-locked to the onset of the visual stimuli. EEG segments contaminated by blink and saccade were corrected using BESA. Both eye blinks and lateral movements were first identified in the continuous EEG and then modeled using artifact correction with a surrogate model. After ocular correction, traces were then scanned for artifacts and epochs including deflections exceeding 120 μV were marked and excluded from the analysis. The remaining epochs were averaged according to electrode position, trial type (e.g., Go, NoGo), and session (i.e., pre-training, post-training, follow-up). Each average was baseline-corrected with respect to the pre-stimulus interval.

For the oddball paradigms, the proportion of trials included in the auditory ERPs ranged from 283 to 510 trials for the standard stimuli and from 48 to 98 for deviant stimuli. The number of trials was comparable for the pre- (Standard: $M = 487$; Deviant: $M = 85$) and post-training sessions (Standard: $M = 484$; Deviant: $M = 86$), and was similar for controls (Standard: $M = 493$; Deviant: $M = 88$), music (Standard: $M = 478$; Deviant: $M = 84$) and visual art (Standard: $M = 484$; Deviant: $M = 85$) groups. For the GoNoGo task, the number of trials included in the visual ERPs ranged from 78 to 160 trials for the Go condition and 17 to 40 trials for the NoGo condition. As for the oddball paradigms, the number of trials was comparable before (Go: $M = 141$; NoGo: $M = 34$) and after (Go: $M = 144$; NoGo: $M = 35$) training, and was similar for control (Go: $M = 148$; NoGo: $M = 36$), music (Go: $M = 141$; NoGo: $M = 33$), and visual art (Go: $M = 139$; NoGo: $M = 34$) groups.

Statistical analyses

Training effects on the psychometric measures were assessed using repeated measures ANOVAs. We focused on interactions that involved group and session as factors. Although they were not central to the goal of the present study, we also report other main effects and interactions for sake of completeness. For the psychometric assessments, we used the Benjamini–Hochberg method to adjust the familywise p-value for multiple comparisons ($q = 0.1$, $m = 30$, and $p = 0.05$), resulting in a p-value of 0.005 for significance.

The ERP analyses focused on pre-defined time windows and electrode clusters motivated by prior studies (e.g., Reinke et al., 2003; Moreno et al., 2014; Moussard et al., 2016). For the oddball paradigms, the effects of training on N1 and P2 deflections was assessed during the 90–130 ms and 170-210 ms interval at fronto-central scalp sites (F1, Fz, F2, FC1, FCz, FC2, C1, Cz, C2). The automatic change detection was quantified using the difference waves between standard and deviant. The peak amplitude and latency was quantified during the 100–250 ms window using the same electrode clusters as the N1 and P2 waves. For the GoNoGo task, the processing of go and nogo stimuli was assessed during the 165–205 ms interval (i.e., N1) and the 210–280 ms interval at parieto-occipital electrodes from the left (PO7, P5, P7) and right hemisphere (PO8, P6, P8). The effects of music and art training on the ability to inhibit a motor response on the nogo trials was quantified by comparing mean amplitude for the 375–475 ms interval measured over the left (F1, F3, AF3) and right (F2, F4, AF4) frontal scalp regions. These electrode clusters were chosen because music training in young adults has been shown to modulate visual GoNoGo ERP amplitude over the right hemisphere (Moreno et al., 2014). Thus, we anticipated that music activities in older adults would also show changes in ERP amplitude over the right hemisphere after training.

The effects of art training on auditory evoked responses (i.e., N1, P2, MMN) were assessed using a mixed model ANOVA using groups (control, music, visual art) as between-subject factor, and sequence type (music vs. speech) and stimulus type (standard, deviant) as the within-subject factors. The effects of art training on visual evoked responses recorded during the GoNoGo task was assessed using a mixed model ANOVA with group (control, music, visual art) as the between-subject factors, and stimulus type (Go, NoGo trials) and hemisphere (right, left) as within-subject factors. We used the Benjamini–Hochberg method to adjust the familywise p-value for multiple comparisons with $q = 0.1$, $m = 160$ (i.e., number of p-values) and $p = 0.05$ (Hochberg and Benjamini, 1990), resulting in a p-value of 0.025 for significance.

RESULTS

Psychometric Assessment: Training Effects

The analyses of performance at neuropsychological test revealed a group × session interaction on the Stroop subtest 2 [color naming speed; $F(2,50) = 6.16$, $p = 0.004$, $\eta^2 = 0.20$], where the music group improved in naming speed between pre- and post-assessment [$t(16) = 3.32$, $p = 0.004$, **Figure 2**]. There was also a main effect of session for the Digit Symbol task, with better performance at post-test [compared to pre-test; $F(1,50) = 15.98$, $p < 0.000$, $\eta^2 = 0.24$], but no interaction with group. There were no other significant differences in performance between pre- and post-training session. In the music group, a follow-up analysis showed that the gain in response speed was maintained 3 months after training (post-test vs. follow-up contrast, $p > 0.1$).

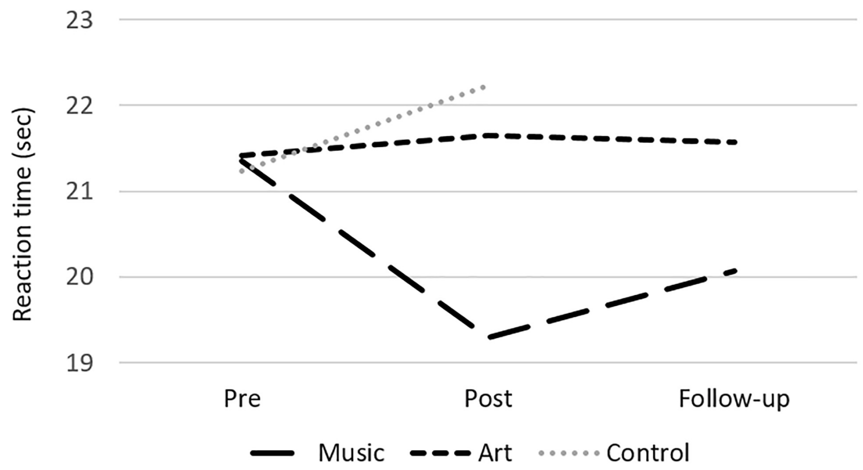

FIGURE 2 | Mean reaction time at the Stroop subtest 2 (color naming) for the music, art, and control groups at pre-test, post-test and follow-up.

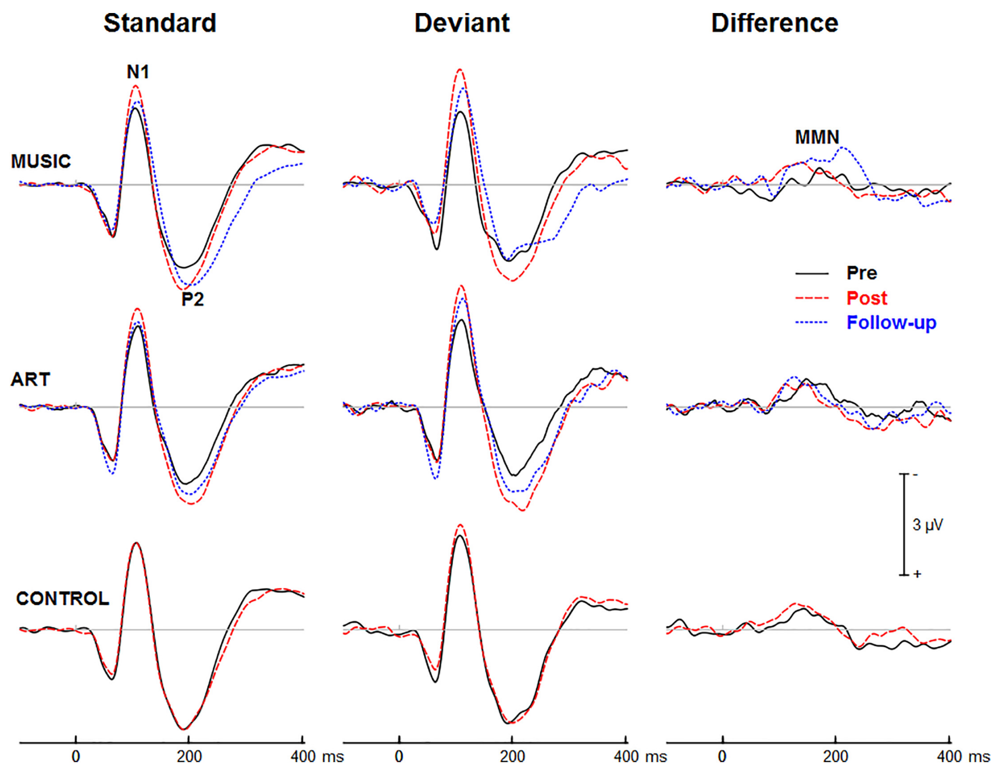

FIGURE 3 | Group mean event-related potentials elicited by standard and deviant piano tones as well as the corresponding difference wave (i.e., MMN). Here and throughout, negativity is plotted upward. Waveforms are from the midline fronto-central electrode (FCz).

Effects of Music and Visual Art Training on Auditory Processing

Figures 3, 4 show group mean auditory ERPs elicited by standard and deviant stimuli as well as the corresponding difference waves in both sequences (piano tones and vowels) at pre- and post-training sessions, as well as from the subset of participants who completed the follow-up. The scalp-recorded ERPs comprised prototypical deflections at ∼60, ∼110, and ∼195 ms after sound onset (i.e., P1-N1-P2). The MMN was isolated as the difference in neural activity between standard and deviant (oddball) stimuli. One participant from the music group and two from the art group were excluded from the analyses because data from one of the two sequences were unavailable due to technical problems.

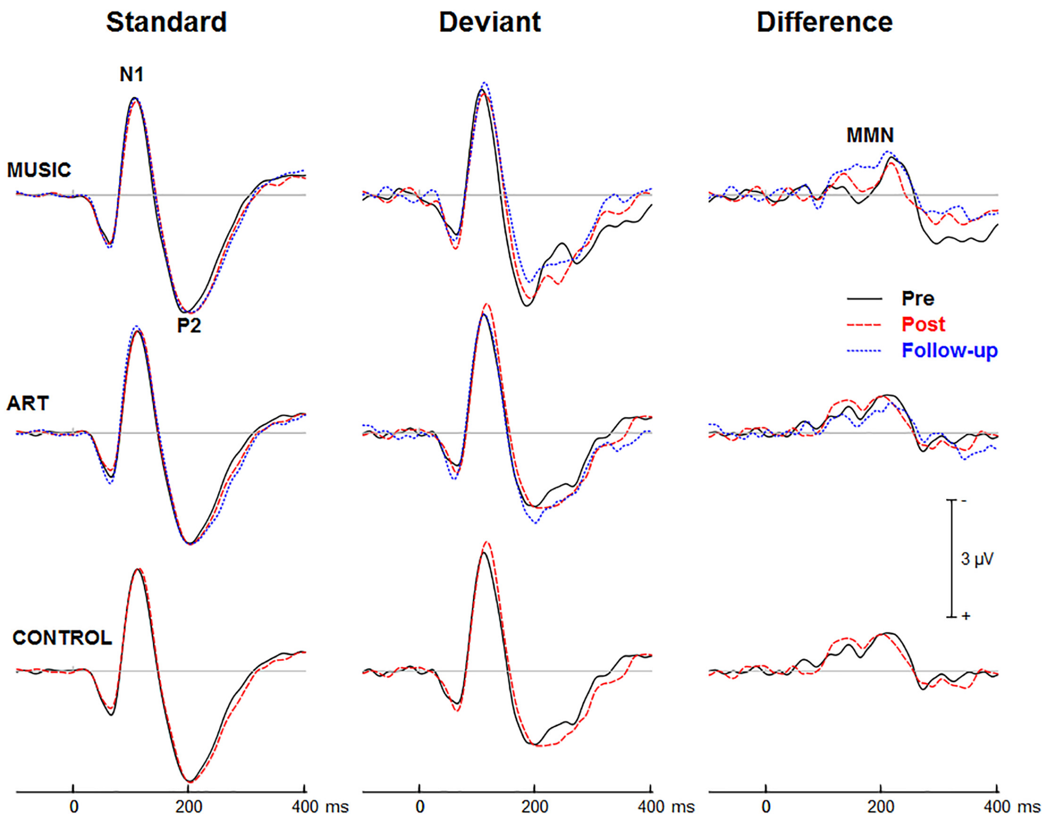

FIGURE 4 | Group mean event-related potentials elicited by standard and deviant vowel stimuli as well as the corresponding difference wave (i.e., MMN). Waveforms are from the midline fronto-central electrode (FCz).

Training Effects on Auditory ERPs

First, we examined whether music and visual art training modulated early cortical processing indexed by the N1 and P2 waves. The ANOVA on the N1 mean amplitude (90–130 ms) yielded a significant group × session × sequence type interaction [$F(2,47) = 4.30$, $p = 0.019$, $\eta^2 = 0.16$]. To better understand this three-way interaction, we examined the effects of training as a function of sequence type. For the piano tones, both music and art groups showed larger N1 amplitude at post-test than pre-test ($p < 0.005$ in both cases). For the control group, there was no difference in N1 amplitude between pre-test and post-test. For the vowel stimuli, there was no significant difference in N1 amplitude between pre-test and post-test ($p > 0.19$ in all three groups). Thus, while the N1 amplitude elicited by vowel stimuli was little affected by training, the N1 generated by piano tones was larger at post-test than pre-test in the music and visual art training groups (**Figures 3**, **4**). The interaction between group × session × stimulus type was not significant.

We also observed a main effect of session [$F(1,47) = 10.15$, $p = 0.003$, $\eta^2 = 0.18$], and a session × sequence type interaction [$F(1,47) = 6.06$, $p = 018$, $\eta^2 = 0.11$], with greater increased in N1 amplitude at post-test for the piano tone than for the vowel stimuli. The main effect of stimulus type was significant [$F(1,47) = 52.19$, $p < 0.001$, $\eta^2 = 0.53$], reflecting larger N1 amplitude for deviant than standard stimuli. The interaction between session and stimulus type was also significant [$F(1,47) = 12.82$, $p = 0.001$, $\eta^2 = 0.21$], which was due to greater difference between standard and deviant at post-test than at pre-test.

For the P2 mean amplitude (175–215 ms), the group × session was not significant, nor was the group × session × stimulus type. However, the group × session × sequence type interaction approached the corrected significance level [$F(2,47) = 3.63$, $p = 0.034$, $\eta^2 = 0.13$]. For the piano tones, both music and visual art groups showed larger P2 amplitude at post-test than pre-test ($p < 0.005$ in both cases). For the control group, there was no difference in P2 amplitude between pre-test and post-test. For the vowel stimuli, there was no significant difference in P2 amplitude between sessions ($p > 0.65$ in all three groups). As for the N1 amplitude, the P2 wave elicited by vowel stimuli was little affected by training while the P2 generated by piano tones was larger at post-test than pre-test in the music and visual art training groups (**Figures 3**, **4**).

The omnibus ANOVA on the P2 mean amplitude also revealed a main effect of session [$F(1,47) = 6.66$, $p = 0.013$, $\eta^2 = 0.12$], and an interaction between session and sequence type [$F(1,47) = 12.80$, $p < 0.001$, $\eta^2 = 0.21$]. The main effect of stimulus type was significant [$F(1,47) = 44.50$, $p < 0.001$, $\eta^2 = 0.49$], with the P2 wave being more negative for deviant than for standard stimuli. The sequence × stimulus type interaction was also significant [$F(1,47) = 21.81$, $p < 0.001$, $\eta^2 = 0.32$], reflecting greater deviance-related activity for the vowel stimuli than for the piano tones.

Training Effects on MMN

Figures 3, **4** show the mean MMN across groups. For the MMN latency, the group × session interaction was not significant [$F(2,47) = 1.70$, $p = 0.193$, $\eta^2 = 0.07$], nor was the group × sequence type interaction ($F < 1$). The three-way group × session × sequence type interaction was not significant [$F(2,47) = 1.80$, $p = 0.177$, $\eta^2 = 0.071$]. However, the ANOVA yielded a main effect of sequence type [$F(1,47) = 49.06$, $p < 0.001$, $\eta^2 = 0.51$], with the MMN elicited by piano tones (M = 150 ms, SE = 2.5 ms) peaking earlier than the MMN elicited vowels (M = 182 ms, SE = 4.1 ms). The main effect of session was also significant [$F(1,47) = 16.42$, $p < 0.001$, $\eta^2 = 0.23$], with earlier peak latency at post- than pre-test.

For the MMN peak amplitude, the group × session interaction was not significant [$F(2,47) = 2.55$, $p = 0.089$, $\eta^2 = 0.10$], nor was the group × sequence type ($F < 1$). However, the MMN was larger for vowel than piano tones [$F(1,47) = 49.22$, $p < 0.001$, $\eta^2 = 0.51$]. All other main effects and interactions were not significant. Thus, neither music nor visual art training had a significant effect on the automatic change detection process as measured by the MMN.

Follow-Up Retention

Three months after the end of training, a subgroup of participants (music N = 15, visual art N = 14) returned for follow-up assessment and evaluation of long-term retention effects. One participant in each group was excluded from the analysis because he/she was missing one of the experimental conditions due to technical problems. The remaining sample comprised 14 from the music group and 13 from the visual art group.

The ANOVA on the N1 mean amplitude with session (pre, post, follow-up) as between-subject factor and sequence (piano tones, vowels) and stimulus type (standard, deviant) as within-subject factors, yielded a significant session × sequence type interaction [$F(2,50) = 4.47$, $p = 0.016$, $\eta^2 = 0.15$]. To better understand this interaction, we performed separate ANOVAs for piano and vowel stimuli. For piano tones, the ANOVA revealed a main effect of session [$F(2,50) = 11.33$, $p < 0.001$, $\eta^2 = 0.31$]. Pairwise comparisons revealed a significant increase in N1 amplitude at post-test and follow-up relative to pre-test ($p < 0.001$ in both cases). There was no difference in N1 amplitude between post-test and follow-up ($p = 0.144$). The group × session interaction was not significant ($F < 1$), nor was the group × session × stimulus type [$F(2,50) = 1.67$, $p = 0.192$, $\eta^2 = 0.31$]. For vowel stimuli, the main effect of session was not significant nor was the group × session interaction ($F < 1$ in both cases). As for the N1, the ANOVA on the P2 mean amplitude yielded a session × sequence interaction [$F(2,50) = 6.27$, $p = 0.004$, $\eta^2 = 0.20$]. For piano tones, the main effect of session was significant [$F(2,50) = 10.29$, $p < 0.001$, $\eta^2 = 0.29$]. Pairwise comparisons revealed larger P2 amplitude at post-test and follow-up than at pre-test ($p < 0.001$ in both cases). There was no difference in P2 amplitude between post-test and follow-up ($p = 0.51$). For vowel stimuli, the main effect of session was not significant ($F < 1$) nor was the group × session interaction ($F < 1$).

In summary, music and visual art training modulated auditory processing, which was retained 3 months after training end.

Effects of Music and Visual Art Training on ERPs During Visual Go NoGo Task

Behavioral Data

All three groups showed ceiling performance on Go trials with few (if any) false positives on NoGo trials (see **Table 1**). There was no difference between the groups nor between the pre- and post-test sessions. The group × session interaction was not significant for accuracy or response time measures.

Training Effects on Visual ERPs

Figure 5 shows group mean visual ERPs elicited during Go and NoGo trials as well as the corresponding difference waves at parietal-occipital sites. The scalp-recorded visual ERPs comprised prototypical deflections at ∼100, ∼185, and ∼325 ms after stimulus onset (i.e., P1-N1-P2). The difference wave between Go and NoGo trials reveals processing associated with suppressing the motor response.

We first examined whether music and visual art training modulated early visual cortical processing indexed by the N1 and P2 waves. The ANOVA on the N1 mean amplitude (165–205 ms) yielded a group × session × hemisphere was significant [$F(2,50) = 4.00$, $p = 0.024$, $\eta^2 = 0.14$]. To better understand this three-way interaction, we examined the effects of training as a function of hemisphere. For the left parietal-occipital areas, the music and visual art group showed comparable visual N1 amplitude before and after training ($p > 0.5$ in both cases) whereas the N1 in the control group was larger at post-test than pre-test ($p < 0.01$). For the right parietal-occipital areas, the music and control group showed comparable N1 amplitude at pre-test and post-test, while the N1 amplitude was significantly enhanced in the visual art group ($p = 0.003$). While the N1 amplitude measured over the left hemisphere was little affected by training, the N1 recorded over the right hemisphere was larger at post-test than pre-test in the visual art group only. No other interactions involving group and sessions were significant.

The omnibus ANOVA also showed that the N1 wave was larger at post-test than pre-test [$F(1,50) = 6.21$, $p = 0.016$, $\eta^2 = 0.11$]. The main effect of stimulus type was also significant [$F(1,50) = 18.78$, $p < 0.001$, $\eta^2 = 0.27$], with larger N1 amplitude during the NoGo than Go trials. The latter could reflect an attention-related negativity that overlaps the N1 wave rather than a modulation of the N1 response.

For the visual P2 mean amplitude (305–345 ms), there was no significant interaction between group and session, nor was the group × session × hemisphere interaction significant [$F(2,50) = 1.35$, $p = 0.269$, $\eta^2 = 0.05$]. The main effect of session was not significant [$F(1,50) = 2.23$, $p = 0.142$, $\eta^2 = 0.04$].

TABLE 1 | Behavioral results on the GoNoGo task.

Group	Session	Group mean response time (ms) and (SE)	Error (%)
Music	Pre-training	444 (17)	2.19 (0.62)
	Post-training	427 (15)	2.56 (0.63)
	Follow-up	431 (10)	3.33 (0.62)
Visual art	Pre-training	434 (16)	3.33 (0.59)
	Post-training	436 (14)	3.17 (0.59)
	Follow-up	443 (15)	5.50 (2.36)
Control	Pre-training	435 (15)	1.71 (0.60)
	Post-training	439 (17)	1.47 (0.61)

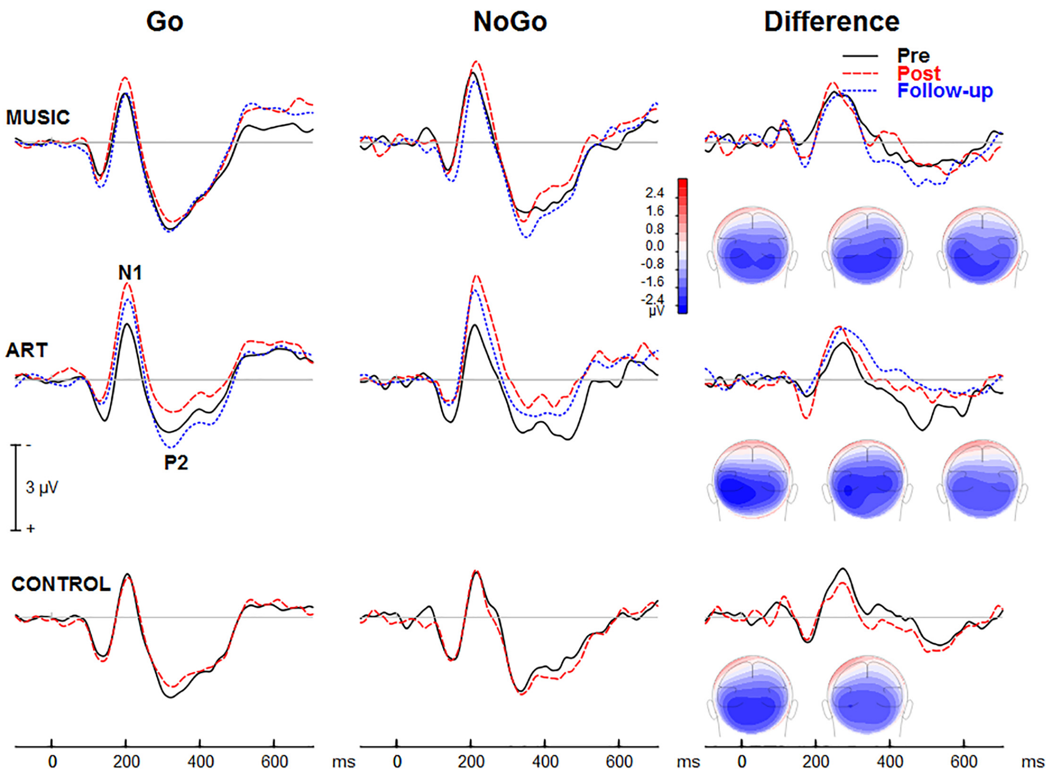

FIGURE 5 | Group mean event-related potentials elicited during the visual GoNoGo task over the right parietal scalp area (i.e., electrode P6). The iso-contour maps (view from the back) show amplitude distribution for the mean voltage between 210 and 280 ms. From left to right, the maps show the distribution at pre-test, post-test, and follow-up, respectively.

However, the session × hemisphere interaction was significant [$F(1,50) = 4.14$, $p = 0.047$, $\eta^2 = 0.08$]. While the P2 measured over the left hemisphere was comparable between pre- and post-training sessions, the P2 recorded over the right parieto-occipital area was larger at post-test.

NoGo-related effects

The visual ERPs elicited during the NoGo trials showed a negative displacement, which could be accounted for by attention-related effects superimposed on the N1 and P2. This is best illustrated by the difference wave between Go and NoGo trials. This difference wave revealed a negative component at parietal-occipital sites that peak at about 230–240 ms after stimulus onset. The mean amplitude for 210–280 was used for left (PO7, P5, P7) and right hemisphere (PO8, P6, P8).

The main effect of group was not significant [$F(2,50) = 1.41$, $p = 0.253$, $\eta^2 = 0.05$], nor was the group × session interaction ($F < 1$). However, there was a significant group × session × hemisphere interaction [$F(2,50) = 6.17$, $p = 0.004$, $\eta^2 = 0.19$]. This was due to a shift in the response laterality between the first and second session in the visual art group (**Figure 6**). That is, at pre-test, the ERP amplitude was greater over the left parietal-occipital sites whereas after visual

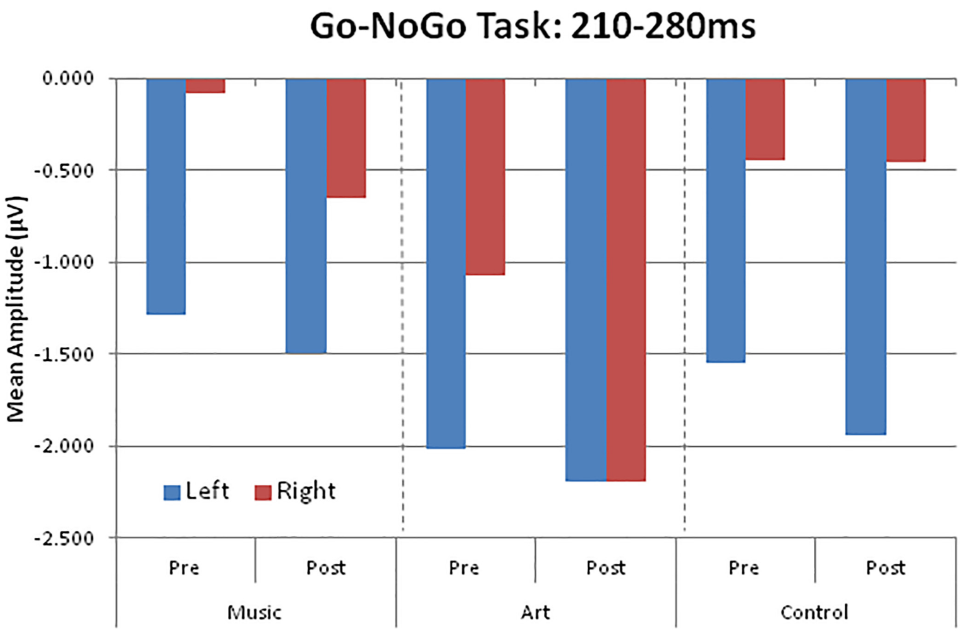

FIGURE 6 | Group mean visual event-related potential amplitudes over left (PO7, P5, P7) and right (PO8, P6, P8) parieto-occipital areas.

art training the ERPs showed a more symmetric amplitude distribution over the left and right hemispheres. In the control and music group, the ERP amplitude was larger over the left and right hemisphere during the pre- and post-training sessions.

There was a main effect of session [$F(1,50) = 6.21$, $p = 0.016$, $\eta^2 = 0.11$], with larger amplitude at post-test. The main effect of condition was also significant [$F(1,50) = 124.47$, $p < 0.001$, $\eta^2 = 0.71$], which reflected enhanced negativity generated by the NoGo trials compare to the Go trials.

Follow-up retention

We examined whether the changes in laterality persisted 3 months after the end of training. An ANOVA comparing ERPs recorded in all three session in the art group revealed a session × hemisphere interaction [$F(2,26) = 6.02$, $p = 0.013$]. Separate ANOVAs for the left and right hemisphere yielded a main effect of session only for ERPs recorded over the right parietal-occipital area [right hemisphere: $F(2,26) = 4.35$, $p = 0.029$; left hemisphere: $F < 1$]. Pairwise comparisons revealed enhanced negativity at post-test relative both pre-test and follow-up ($p < 0.05$ in both cases). The ERPs at follow-up did not differ from those obtained at pre-test ($p = 0.693$). As during the pre-test, the ERPs recorded at follow-up were larger over the left than the right hemisphere. In summary, art training was associated with increased early attention-related effects over the right parietal-occipital area, which was not retained 3 months after training.

ERPs Associated With Response Inhibition

The NoGo trials generated a modulation that peaked at about 425 ms after stimulus onset at fronto-central sites (**Figure 7**). The group × session × condition × hemisphere interaction was significant [$F(2,50) = 4.24$, $p = 0.020$, $\eta^2 = 0.15$]. To better understand this four-way interaction, we performed separate ANOVAs for each group. In the music group, the main effect of condition was significant [$F(1,16) = 8.19$, $p = 0.011$, $\eta^2 = 0.339$], so was the session × condition interaction [$F(1,16) = 8.67$, $p = 0.010$, $\eta^2 = 0.351$], with greater increased in ERP amplitude at post-test for the NoGo than Go condition. The condition × hemisphere was significant [$F(1,16) = 13.31$, $p = 0.002$, $\eta^2 = 0.454$], reflecting greater difference between Go and NoGo trials over the left hemisphere. The session × hemisphere was not significant ($F < 1$). In the visual art group, the main effect of condition was significant [$F(1,18) = 21.18$, $p < 0.001$, $\eta^2 = 0.541$]. The session × condition was also significant [$F(1,18) = 8.038$, $p = 0.011$, $\eta^2 = 0.309$], with greater increased in ERP amplitude at post-test for the NoGo than Go condition. The session × hemisphere trended toward significance [$F(1,18) = 3.51$, $p = 0.077$, $\eta^2 = 0.163$]. However, the session × condition × hemisphere was significant [$F(1,18) = 5.78$, $p = 0.027$, $\eta^2 = 0.243$]. This was due to greater difference in ERP amplitude between Go and NoGo trials over the left hemisphere after training. In the control group, the main effect of condition was significant [$F(1,16) = 17.12$, $p = 0.001$, $\eta^2 = 0.517$]. However, neither the main effect of session or the session × condition interaction were significant ($F < 1$ in both cases). The condition × hemisphere was significant [$F(1,16) = 29.04$, $p < 0.001$, $\eta^2 = 0.645$], reflecting greater difference between Go and NoGo trials over the left hemisphere. The other main effects or interactions were not significant.

The ANOVA on the mean amplitude (375–475 ms) yielded a main effect of session [$F(1,50) = 4.37$, $p = 0.042$, $\eta^2 = 0.08$], and a main effect of condition [$F(1,50) = 43.59$, $p < 0.001$, $\eta^2 = 0.466$]. That is, the ERP amplitude was more positive at post-test than at pre-test, and more positive for NoGo trials than

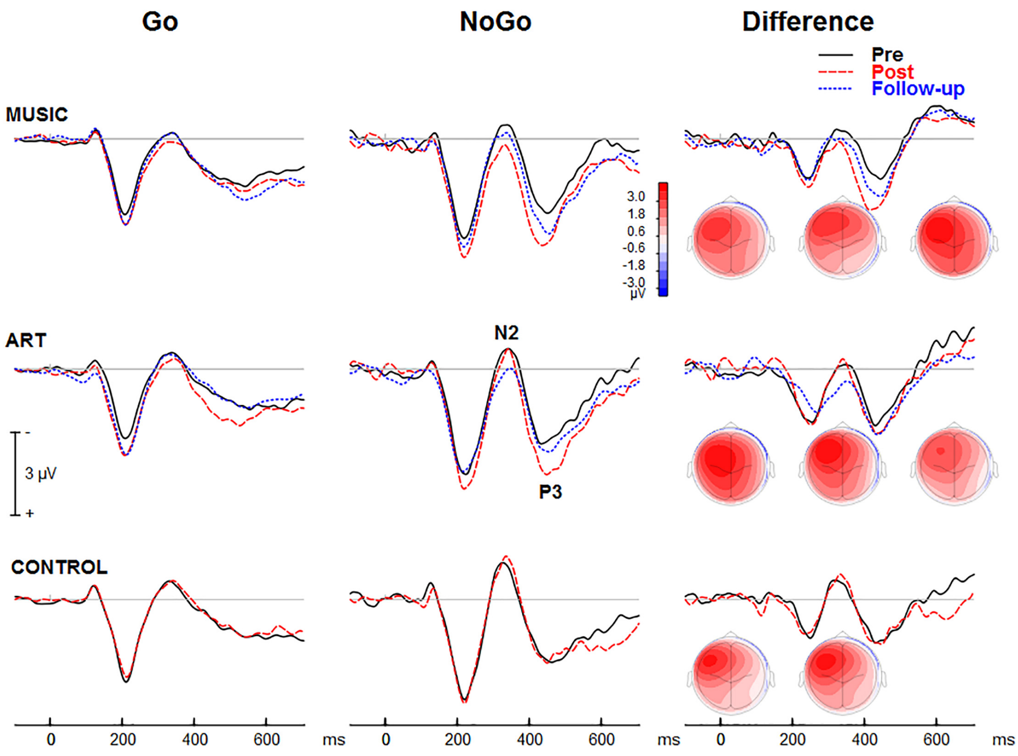

FIGURE 7 | Group mean visual event-related potential elicited during the visual GoNoGo task over the right frontal scalp region (i.e., electrode F2). The iso-contour maps (view from the top) show amplitude distribution for the mean voltage between 375 and 475 ms. From left to right, the maps show the distribution at pre-test, post-test, and follow-up, respectively.

for Go trials. The session × condition interaction was significant [$F(1,50) = 12.50$, $p = 0.001$, $\eta^2 = 0.20$]. This reflected greater difference between Go and NoGo trials (NoGo ERP effect) at post-test than pre-test. The condition × hemisphere interaction was also significant [$F(1,50) = 62.18$, $p < 0.001$, $\eta^2 = 0.55$]. This was due to larger NoGo responses over the left compared to right frontal scalp region.

Follow-up retention

In both music and visual art groups, the NoGo ERP effect was slightly reduced at follow-up compared to post-test, but the difference was not statistically significant. Moreover, the NoGo ERP effect at follow-up did not differ from the effects observed at pre-test. These results suggest that some training effects remained three months after the cessation of training. However, this finding should be interpreted with caution because of the small sample size at follow-up and the lack of difference between pre-test and follow-up session.

DISCUSSION

Using a partially randomized intervention design, our study reveals changes in older adults' brain responses following short-term arts training (music and visual art engagement). As such, we provide important new evidence suggesting a causal relationship between these activities and neuroplastic changes in older adults. In the present study, we also observed some training-specific effects using auditory oddball and visual GoNoGo paradigms.

Arts Training and Auditory Processing

In both groups, we observed increased N1 and P2 amplitude after training, which was retained at least 3 months after the training ended. Although enhanced N1 and P2 amplitude has been observed after training in several studies (e.g., Tremblay et al., 2001; Reinke et al., 2003), this is, to our knowledge, the first study showing training-related increased in N1 and P2 amplitude to untrained stimuli in older adults. In the present study, the effect of training was more pronounced for the piano tones. This difference in training-related N1 effect between piano tones and vowels could be related to familiarity with the material prior to study. Prior research has shown increased N1 and P2 amplitude with increased familiarity (Sheehan et al., 2005; Alain et al., 2015). For most participants, speech sounds such as vowels are over-learned and highly familiar stimuli leaving less opportunity to observe neuroplastic effects. In comparison, the piano tones used in the present study were more novel thereby benefiting more from training. The music group may thus have benefited from exposure to musical sounds; as for the visual art group, it is possible that such training may predispose the brain to be more receptive to new material than over-learned stimuli.

Training-specific changes were not observed in the auditory MMN as response latency peaked earlier at post-test than pre-test in all groups including controls. This suggests that exposure to stimuli at pre-test may be sufficient to facilitate the change detection process. Further research is needed to examine whether more specific training using auditory discrimination tasks would yield greater changes in older adults' MMN responses.

Arts Training and Visual Processing

Participants engaged in visual art training showed differences in early attention-related brain processing at posterior parietal-occipital scalp regions. This suggests that visual art training may improve processing of visual features. No such changes in early visual responses were observed in the control group or in participants involved in the music training program. Given that the visuals art group showed changes in both auditory and visual neural processing, these findings reveal an important property about the nature of brain plasticity in aging, showing cross-modality transfer of benefits (here from visual art training to auditory processing).

Arts Training and Cognitive Control

Following a short 3-month music or visual art training program, functional brain changes in inhibitory control were observed in both training groups. While both forms of training offered similar improvements (i.e., enhanced P3), notably, they also yielded training-specific changes (i.e., differential changes in N1 and P2 for visual art versus music groups). These findings are consistent with earlier reports of training-driven modulations in prefrontal cortical activity of older adults (Voss et al., 2010; Anguera et al., 2013).

At the behavioral level, the music group improved in color naming speed (subtest of the Stroop task) between pre- and post-assessment. This effect of music training could reflect improvement in processing speed. Decline in processing speed has been linked to general cognitive decline (Sliwinski and Buschke, 1999) and may have major consequences for the lives of older adults. Indeed, processing speed plays a critical role in everyday activities by facilitating important cognitive functions like learning and long-term memory, comprehension, decision making, and planning (West, 1996; Baddeley, 2012). Previous correlational studies have reported a link between higher cognitive skills and musicianship (Hanna-Pladdy and MacKay, 2011; Hanna-Pladdy and Gajewski, 2012; Amer et al., 2013). Our study extends these earlier findings by demonstrating a causal relationship between musical training and processing speed in older adults. This finding offers hope for improving the aging process using music intervention strategies that aim to strengthen cognitive skills.

Our results also revealed changes in the neural correlates of inhibitory control during a GoNoGo task following only 3 months of training. In NoGo trials, both training groups, as compared to the control group, showed increased and protracted P3 amplitude over the left hemisphere at post-test while the music group also showed similar effects over the right hemisphere. This is consistent with a prior study in older expert musicians (Moussard et al., 2016). It is noteworthy that the enhancement in NoGo-P3 in left frontal sites actually increased hemispheric symmetry following training. This finding is interesting because such results could be interpreted as a compensatory process in cognitive aging. Neuroimaging work has shown that high-performing older adults recruit additional resources and engage prefrontal cortex bilaterally during demanding tasks (Cabeza, 2002; Cabeza et al., 2002; Grady, 2012; Du et al., 2016). It is possible that training for both groups improved functioning of left frontal brain regions that had declined with age. In Go trials, the music group showed enhanced P3 amplitude at post-training compared to the visual art and control groups. P3 may reflect closure of the inhibition processing of an overt response (Gajewski and Falkenstein, 2013) or the ongoing evaluation of an intention to inhibit (Liotti et al., 2005). Thus, we infer that music training improves supervisory mechanisms that act to ensure desired responses and reinforce interference monitoring (Moreno et al., 2014; Moreno and Farzan, 2015).

Training-specific effects were expressed in P2 and N2 waves, in which we observed seemingly opposite effects for each training group: music students showed increased P2 and decreased N2 amplitudes after training whereas the visual art group showed decreased P2 and increased N2 amplitudes (no-contact controls showed no changes). In our previous study of younger adults undergoing musical instruction (Moreno et al., 2014), larger P2 was also observed in the music group. Taken alongside present findings, this suggests P2 is a common marker of plasticity in the brain's inhibitory control across the lifespan. The P2 wave is thought to index the ability to construct a representation of the current task context and the associated behavioral response in the early stages of processing (Gajewski and Falkenstein, 2013). Electrophysiological evidence suggests that this early aspect of visual processing has links to higher cognitive functions by facilitating stronger internal representations of behaviorally relevant stimuli (Moreno et al., 2014; Moreno and Farzan, 2015). Here, the larger P2 amplitude in the music group may reflect earlier processing and stronger representation of stimuli and the appropriate response (or non-response) pairing strengthened through training. Our results also showed a reduced N2 after music training, consistent with previous work in young adults (Moreno et al., 2014). N2 has been described as a marker of inhibition and conflict detection/attention load (Nieuwenhuis et al., 2003; Burle et al., 2004; Falkenstein, 2006). We interpret this effect in conjunction with the increased P2 amplitude such that music training facilitates dissociation of desired and undesired stimulus-response planning reflected by increased P2, and this enhanced effect of P2 subsequently reduces the need for cognitive control processes reflected by decreased N2 (Bokura et al., 2001; Nieuwenhuis et al., 2003; Donkers and van Boxtel, 2004; Kok et al., 2004).

On the other hand, the opposite pattern observed in the visual art training group may suggest that this form of training reduced early perceptual demands (reduced P2). This is plausible given that our GoNoGo was a visual paradigm (same domain as visual art training). Subsequent enhancements in later N2 may reflect improved post-perceptual conflict detection and response inhibition. Our findings agree well with existing evidence suggesting an impact of visual art instructions on the ventral visual pathway (Draganski et al., 2004; Op de Beeck and Baker, 2010; Pollmann and von Cramon, 2000) as well as higher-order cognitive brain networks (Chamberlain et al., 2014). Overall, the specific nature of changes induced by music and visual art instructions indicate that these divergent forms of training offer unique influences on brain function as well as enhancements to domain-general skills outside the direct scope of training (i.e., inhibitory control).

Limitations

A limitation of the current study is that our sample showed a gender imbalanced, which could affect the generalizability of our findings. All three groups comprised a much larger proportion of women than men. In older women, the decrease in estrogen level that occurs post-menopause may affect cognitive functions. Further research should ensure a more balanced representation of men and women and also monitor more closely whether women participants are receiving hormonal replacement therapy.

In the present study, the passive control group was added to assess test–retest effects at post-test (i.e., an improvement that would be due to repeating the same battery of tests a second time). This allowed us to better identify the nature and specificity of improvements at post-test. The purpose of the follow-up assessment was to test whether these training-related improvements (or neural changes) were maintained after training has stopped. Given that the control group did not receive any training, it was not justified to test for maintenance of training-related benefits/changes for this group. Although the control group showed little changes in performance and brain activity, we cannot rule out the possibility that differences would have emerged later due to either repeated testing or normal age-related decline. However, we should note that our study did not aim to directly test whether art training slows down cognitive decline: a much longer follow-up would have been required for this purpose (as healthy older adults do not usually show measurable declines after 3 months). Future longitudinal studies should consider adding additional testing for the control group(s) as well as longer follow-up.

Finally, although quite intensive (three sessions per week), the training program was relatively short (3 months). This may have limited the potential benefits of music training on behavioral performance. Future studies could consider longer periods of training, in order to better reflect the real experience of learning music.

CONCLUSION

Collectively, our findings expand current knowledge of neuroplasticity in aging by demonstrating dynamic changes in older adults' brain function following short-term music and visual arts training. Although the neuroplastic changes remain modest, especially for behavioral measures, our results offer clear causal evidence that the aged brain is more plastic than traditionally thought and suggests new possibilities for cognitive training and rehabilitation. Future studies should use longer training regimens to explore transfer effects to everyday life. With the growth of the aging population in modern society, there is a pressing need to find remedies which counteract cognitive decline, improve the aging process, and ultimately reduce health-related costs. Our study establishes that both visual art and music programs might be effective, engaging, and cost-effective solutions to boost older adults' brain plasticity. These programs could improve essential skills, bolster inhibitory control, and ultimately improve the quality of life for older adults.

ETHICS STATEMENT

The experimental protocol was approved by the Human Research and Ethics Committee at Baycrest Centre, Toronto, ON, Canada.

AUTHOR CONTRIBUTIONS

CA and SM designed the experiments. YL, AM, and GB performed the experiments and collected the data. CA, AM, GB, YL, and JS analyzed the data. CA, AM, GB, YL, and SM interpreted results of experiments. CA, AM, and SM drafted the manuscript. All authors edited and revised the manuscript, and approved the final version of manuscript.

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REFERENCES

Alain, C., Campeanu, S., and Tremblay, K. (2010). Changes in sensory evoked responses coincide with rapid improvement in speech identification performance. *J. Cogn. Neurosci.* 22, 392–403. doi: 10.1162/jocn.2009.21279

Alain, C., and Woods, D. L. (1999). Age-related changes in processing auditory stimuli during visual attention: evidence for deficits in inhibitory control and sensory memory. *Psychol. Aging* 14, 507–519.

Alain, C., Zhu, K. D., He, Y., and Ross, B. (2015). Sleep-dependent neuroplastic changes during auditory perceptual learning. *Neurobiol. Learn. Mem.* 118, 133–142. doi: 10.1016/j.nlm.2014.12.001

Aljondi, R., Szoeke, C., Steward, C., Yates, P., and Desmond, P. (2018). A decade of changes in brain volume and cognition. *Brain Imaging Behav.* doi: 10.1007/s11682-018-9887-z [Epub ahead of print]. doi: 10.1007/s11682-018-9887-z

Amer, T., Kalender, B., Hasher, L., Trehub, S. E., and Wong, Y. (2013). Do older professional musicians have cognitive advantages? *PLoS One* 8:e71630. doi: 10.1371/journal.pone.0071630

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., et al. (2013). Video game training enhances cognitive control in older adults. *Nature* 501, 97–101. doi: 10.1038/nature12486

Baddeley, A. (2012). Working memory: theories, models, and controversies. *Annu. Rev. Psychol.* 63, 1–29. doi: 10.1146/annurev-psych-120710-100422

Bidelman, G. M., and Alain, C. (2015). Musical training orchestrates coordinated neuroplasticity in auditory brainstem and cortex to counteract age-related declines in categorical vowel perception. *J. Neurosci.* 35, 1240–1249. doi: 10.1523/JNEUROSCI.3292-14.2015

Bidelman, G. M., Lowther, J. E., Tak, S. H., and Alain, C. (2017). Mild cognitive impairment is characterized by deficient brainstem and cortical representations of speech. *J. Neurosci.* 37, 3610–3620. doi: 10.1523/JNEUROSCI.3700-16.2017

Bidelman, G. M., Villafuerte, J. W., Moreno, S., and Alain, C. (2014). Age-related changes in the subcortical-cortical encoding and categorical perception of speech. *Neurobiol. Aging* 35, 2526–2540. doi: 10.1016/j.neurobiolaging.2014.05.006

Bokura, H., Yamaguchi, S., and Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clin. Neurophysiol.* 112, 2224–2232. doi: 10.1016/S1388-2457(01)00691-5

Brydges, C. R., Fox, A. M., Reid, C. L., and Anderson, M. (2014). Predictive validity of the N2 and P3 ERP components to executive functioning in children: a latent-variable analysis. *Front. Hum. Neurosci.* 8:80. doi: 10.3389/fnhum.2014.00080

Bugaiska, A., Clarys, D., Jarry, C., Taconnat, L., Tapia, G., Vanneste, S., et al. (2007). The effect of aging in recollective experience: the processing speed and executive functioning hypothesis. *Conscious Cogn.* 16, 797–808. doi: 10.1016/j.concog.2006.11.007

Bugos, J. A., Perlstein, W. M., McCrae, C. S., Brophy, T. S., and Bedenbaugh, P. H. (2007). Individualized piano instruction enhances executive functioning and working memory in older adults. *Aging Ment. Health* 11, 464–471. doi: 10.1080/13607860601086504

Burle, B., Vidal, F., and Bonnet, M. (2004). Electroencephalographic nogo potentials in a no-movement context: the case of motor imagery in humans. *Neurosci. Lett.* 360, 77–80. doi: 10.1016/j.neulet.2004.02.034

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol. Aging* 17, 85–100. doi: 10.1037/0882-7974.17.1.85

Cabeza, R., Anderson, N. D., Locantore, J. K., and McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage* 17, 1394–1402. doi: 10.1006/nimg.2002.1280

Chamberlain, R., McManus, I. C., Brunswick, N., Rankin, Q., Riley, H., and Kanai, R. (2014). Drawing on the right side of the brain: a voxel-based morphometry analysis of observational drawing. *Neuroimage* 96, 167–173. doi: 10.1016/j.neuroimage.2014.03.062

Dempster, F. N. (1992). The rise and fall of the inhibitory mechanism: toward a unified theory of cognitive development and aging. *Dev. Rev.* 12, 45–75. doi: 10.1016/0273-2297(92)90003-K

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Donkers, F. C., and van Boxtel, G. J. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain Cogn.* 56, 165–176. doi: 10.1016/j.bandc.2004.04.005

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., and May, A. (2004). Neuroplasticity: changes in grey matter induced by training. *Nature* 427, 311–312. doi: 10.1038/427311a

Du, Y., Buchsbaum, B. R., Grady, C. L., and Alain, C. (2016). Increased activity in frontal motor cortex compensates impaired speech perception in older adults. *Nat. Commun.* 7:12241. doi: 10.1038/ncomms12241

Dunn, L. M., and Dunn, D. M. (2007). *Peabody Picture Vocabulary Test*, 4th Edn. London: Pearson Education.

Erber, J. T. (2013). *Aging and Older Adulthood*. New Jersey, NJ: Wiley-Blackwell.

Falkenstein, M. (2006). Inhibition, conflict and the Nogo-N2. *Clin. Neurophysiol.* 117, 1638–1640. doi: 10.1016/j.clinph.2006.05.002

Fujioka, T., Ross, B., Kakigi, R., Pantev, C., and Trainor, L. J. (2006). One year of musical training affects development of auditory cortical-evoked fields in young children. *Brain* 129(Pt 10), 2593–2608. doi: 10.1093/brain/awl247

Gajewski, P. D., and Falkenstein, M. (2013). Effects of task complexity on ERP components in Go/Nogo tasks. *Int. J. Psychophysiol.* 87, 273–278. doi: 10.1016/j.ijpsycho.2012.08.007

Gazzaley, A., Rissman, J., Cooney, J., Rutman, A., Seibert, T., Clapp, W., et al. (2007). Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing. *Cereb. Cortex* 17(Suppl. 1), i125–i135. doi: 10.1093/cercor/bhm113

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi: 10.1038/nrn3256

Hanna-Pladdy, B., and Gajewski, B. (2012). Recent and past musical activity predicts cognitive aging variability: direct comparison with general lifestyle activities. *Front. Hum. Neurosci.* 6:198. doi: 10.3389/fnhum.2012.00198

Hanna-Pladdy, B., and MacKay, A. (2011). The relation between instrumental musical activity and cognitive aging. *Neuropsychology* 25, 378–386. doi: 10.1037/a0021895

Hasher, L., and Zacks, R. T. (1988). "Working memory, comprehension, and aging: a review and a new view," in *The Psychology of Learning and Motivation*, ed. G. H. Bower (New York, NY: Academic Press.), 193–225.

Hochberg, Y., and Benjamini, Y. (1990). More powerful procedures for multiple significance testing. *Stat. Med.* 9, 811–818. doi: 10.1002/sim.4780090710

Hyde, K. L., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., et al. (2009). The effects of musical training on structural brain development: a longitudinal study. *Ann. N. Y. Acad. Sci.* 1169, 182–186. doi: 10.1111/j.1749-6632.2009.04852.x

Knight, R. T. (1994). "Attention regulation and human prefrontal cortex," in *Motor and Cognitive Functions of the Prefrontal Cortex*, ed. A.-M. Thierry (Berlin: Springer-Verlag), 160–173. doi: 10.1007/978-3-642-85007-3_11

Kok, A., Ramautar, J. R., De Ruiter, M. B., Band, G. P., and Ridderinkhof, K. R. (2004). ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology* 41, 9–20. doi: 10.1046/j.1469-8986.2003.00127.x

Kropotov, J., Ponomarev, V., Tereshchenko, E. P., Muller, A., and Jancke, L. (2016). Effect of aging on erp components of cognitive control. *Front. Aging Neurosci.* 8:69. doi: 10.3389/fnagi.2016.00069

Liotti, M., Pliszka, S. R., Perez, R., Kothmann, D., and Woldorff, M. G. (2005). Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex* 41, 377–388. doi: 10.1016/S0010-9452(08)70274-0

Lustig, C., Hasher, L., and Zacks, R. T. (2007). "Inhibitory deficit theory: recent developments in a "new view"," in *Inhibition in Cognition*, eds D. S. Gorfein and C. M. MacLeod (Washington, DC: American Pschological Association), 145–162.

May, C. P., Hasher, L., and Kane, M. J. (1999). The role of interference in memory span. *Mem. Cogn.* 27, 759–767. doi: 10.3758/BF03198529

Moreno, S., Bialystok, E., Barac, R., Schellenberg, E. G., Cepeda, N. J., and Chau, T. (2011). Short-term music training enhances verbal intelligence and executive function. *Psychol. Sci.* 22, 1425–1433. doi: 10.1177/0956797611416999

Moreno, S., and Farzan, F. (2015). Music training and inhibitory control: a multidimensional model. *Ann. N. Y. Acad. Sci.* 1337, 147–152. doi: 10.1111/nyas.12674

Moreno, S., Marques, C., Santos, A., Santos, M., Castro, S. L., and Besson, M. (2009). Musical training influences linguistic abilities in 8-year-old children: more evidence for brain plasticity. *Cereb. Cortex* 19, 712–723. doi: 10.1093/cercor/bhn120

Moreno, S., Wodniecka, Z., Tays, W., Alain, C., and Bialystok, E. (2014). Inhibitory control in bilinguals and musicians: event related potential (ERP) evidence for experience-specific effects. *PLoS One* 9:e94169. doi: 10.1371/journal.pone.0094169

Moussard, A., Bermudez, P., Alain, C., Tays, W., and Moreno, S. (2016). Life-long music practice and executive control in older adults: an event-related potential study. *Brain Res.* 1642, 146–153. doi: 10.1016/j.brainres.2016.03.028

Nieuwenhuis, S., Yeung, N., van den Wildenberg, W., and Ridderinkhof, K. R. (2003). Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. *Cogn. Affect. Behav. Neurosci.* 3, 17–26. doi: 10.3758/CABN.3.1.17

Nikjeh, D. A., Lister, J. J., and Frisch, S. A. (2009). Preattentive cortical-evoked responses to pure tones, harmonic tones, and speech: influence of music training. *Ear Hear.* 30, 432–446. doi: 10.1097/AUD.0b013e3181a61bf2

Op de Beeck, H. P., and Baker, C. I. (2010). The neural basis of visual object learning. *Trends Cogn. Sci.* 14, 22–30. doi: 10.1016/j.tics.2009.11.002

Parbery-Clark, A., Anderson, S., Hittner, E., and Kraus, N. (2012). Musical experience offsets age-related delays in neural timing. *Neurobiol. Aging* 33:1483e1-e4. doi: 10.1016/j.neurobiolaging.2011.12.015

Parbery-Clark, A., Strait, D. L., Anderson, S., Hittner, E., and Kraus, N. (2011). Musical experience and the aging auditory system: implications for cognitive abilities and hearing speech in noise. *PLoS One* 6:e18082. doi: 10.1371/journal.pone.0018082

Pichora-Fuller, K., Alain, C., and Schneider, B. (2017). "Older adults at the cocktail party," in *The Auditory System at the Cocktail Party*, eds J. C. Middlebrook, J. Z. Simon, A. N. Popper, and R. R. Fay (Berlin: Springer), 227–259. doi: 10.1007/978-3-319-51662-2_9

Pichora-Fuller, M. K., Schneider, B. A., and Daneman, M. (1995). How young and old adults listen to and remember speech in noise. *J. Acoust. Soc. Am.* 97, 593–608. doi: 10.1121/1.412282

Pollmann, S., and von Cramon, D. Y. (2000). Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Exp. Brain Res.* 133, 12–22. doi: 10.1007/s002210000396

Reinke, K. S., He, Y., Wang, C., and Alain, C. (2003). Perceptual learning modulates sensory evoked response during vowel segregation. *Brain Res. Cogn. Brain Res.* 17, 781–791. doi: 10.1016/S0926-6410(03)00202-7

Rogenmoser, L., Kernbach, J., Schlaug, G., and Gaser, C. (2018). Keeping brains young with making music. *Brain Struct. Funct.* 223, 297–305. doi: 10.1007/s00429-017-1491-2

Schellenberg, E. G. (2004). Music lessons enhance IQ. *Psychol. Sci.* 15, 511–514. doi: 10.1111/j.0956-7976.2004.00711.x

Seinfeld, S., Figueroa, H., Ortiz-Gil, J., and Sanchez-Vives, M. V. (2013). Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults. *Front. Psychol.* 4:810. doi: 10.3389/fpsyg.2013.00810

Seither-Preisler, A., Parncutt, R., and Schneider, P. (2014). Size and synchronization of auditory cortex promotes musical, literacy, and attentional skills in children. *J. Neurosci.* 34, 10937–10949. doi: 10.1523/JNEUROSCI.5315-13.2014

Shahin, A., Bosnyak, D. J., Trainor, L. J., and Roberts, L. E. (2003). Enhancement of neuroplastic P2 and N1c auditory evoked potentials in musicians. *J. Neurosci.* 23, 5545–5552. doi: 10.1523/JNEUROSCI.23-13-05545.2003

Sheehan, K. A., McArthur, G. M., and Bishop, D. V. (2005). Is discrimination training necessary to cause changes in the P2 auditory event-related brain potential to speech sounds? *Brain Res. Cogn. Brain Res.* 25, 547–553. doi: 10.1016/j.cogbrainres.2005.08.007

Sliwinski, M., and Buschke, H. (1999). Cross-sectional and longitudinal relationships among age, cognition, and processing speed. *Psychol. Aging* 14, 18–33. doi: 10.1037/0882-7974.14.1.18

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi: 10.1037/h0054651

Tervaniemi, M., Ilvonen, T., Karma, K., Alho, K., and Naatanen, R. (1997). The musical brain: brain waves reveal the neurophysiological basis of musicality in human subjects. *Neurosci. Lett.* 226, 1–4. doi: 10.1016/S0304-3940(97)00217-6

Tierney, A., and Kraus, N. (2015). Neural entrainment to the rhythmic structure of music. *J. Cogn. Neurosci.* 27, 400–408. doi: 10.1162/jocn_a_00704

Tremblay, K., Kraus, N., McGee, T., Ponton, C., and Otis, B. (2001). Central auditory plasticity: changes in the N1-P2 complex after speech-sound training. *Ear Hear.* 22, 79–90. doi: 10.1097/00003446-200104000-00001

Voss, M. W., Prakash, R. S., Erickson, K. I., Basak, C., Chaddock, L., Kim, J. S., et al. (2010). Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front. Aging Neurosci.* 2:32. doi: 10.3389/fnagi.2010.00032

Wallentin, M., Nielsen, A. H., Friis-Olivarius, M., Vuust, C., and Vuust, P. (2010). The musical ear test, a new reliable test for measuring musical competence. *Learn. Individ. Differ.* 20, 188–196. doi: 10.1016/j.lindif.2010.02.004

West, R., and Alain, C. (2000). Age-related decline in inhibitory control contributes to the increased Stroop effect observed in older adults. *Psychophysiology* 37, 179–189. doi: 10.1111/1469-8986.3720179

West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychol. Bull.* 120, 272–292. doi: 10.1037/0033-2909.120.2.272

White-Schwoch, T., Woodruff Carr, K., Anderson, S., Strait, D. L., and Kraus, N. (2013). Older adults benefit from music training early in life: biological evidence for long-term training-driven plasticity. *J. Neurosci.* 33, 17667–17674. doi: 10.1523/JNEUROSCI.2560-13.2013

Zendel, B. R., and Alain, C. (2009). Concurrent sound segregation is enhanced in musicians. *J. Cogn. Neurosci.* 21, 1488–1498. doi: 10.1162/jocn.2009.21140

Zendel, B. R., and Alain, C. (2012). Musicians experience less age-related decline in central auditory processing. *Psychol. Aging* 27, 410–417. doi: 10.1037/a0024816

Zendel, B. R., and Alain, C. (2014). Enhanced attention-dependent activity in the auditory cortex of older musicians. *Neurobiol. Aging* 35, 55–63. doi: 10.1016/j.neurobiolaging.2013.06.022

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REVIEW
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Music Intervention Approaches for Alzheimer's Disease: A Review of the Literature

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Music interventions have been widely adopted as a potential non-pharmacological therapy for patients with Alzheimer's disease (AD) to treat cognitive and/or behavioral symptoms of the disease. In spite of the prevalence of such therapies, evidence for their effectiveness report mixed results in the literature. The purpose of this narrative review is to investigate the effectiveness of various intervention strategies (music therapy vs. music listening techniques) and music type used in the intervention (individualized vs. non-individualized music) on cognitive and behavioral outcomes for persons with AD. Databases were searched for studies using either active music therapy or music listening techniques over the last 10 years. These studies were in English, included persons with AD dementia, and whose protocol gathered pre- and post-intervention outcome measures. We initially identified 206 papers which were then reduced to 167 after removing duplicates. Further review yielded 13 papers which were extensively reviewed, resulting in a final sample of six papers. Our analysis of these papers suggested that, regardless of the music intervention approach, individualized music regimens provided the best outcomes for the patient. Furthermore, music listening may act as a relaxation technique and therefore provide a long-term impact for the patient, while active music therapy may acts to engage participants through social interaction and provide acute benefits. Our findings suggest that music techniques can be utilized in various ways to improve behavior and cognition.

Keywords: Alzheimer's disease, music therapy, music-based intervention, music listening, cognitive function

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia with an estimated 50 million people living with the disease today (World Health Organization, 2018). It is marked by decreased cognitive functioning (memory, visuospatial issues, and executive functioning), emotional control, and neuropsychiatric symptoms such as apathy, depression, and agitation (Lyketsos et al., 2002). Medications for AD aim to improve cognition and relieve behavioral symptoms, however, many approved drugs provide only modest benefits for the patient (Lanctôt et al., 2003; Casey et al., 2010). As a result, there has been an increase for research for non-pharmacological interventions to reduce symptom burden for AD persons and their caregivers.

In recent years, music interventions have grown in popularity as a method of non-pharmacological treatment for persons with AD for a number of reasons. First, there is evidence to suggest that music for memory can remain intact for persons with AD, even while experiencing rapid cognitive decline (Cuddy et al., 2012). This is thought to be because musical memory networks are separate from traditional temporal lobe memory networks (Platel et al., 2003; Satoh et al., 2006) which are spared until the later stages of the disease (Jacobsen et al., 2015). According to these studies, music activates a broad network in the brain rather than a single "music area." Particularly, when listening to familiar music (such as popular folk songs, nursery rhymes, and songs on top 100 charts), musical memory retrieval involved areas both within and outside of the temporal lobes, including frontal and parietal regions (Platel et al., 2003; Satoh et al., 2006; Jacobsen et al., 2015). This diffuse network may allow sparing of musical memory functions. Furthermore, Jacobsen et al. (2015) utilized PET to investigate the degree in which music listening areas are affected by AD pathology, such as such as amyloid build up and glucose metabolism, compared to the rest of the brain and found that music listening areas experienced less pathology. The ability for persons with remember music makes music a unique stimuli which effectively engages persons with AD.

Another reason why music interventions are becoming popular with this population is because behavioral studies have shown that music can improve some cognitive functions in AD persons. For example, music in the background has been shown to improve autobiographical recall (Foster and Valentine, 2001; Irish et al., 2006; El Haj et al., 2012b). According to Moscovitch (1992), "involuntary memories" are memories which can be retrieved automatically by a cue. El Haj et al. (2012a) believe that memories evoked by music contain the same properties as involuntary memories. In other words, music can be used as a cue to evoke involuntary autobiographical memories which are specific and invoke an emotional response. Furthermore, Simmons-Stern et al. (2010, 2012) found than music enhanced verbal encoding of information. The ability of music to enhance encoding, memory and cognition in AD persons has been attributed to modulating physiological responses. It has been postulated that music's ability to induce arousal and evoke positive emotional responses can activate the parasympathetic or sympathetic nervous system, depending on the type of music and rhythm, to in turn alleviate neuropsychological symptoms and enhance encoding efforts (Peck et al., 2016). One study by de la Rubia Ortí et al. (2018) provided evidence that music can improve emotional state in persons with AD lowering stress levels as measured by cortisol in saliva. Music interventions have also been shown to have other positive physiological effects on AD persons that may affect cognition and behavior, such as improving sleep by increasing melatonin levels (Kumar et al., 1999) and balancing hormones without the adverse effects of hormone replacement therapy (Fukui et al., 2012).

Lastly, music interventions have gained an increasing amount of interest in researchers and caregivers because, conceptually, it is an inexpensive, easily implemented, and highly enjoyable means of treatment for persons with AD. Behavioral studies investigating music interventions in AD report of low drop-out rates and high engagement in those with the disease (Guétin et al., 2009; Arroyo-Anlló et al., 2013; Sakamoto et al., 2013; Li et al., 2015; Giovagnoli et al., 2017; Gómez Gallego and Gómez García, 2017).

Music is highly versatile and accessible, which allows it to be used in patient populations in a variety of ways. Raglio and Oasi (2015) described three music approaches used in clinical settings: music therapy, music listening, and general music-based interventions. Music therapy is defined by the Canadian Association of Music Therapists (2016) as "a discipline in which credentialed professionals use music purposefully within therapeutic relationships to support development, health, and well-being." Music therapy involves a crucial component of client/therapist interaction through an empirically supported model, and can consist of active (involving improvisation, singing, clapping, or dancing) and/or receptive (music listening purposefully to identify emotional content emerging from music) techniques (Raglio and Oasi, 2015). Music listening approaches involve a music therapist to create a music playlist for the client, which can be individualized programs or chosen by the therapist (Raglio and Oasi, 2015). Recent literature suggests that individualized music is most beneficial in AD by improving autobiographical memory (Foster and Valentine, 2001; Irish et al., 2006; García et al., 2012; Peck et al., 2016). Generalized music interventions involve the use of music without a music therapist with the goal of improving the well-being of the patient. These methods can also use active or music listening protocols. Music listening is used to "stimulate verbalization, memories, or to encourage of relaxation" (Raglio and Oasi, 2015).

Previous reviews have been published investigating the impact of music intervention on persons with dementia.Abraha et al. (2017) conducted a systematic review which summarized the results of six previously published systematic reviews on various non-pharmacological interventions. They found that interventions which included music were best at reducing behavioral symptoms of dementia. Specifically, music reduced agitation and anxiety. Another large review by van der Steen et al. (2018) found that music therapy was effective in reducing depressive and overall behavioral symptoms in their dementia participants. However, their investigation found little evidence to suggest there are benefits for anxiety, cognition, or overall quality of life. Another systematic review and meta-analysis (Tsoi et al., 2018) found that music therapy involving listening to music was more effective in reducing behavioral symptoms compared to active music therapies. Again, this study found a lack of evidence to suggest that music interventions provide benefits on cognition for persons with dementia. Contrary to these results, Fusar-Poli et al. (2017) found that active music therapy improved global cognition for persons with dementia. As well, Zhang et al. (2017) found that, after assessing for heterogeneity, music therapy had a positive outcomes for cognition for dementia.

Regardless of the mixed results in the literature, many clinicians and researchers suggest that music should be used in a medical setting (Koelsch, 2009; Kobets, 2011). In this review, we will examine the existing literature on music interventions involving individuals with AD dementia and summarize the various techniques used and their impact on cognition and behavior for this population.

METHODS

Inclusion and Exclusion Criteria

For this review, we included studies published in the last 10 years (2008–2018), and available in English with pre- and post-intervention data collection in cognitive and/or behavioral domains. The intervention must meet the definition as either music therapy, music listening or generalized music-based interventions (active or music listening), and can be individualized or non-individualized (Raglio and Oasi, 2015). Generalized music approaches without a music therapist must be validated by a caregiver or conducted in a controlled setting to ensure adherence to protocol. The studies gathered in our review included only patients with AD dementia. Studies that were excluded included reviews, letters to the editors, studies which did not involve a music intervention or included an intervention other than music approaches, studies using a mixed intervention strategy, or studies that included a diagnosis of dementia other than AD, such as vascular dementia, Lewy body dementia, or mixed dementia.

Search Strategy

The electronic databases MEDLINE, Pubmed, and PSYCHINFO were searched using the terms "AD" and "music intervention" or "music therapy" or "music based intervention." The abstracts of all results from this search were read and sorted whether they adhered to our inclusion or exclusion criteria. These papers were then read for their entirety and further exclusions were made based on the inclusion criteria.

RESULTS

Search Results

Our initial search of the databases resulted in 206 papers meeting search criteria. After removing repeated articles between the databases, 167 papers were included in the search. After reviewing titles and abstracts for meeting the criteria above, 13 papers were identified. A thorough reading of the papers resulted in size papers meeting criteria of this review (**Table 1**) (Guétin et al., 2009; Arroyo-Anlló et al., 2013; Sakamoto et al., 2013; Li et al., 2015; Giovagnoli et al., 2017; Gómez Gallego and Gómez García, 2017). The seven exclusions from the 13 papers identified were excluded due to: including no primary outcome of cognition or behavioral measure, non-AD dementia population included in the study, a study investigating acute effects on a small population after an 18-min live one-on-one session, and AD being assessed only as a covariate.

Music Approaches for Studies That Met Inclusion Criteria

All studies included in this review involved an intervention classified as either an active music therapy or music listening (Raglio and Oasi, 2015). The music was gathered by the authors based on either the patient's preferences (individualized) or chosen by the experimenter (not individualized). All the participants were diagnosed with AD dementia. Studies varied in the method of music exposure, setting, and type of music used.

Three studies included in this review implemented a music listening approach without an active component or music therapist (Guétin et al., 2009; Arroyo-Anlló et al., 2013; Li et al., 2015). These studies involved listening to music streamed to their rooms or headphones under the supervision of their caregivers. Li et al. (2015) used a non-individualized general music listening approach involving listening to classical music daily with their caregivers. Participants were instructed to listen to Mozart's Sonata for Two Pianos in D major for 30 min in morning and Pachelbel's Canon in D major for Violins for 30 min before sleep. Conversely, Guétin et al. (2009) and Arroyo-Anlló et al. (2013) used individualized playlists based on their participant's interests. Arroyo-Anlló et al. (2013) compared a familiar music listening group to a non-familiar music listening group. Participants were asked to listen to their given music program and listen attentively in a quiet room with headphones and without distractions. Interestingly, the approach used by Guétin et al. (2009) used a specific method of music listening to induce relaxation, called the "U Sequence" (Guétin et al., 2005; Jaber et al., 2007), where rhythm, orchestral formation, frequency, and volume is slowly reduced, then increased again in a "re-enlivening" phase. The music was streamed via headphones to patient's room.

Two studies investigated solely active music therapy led by at least one music therapist (Giovagnoli et al., 2017; Gómez Gallego and Gómez García, 2017). Giovagnoli et al. (2017) used active music therapy which adopted a "non-verbal approach with free sound–music interactions, using rhythmical and melodic instruments." This involved allowing participants to choose instruments and play them freely. They were instructed to appreciate sounds and movement and to create interpersonal relationships with others and evoke emotions. The intervention was not individualized to the participant. Gómez Gallego and Gómez García (2017) used active music therapy with individualized music based on the participant's tastes. Sessions included a welcome song (patients greeted and introduced themselves), rhythmic accompaniment (clapping hands or playing music instruments), moving to background music (moving arms and legs to music, dance therapy with hoops and balls), guessing songs, and farewell song.

One study compared outcomes between a music listening intervention group to an active music therapy group led by a team of clinicians. The study by Sakamoto et al. (2013) contained three experimental groups (music listening, active music therapy, control groups) in order to compare active music therapy vs. music listening vs. a control group. The music listening sessions involved an individualized music playlist via a CD player with no interaction with their caregivers or a music therapist. The active group also used the CD player with individualized music but the sessions were led by music therapists, occupational therapists, and nurses, who facilitated activities such as clapping, singing, and dancing. Participants in control group remained in a silent room with their caregiver.

TABLE 1 | Studies investigating music interventions for AD.

Study	Participants	Music intervention length	Music intervention method	Outcome measures	Summary of Results
Giovagnoli et al. (2017) *Neurological Sciences*	Probable mild to moderate AD (MMSE > 15). CT ($n = 13$) vs. Active music therapy (AMT) ($n = 13$) vs. Neuro-education (NE) ($n = 13$)	12-weeks, including two 25 min group sessions per week	Active music therapy Led by music therapist Non-verbal approach with free sound–music interactions, using rhythmical and melodic instruments. Participants choose instruments and played them freely. Participants and were instructed to appreciate sounds and movement and to create interpersonal relationships with others and evoke emotions. Not individualized	Measures taken at beginning and end of intervention (Week 1 and week 12). Follow up 3 months after intervention completion *Cognitive:* Word Fluency Task (WFT) on phonemic and semantic cue Short Story Test (SST) Corsi Blocks Span Rey Complex Figure copying and delayed recall Rey Auditory Verbal Learning (RAVLT) Trail Making Attentive Matrices Weigl Sorting Raven Colored Progressive Matrices (RCPM) Street Completion tests *Behavioral:* Beck Depression Inventory (BDI) State Trait Anxiety Inventory (STAI Y-1, STAI Y-2) Lubben Social Network Scale (LSNS)	*Cognitive:* AMT showed less clinically significant improvements in WFT scores than CT (7.69% and 61.54%, respectively), but more than the NE group (none). AMT showed less clinically significant improvements in SST scores than CT (23.08% and 38.46%, respectively), but more than the NE group (none). *Behavioral:* AMT showed improvement of mood similarly to CT and NE.
Gómez Gallego and Gómez García (2017) *Neurologia*	Probable mild to moderate AD (CDR = 1–2) Music intervention group only ($n = 42$)	6-weeks, including two 45 min group sessions per week	Active music therapy Led by 2 music therapists Sessions included a welcome song (patients greeted and introduced themselves), rhythmic accompaniment (clapping hands or playing music instruments), moving to background music (moving arms and legs to music, dance therapy with hoops and balls), guessing songs, and farewell song. Individualized	Measures taken at 3 and 6 weeks. No follow up. *Cognitive:* Mini-Mental Status Examination (MMSE) *Behavioral:* Neuropsychiatric Inventory (NPI) Hospital Anxiety and Depression Scale (HADS) Barthel Index (BI)	*Cognitive:* Significant increase in MMSE scores for orientation, language and memory from beginning to end of sessions. *Behavioral:* Non-significant decrease in total NPI scores (decreased subscores in delusions, hallucinations, agitation, anxiety, apathy, and irritability in moderate dementia). Decreased especially anxiety and depression according to HADS. No change in functional dependence according to BI
Li et al. (2015) *Neuropsych-iatric Disease and Treatment*	Mild AD (CDR = 0.5∼1) $n = 41$ AD participants divided into music intervention group ($n = 21$) vs. control group ($n = 21$)	24-weeks, including seven 1 h sessions per week (divided into 30 min in morning and 30 min at night)	Music listening Listening with caregivers Listen to Mozart's Sonata for Two Pianos in D major for 30 min in morning and Pachelbel's Canon in D major for Violins for 30 min before sleep Not individualized	Measures taken at baseline and at 6 months. No follow up. *Cognitive:* Cognitive Abilities Screening Instrument (CASI) Clinical Dementia Rating Scale with sum of box scores (CDR-SB) Mini-Mental State Exam CASI-estimated (MMSE-CE) *Behavioral:* NPI	*Cognitive:* No significant difference in total cognitive scores in MBI vs. control groups. Significant difference found in abstraction, slight improvement of short term memory *Behavioral:* No significant findings

(Continued)

TABLE 1 | Continued

Study	Participants	Music intervention length	Music intervention method	Outcome measures	Summary of Results
Arroyo-Anlló et al. (2013) *BioMed Research International*	Mild-moderate AD (average MMSE of 19) *n* = 40 AD participants divided into individualized music group (*n* = 20) vs. non-individualized group	12 weeks, including three 2–4 min sessions per week	*Music listening* Listening with caregivers Listen to music attentively at home, in a quiet room with headphones and without distractions Individualized and not individualized groups	Measures then 1–2 weeks before and 1–2 weeks after MBI completion. No Follow up. *Cognitive:* Mini-Mental State Exam (MMSE) F-A-S Test Self-Consciousness Questionnaire	*Cognitive:* No change in cognition for familiar group, although unfamiliar group experienced decline. Significant differences of self-consciousness in familiar music group, specifically personal identity, affective state, moral judgement, and body representation.
Sakamoto et al. (2013) *International Psychogeri-atrics*	Severe AD (CDR = 3) *n* = 39 AD participants divided into music listening group (*n* = 13), active group (*n* = 13) and no intervention group (*n* = 12)	10 weeks, including one 30-min session per week	Active and music listening *Active:* Led by two music therapists, four occupational therapists, and six nurses. Listening to music on a CD player, while doing activities such as clapping, singing, and dancing. *Receptive:* Listening with caregiver Passively listened to the selected music via a CD player Both individualized	Measures taken 2 weeks before study and at MBI completion. Follow up 3 weeks after MBI completion *Behavioral:* Faces Scale Behavioral Pathology in Alzheimer's Disease Autonomic nerve index [Heart rate (HR) and high-frequency (HF)]	*Behavioral:* Immediately after one session: Increased parasympathetic activity (HR and HF) in receptive and active MBI, as well as improved emotional state (active slightly better) resulting in reduced stress After 10-week MBI completion: decreased anxiety, affective disturbance in receptive group and active group; decreased anxiety, affective disturbance, paranoid/delusion, aggression, activity disturbance and Global Rating in active only, as well as reduced caregiver burden. Post intervention: Effects disappeared after 3 weeks.
Guétin et al. (2009) *Dementia and Geriatric Cognitive Disorders*	Mild-moderate AD (MMSE 12–25) *n* = 30 AD participants, divided into MBI group (*n* = 15) and no MBI group/reading (*n* = 15)	16 weeks, including one 20-min session per week	Music listening Listening to music alone in controlled setting Music streamed to nursing home rooms via headphones Individualized	Measures taken at MBI initiation, 4, 8, and 16 weeks. Follow up 8 weeks after MBI completion *Behavioral:* Hamilton Scale Geriatric Depression Scale	*Behavioral:* Significant decrease in anxiety at 4 weeks and persisted after 2 months; significant decrease in depression after 3 weeks and persisted at 6 months

AD, Alzheimer's disease; n, number of participants; MMSE, Mental Status Examination; CT, cognitive training; AMT, Active Music Therapy; NE, Neuro-education; WFT, Word Fluency Task; SST, Short Story Test; RAVLT, Rey Auditory Verbal Learning Test; RCPM, Raven Colored Progressive Matrices; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory; LSNS, Lubben Social Network Scale; CDR, Clinical Dementia Rating; NPI, Neuropsychiatric Inventory; HADS, Hospital Anxiety and Depression Scale; BI, Barthel Index; CASI, Cognitive Abilities Screening Instrument; CDR-SB, CDR-sum of boxes; MMSE-CE, MMSE-CASI estimated; MBI, music-based intervention.

DISCUSSION

A diverse method of approaches for intervention were implemented across studies, including varying music selection and method of exposure. In this discussion, we will look at the effects of music selection and intervention approach on cognition or behavior in persons with AD.

Studies which used individualized playlists (Guétin et al., 2009; Arroyo-Anlló et al., 2013; Sakamoto et al., 2013; Gómez Gallego and Gómez García, 2017) resulted in improved outcomes for cognition and behavior in both active music therapy and music listening compared to methods that used experimenter chosen music. For example, Li et al. (2015) selected pre-determined classical music pieces for the participants. The use of classical music in order to enhance cognition is known as the "Mozart Effect" (Rauscher et al., 1993). This phenomenon has been attributed to acute arousal caused by the enjoyment of listening to music, and not because classical music has the ability to enhance cognition beyond the music listening session (Chabris, 1999; Thompson et al., 2001). Li et al. (2015) did not find any changes in behavior correlated to their intervention and found only small changes in cognition when looking into subcategories of cognitive tests. Additionally, Giovagnoli et al. (2017) active music therapy did not engage participants to music that was known to them. The authors found only slight clinical improvements in a verbal initiative executive functioning task and episodic memory (in 7.69 and 23.08% of participants, respectively), but much less so than the cognitive training (CT) condition (61.54 and 38.46%, respectively). This study also found that, although some mood improvements were found in their intervention, the same improvements were found in CT and Neuroeducation (NE) groups, and therefore can be attributed to the creation interpersonal relationships with group members, experience of a change of setting from their regular routine, or interaction between group members and clinicians and music therapists (Raglio and Oasi, 2015) rather than a unique effect of music on mood, behavior, or cognition.

Conversely, our investigation found that intervention approaches which provided individualized music playlists generally found positive outcomes in both cognition and behavior for their participants (Guétin et al., 2009; Arroyo-Anlló et al., 2013; Sakamoto et al., 2013; Gómez Gallego and Gómez García, 2017). Arroyo-Anlló et al. (2013) compared familiar and unfamiliar generalized music listening groups and found improvements in self-consciousness and global cognition in the familiar music group compared to the unfamiliar group. Gómez Gallego and Gómez García (2017) used individualized music in their active intervention and found improvement in orientation, language and memory domains cognitively, as well as improvements in anxiety and depression. Sakamoto et al. (2013) investigated only behavioral outcome measures and found acute improvements in anxiety, affective disturbance, aggression, psychosis, and activity disturbance. Finally, Guétin et al. (2009) found improvement in anxiety and depression in their individualized music listening intervention. The benefit of music on cognition and behavioral symptoms of AD have been commonly attributed to arousal and improved mood (Chabris, 1999; Thompson et al., 2001). However, our investigation showed that music that is individualized to the patient show greater benefits than music that the patient does not know, suggesting more than arousal is involved in improving cognitive and behavioral outcomes for patients. We suggest this is due to the positive effects that long-known music can have on the brain of AD persons. Previous literature suggests that music can evoke autobiographical memories in persons with AD (Foster and Valentine, 2001; Irish et al., 2006; El Haj et al., 2012b), particularly if the music is self-chosen and known to the patient (El Haj et al., 2015). The deterioration of memory in AD is often linked with impairment of autonomy and the sense of Self (Fargeau et al., 2010). Since music that is known to the patient has the ability evoke autobiographical memories (El Haj et al., 2015), this can in turn improve self-consciousness, global cognitive functioning, and neuropsychiatric symptoms in individuals with AD (Arroyo-Anlló et al., 2013).

Our investigation provided evidence that the intervention approach used may also have an effect on cognition and behavior. Namely, Sakamoto et al. (2013) uniquely compared their generalized music listening intervention to an active music therapy group, and found that both methods of treatment showed generally significant results in behavioral symptoms such as anxiety and affective disturbance. However, those who underwent music therapy experienced additional benefits compared to the music listening group in the domains of paranoid/delusion, aggression, activity disturbance and overall rating of behavioral symptoms in persons with more severe AD. However, these results disappeared after the intervention. Conversely, the other two studies utilizing active music therapy provided conflicting results on both cognition and mood (Giovagnoli et al., 2017; Gómez Gallego and Gómez García, 2017), where Giovagnoli et al.'s (2017) active music therapy saw no better improvements on mood than NE or CT and significantly less cognitive outcomes than CT, while Gómez Gallego and Gómez García (2017) found significant cognitive improvement in both cognition and mood. Since Gómez Gallego and Gómez García (2017) used an individualized approach and Giovagnoli et al. (2017) did not, these improvements may be due to type of music used (individualized vs. not individualized) and not the intervention approach (music listening vs. active music therapy).

The music intervention approach may also have different impacts on the sympathetic and parasympathetic nervous systems of participants, which may affect acute and long-term outcomes. Active music therapy tends to focus more on and activity and the social aspects of participation (Raglio and Oasi, 2015), such as interactions between client and clinician and the act of clapping, dancing and playing instruments. While all the active music therapies encouraged interpersonal relationships with others and emotional introspection, the music listening approaches undergone by the studies in this review focused more on engaging participants to music they enjoy and know from their past. Additionally, music listening approaches provided a calm and relaxing environment to induce relaxation, while active music therapies increased arousal with participation (Sakamoto et al., 2013). As postulated by Peck et al. (2016) music can modulate the sympathetic and parasympathic autonomic nervous systems and, as a consequence, physiological responses. During active music therapy sessions, Sakamoto et al. (2013) measured heart rate immediately after active sessions and music listening as part of their protocol and found that heart rate was elevated after active music sessions when compared to the music listening sessions. Therefore, the effects of active sessions may be based more on arousal mechanisms to reduce behavioral symptoms acutely, while music listening may act to train participants in relaxation techniques that provide parasympathetic regulation and prolonged benefits to the patients. Additionally, Guétin et al. (2009) used a specific music listening technique called the "U Sequence" which was developed specifically to gradually relax the listener (Guétin et al., 2005; Jaber et al., 2007). The authors created this type of music program with individualized music for each participant. In addition to providing benefits for anxiety and depression after completion of intervention, the authors found the effects of the therapy lasted 6 months after completion. Of the three studies that followed up with participates after completion of the intervention (Guétin et al., 2009; Sakamoto et al., 2013; Giovagnoli et al., 2017), no other study included in our review found the benefits from their program persisted after termination of the intervention. Our findings of the benefits of music listening for persons with AD compared to active music therapy is supported by a recent review by Tsoi et al. (2018), who also found that music therapies involving music listening provided greater benefits than active music therapy.

Our review has limitations that should be addressed. The aim of this narrative review was to determine the impact of various music intervention approaches specifically for persons with AD. However, the studies included vary in other aspects which may impact the results, such as participant age, disease severity, cognitive level, outcome measures, length of intervention, etc. Furthermore, the methodology differed within musical approaches. For example, music listening regimens ranged in their method of exposing participants to music, such as via headphones or streamed through the room. Music therapy techniques differed in the activities conducted during the sessions. As well, our investigation included only a small amount of studies, which may result in low power of our results.

CONCLUSION

In this review, we discussed six studies involving a music intervention approach for AD persons that met our search criteria. In summary, our investigation into the aforementioned studies suggested music interventions which used individualized music playlists and focused on relaxation techniques tended to yield greater benefits on AD persons. We hypothesize this is due the enhancement of autobiographical memory, autonomy, and parasympathetic modulation which in turn has positive effects on cognition and behavior.

While there are many reviews available looking at the effect of music on various symptoms, intervention studies that assess music, cognition, and memory are less common. As cognitive decline is a main effect of AD and can contribute further to increasing neuropsychiatric symptoms, medication use, and visits to the emergency room, investigation of music on cognition in the future is imperative. As well, more rigorous behavioral studies, as well as systematic reviews and meta-analyses, are needed to investigate the impact of individualized vs. not individualized music to make stronger evidence-based conclusions. Lastly, although many studies have investigated outcomes pre- and post-music intervention for AD persons, there is a lack of studies investigating brain changes associated with a music intervention. As well, imaging studies investigating brain areas involved in music listening have thus far only been investigated in healthy, young controls. Such studies could provide empirical evidence to further the understanding of mechanisms involved in musical memory, and how music can work to improve cognition and behavior in persons with AD.

AUTHOR CONTRIBUTIONS

ML formulated the research paper idea, wrote the main body of the manuscript, participated in revisions, and submitted the final manuscript. MT provided substantial edits to the paper and final draft, and aided in the interpretation of the paper. LF contributed to the formulation of the research paper idea, provided substantial edits to the paper and the final draft, and aided in the interpretation of the paper. TS provided substantial edits to the paper and final draft, and aided in the interpretation of the paper. JB provided edits to the final draft, and aided in the interpretation of the paper. DM provided edits to the final draft, and aided in the interpretation of the paper. CF contributed to the formulation of the research paper idea, provided substantial edits to the paper and the final draft, and aided in the interpretation of the paper.

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REFERENCES

Abraha, I., Rimland, J. M., Trotta, F. M., Dell'Aquila, G., Cruz-Jentoft, A., Petrovic, M., et al. (2017). Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. the SENATOR-OnTop series. *BMJ. Open* 7:e012759. doi: 10.1136/bmjopen-2016-012759

Arroyo-Anlló, E. M., Díaz, J. P., and Gil, R. (2013). Familiar music as an enhancer of self-consciousness in patients with alzheimer's disease. *BioMed. Res. Int.* 2013:752965. doi: 10.1155/2013/752965

Canadian Association of Music Therapists. (2016). *About Music Therapy*. Available at: https://www.musictherapy.ca/about-camt-music-therapy/about-music-therapy/

Casey, D. A., Antimisiaris, D., and O'Brien, J. (2010). Drugs for alzheimer's disease: are they effective? *Phar. Ther.* 35, 208–211.

Chabris, C. F. (1999). Prelude or requiem for the 'Mozart effect'? *Nature* 400, 826–827. doi: 10.1038/23611

Cuddy, L. L., Duffin, J., Brown, C. L., and Sikka, R. (2012). Memory for melodies and lyrics in alzheimer's disease. *Music Percept.* 29, 479–491. doi: 10.1525/mp.2012.29.5.479

de la Rubia Ortí, J. E., García-Pardo, M. P., Cabañés Iranzo, C., Cerón Madrigal, J. J., Castillo, S. S., Julián Rochina, M., et al. (2018). Does music therapy improve anxiety and depression in alzheimer's patients? *J. Altern. Compl. Med.* 24, 33–36. doi: 10.1089/acm.2016.0346

El Haj, M., Antoine, P., Nandrino, J. L., Gély-Nargeot, M. C., and Raffard, S. (2015). Self-defining memories during exposure to music in alzheimer's disease. *Int. Psychogeriatr.* 27, 1719–1730. doi: 10.1017/S1041610215000812

El Haj, M., Fasotti, L., and Allain, P. (2012a). The involuntary nature of music-evoked autobiographical memories in alzheimer's disease. *Cons. Cogn.* 21, 238–246. doi: 10.1016/j.concog.2011.12.005

El Haj, M., Postal, V., and Allain, P. (2012b). Music enhances autobiographical memory in mild alzheimer's disease. *Educ. Gerontol.* 38, 30–41. doi: 10.1080/03601277.2010.515897

Fargeau, M. N., Jaafari, N., Ragot, S., Houeto, J. L., Pluchon, C., and Gil, R. (2010). Alzheimer's disease and impairment of the Self. *Cons. Cogn.* 19, 969–976. doi: 10.1016/j.concog.2010.06.014

Foster, N. A., and Valentine, E. R. (2001). The effect of auditory stimulation on autobiographical recall in dementia. *Exp. Aging Res.* 27, 215–228. doi: 10.1080/036107301300208664

Fukui, H., Arai, A., and Toyoshima, K. (2012). Efficacy of music therapy in treatment for the patients with alzheimer's disease. *Int. J. Alzheimers Dis.* 2012:531646. doi: 10.1155/2012/531646

Fusar-Poli, L., Bieleninik, Ł, Brondino, N., Chen, X. J., and Gold, C. (2017). The effect of music therapy on cognitive functions in patients with dementia: a systematic review and meta-analysis. *Aging Ment. Health* 22, 1097–1106. doi: 10.1080/13607863.2017.1348474

García, J. J. M., Iodice, R., Carro, J., Sánchez, J. A., Palmero, F., and Mateos, A. M. (2012). Improvement of autobiographic memory recovery by means of sad music in alzheimer's disease type dementia. *Aging Clin. Exp. Res.* 24, 227–232. doi: 10.3275/7874

Giovagnoli, A. R., Manfredi, V., Parente, A., Schifano, L., Oliveri, S., and Avanzini, G. (2017). Cognitive training in alzheimer's disease: a controlled randomized study. *Neurol. Sci.* 38, 1485–1493. doi: 10.1007/s10072-017-3003-9

Gómez Gallego, M., and Gómez García, J. (2017). Music therapy and alzheimer's disease: cognitive, psychological, and behavioural effects. *Neurología* 32, 300–308. doi: 10.1016/j.nrleng.2015.12.001

Guétin, S., Coudeyre, E., Picot, M. C., Ginies, P., Graber-Duvernay, B., Ratsimba, D., et al. (2005). Effect of music therapy among hospitalized patients with chronic low back pain: a controlled, randomized trial. *Ann. Readapt. Med. Phys.* 48, 217–224. doi: 10.1016/j.annrmp.2005.02.003

Guétin, S., Portet, F., Picot, M. C., Pommié, C., Messaoudi, M., Djabelkir, L., et al. (2009). Effect of music therapy on anxiety and depression in patients with alzheimer's type dementia: randomised, controlled study. *Dement Geriatr. Cogn. Disord.* 28, 36–46. doi: 10.1159/000229024

Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., et al. (2006). Investigating the enhancing effect of music on autobiographical memory in mild alzheimer's disease. *Dement Geriatr. Cogn. Disord.* 22, 108–120. doi: 10.1159/000093487

Jaber, S., Bahloul, H., Guetin, S., Chanques, G., Sebbane, M., and Eledjam, J. J. (2007). Effects of music therapy in itensive care unit without sedation in weaning patients versus non-ventilated patients. *Ann. Fr. Anesth. Reanim.* 26, 30–38. doi: 10.1016/j.annfar.2006.09.002

Jacobsen, J. H., Stelzer, J., Fritz, T. H., Chételat, G., La Joie, R., and Turner, R. (2015). Why musical memory can be preserved in advanced alzheimer's disease. *Brain* 138, 2438–2450. doi: 10.1093/brain/awv135

Kobets, A. J. (2011). Harmonic medicine: The influence of music over mind and medical practice. *Yale J. Biol. Med.* 84, 161–167.

Koelsch, S. (2009). A neuroscientific perspective on music therapy. *Ann. N. Y. Acad. Sci.* 1169, 374–384. doi: 10.1111/j.1749-6632.2009.04592.x

Kumar, A. M., Tims, F., Cruess, D. G., Mintzer, M. J., Ironson, G., Loewenstein, D., et al. (1999). Music therapy increases serum melatonin levels in patients with alzheimer's disease. *Altern. Ther. Health Med.* 5, 49–57.

Lanctôt, K. L., Herrmann, N., Yau, K. K., Khan, L. R., Liu, B. A., LouLou, M. M., et al. (2003). Efficacy and safety of cholinesterase inhibitors in alzheimer's disease: a meta-analysis. *CMAJ* 169, 557–564.

Li, C., Liu, C., Yang, Y., Chou, M., Chen, C., and Lai, C. (2015). Adjunct effect of music therapy on cognition in alzheimer's disease in taiwan: a pilot study. *Neuropsychiatr. Dis. Treat.* 4, 291–296. doi: 10.2147/NDT.S73928

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., and DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* 288, 1475–1483. doi: 10.1001/jama.288.12.1475

Moscovitch, M. (1992). Memory and working-with-memory: a component process model based on modules and central cystems. *J. Cogn. Neurosci.* 4, 257–267. doi: 10.1162/jocn.1992.4.3.257

Peck, K. J., Girard, T. A., Russo, F. A., and Fiocco, A. J. (2016). Music and memory in alzheimer's disease and the potential underlying mechanisms. *J. Alzheimers Dis.* 51, 949–959. doi: 10.3233/JAD-150998

Platel, H., Baron, J. C., Desgranges, B., Bernard, F., and Eustache, F. (2003). Semantic and episodic memory of music are subserved by distinct neural networks. *Neuroimage* 20, 244–256. doi: 10.1016/S1053-8119(03)00287-8

Raglio, A., and Oasi, O. (2015). Music and health: what interventions for what results? *Front. Psychol.* 6:230. doi: 10.3389/fpsyg.2015.00230

Rauscher, F. H., Shaw, G. L., and Ky, C. N. (1993). Music and spatial task performance. *Nature* 365:661. doi: 10.1038/365611a0

Sakamoto, M., Ando, H., and Tsutou, A. (2013). Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. *Int. Psychoger.* 25, 775–784. doi: 10.1017/S1041610212002256

Satoh, M., Takeda, K., Nagata, K., Shimosegawa, E., and Kuzuhara, S. (2006). Positron-emission tomography of brain regions activated by recognition of familiar music. *AJNR* 27, 1101–1106.

Simmons-Stern, N. R., Budson, A. E., and Ally, B. A. (2010). Music as a memory enhancer in patients with Alzheimer's disease. *Neuropsychologia* 48, 3164–3167. doi: 10.1016/j.neuropsychologia.2010.04.033

Simmons-Stern, N. R., Deason, R. G., Brandler, B. J., Frustace, B. S., O'Connor, M. K., Ally, B. A., et al. (2012). Music-based memory enhancement in Alzheimer's disease: promise and limitations. *Neuropsychologia* 50, 3295–3303. doi: 10.1016/j.neuropsychologia.2012.09.019

Thompson, W. F., Schellenberg, E. G., and Husain, G. (2001). Arousal, mood, and the mozart effect. *Psychol. Sci.* 12, 248–251. doi: 10.1111/1467-9280.00345

Tsoi, K. K. F., Chan, J. Y. C., Ng, Y. M., Lee, M. M. Y., Kwok, T. C. Y., and Wong, S. Y. S. (2018). Receptive music therapy is more effective than interactive music therapy to relieve behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. *J. Am. Med. Dir. Assoc.* 19, 568–576. doi: 10.1016/j.jamda.2017.12.009

van der Steen, J. T., Smaling, H. J. A., van der Wouden, J. C., Bruinsma, M. S., Scholten, R. J. P. M., and Vink, A. C. (2018). Music-based therapeutic interventions for people with dementia. *Coch. Database Syst. Rev.* 5:CD003477. doi: 10.1002/14651858.CD003477.pub4

World Health Organization (2018). *Dementia Fact Sheet*. Available at: http://www.who.int/mediacentre/factsheets/fs362/en/

Zhang, Y., Cai, J., An, L., Hui, F., Ren, T., Ma, H., et al. (2017). Does music therapy enhance behavioral and cognitive function in elderly dementia patients? A systematic review and meta-analysis. *Ageing Res. Rev.* 35, 1–11. doi: 10.1016/j.arr.2016.12.003

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Musical Attention Control Training for Psychotic Psychiatric Patients: An Experimental Pilot Study in a Forensic Psychiatric Hospital

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Poor attention skills constitute a major problem for psychiatric patients with psychotic symptoms, and increase their chances of treatment drop-out. This study investigated possible benefits of musical attention control training (MACT). To examine the effect of MACT on attention skills of psychiatric patients with psychotic features a randomized controlled trial (RCT) was conducted in a forensic psychiatric clinic. Participants (N = 35, age M = 34.7, 69% male) were pair matched (on age, gender, and educational level), and randomly assigned to an experimental and control group. The experimental group received a 30-min MACT training once a week over 6 weeks' time, whereas the controls received treatment as usual without attention training. Single blind pre- and post-neuropsychological assessments were performed to measure different attention levels. The experimental MACT group outperformed the control group in selective, sustained and alternating attention. In addition, overall attendance of MACT participants was high (87.1%). This result suggests that in this experimental pilot study MACT was effective for attention skills of psychiatric patients with psychotic features. To obtain larger intervention effects additional research is necessary, with a larger sample and a more specific MACT intervention.

Keywords: musical attention control training, forensic psychiatry, psychosis, psychiatric patients, randomized controlled trial, sustained, selective, alternating

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INTRODUCTION

About 0.4% of the world population suffers from psychotic episodes or schizophrenia (McGrath et al., 2004). Most of the patients receive regular treatment (Vancampfort et al., 2016). However, 26.7% of these patients cannot complete treatment (Vancampfort et al., 2016). Some patients might become a possible threat to themselves or other people (Pompili et al., 2007; Large and Nielssen, 2011). Yearly roughly 30 thousand of them are placed under a legal order in secure psychiatric setting in the Netherlands (Eshuis and Diephuis, 2017; Dienst Justitiële Inrichtingen, 2018) due to conviction for criminal offenses or severe violent threats to themselves or others. The number of patients in these settings has doubled over the last 10 years (Broer et al., 2015). Treatment costs differ from €402 to €528 per patient per day. Treatment can take years and can cost up to 1.5 million euro per patient (Nagtegaal et al., 2016). These costs are covered because of the positive effects of forensic treatment. Of these patients, 20.7% relapse into a severe criminal offense compared to the three times higher 64% of largely untreated adult delinquents, who only served a prison sentence (Boonmann et al., 2015). Treatment success is often measured as reduction of relapses. Effective treatment is essential for rehabilitation of patients, and reduction of costs.

Patients with psychotic features in forensic psychiatric settings have many cognitive problems (Heinrichs and Zakzanis, 1998; Kavanagh et al., 2010; Meyer et al., 2014). Often judgment functions fail, patients are easily distracted, and they show neurocognitive deficits, such as sustained attention problems, impulsivity and executive dysfunction. One could be motivated to partake in treatment, but when constantly distracted, it is hard to learn new skills or gain new insights. In search of predictors and moderators of treatment success, research suggests that the inability to focus and sustain attention are neurobiological predictors of negative treatment outcomes (Cornet et al., 2015). The worse the attention span of a patient the more difficulties are denoted in maintaining and completing treatment programs.

Attention span and related problems evolve around a person's capacity to absorb and apply information. In daily life, we are (over)exposed to information. This information can be auditory-, tactile-, visual stimuli (external) as well as thoughts, sensations, emotions, and memories (internal). It is estimated that our human system unconsciously can process 11,2 million bits of information every second (Dijksterhuis and Nordgren, 2006). In contrast, most people are aware of only 45 bits per second; 200.000 times less. The selection mechanism that filters this information is called attention (Kessels et al., 2012).

Humans have only a limited attention capacity (Dijksterhuis and Nordgren, 2006), which even slims when alternating between multiple stimuli. When learning a new task, like playing a guitar, our attention is heavily occupied. Processing all the new information takes time, and it is extremely difficult to focus attention on other tasks in that situation. After repetition and training, these processes proceed more automatically, and therefore demand less attention capacity (Shiffrin and Schneider, 1977). After many hours of rehearsal, we can even sing and play guitar at the same moment. Attention is an essential skill to be able to reason, read, learn and communicate. Attention helps us to cope with and solve problems (Petersen and Posner, 2012).

Cognitive function disorders appear to be one of the core characteristics of schizophrenia and psychotic episodes and are observable to varying degrees within the areas of attention, memory, language and executive functions (Kavanagh et al., 2010). Cornet et al. (2015) have suggested that there is a significant treatment attrition of psychiatric patients with poor attention skills. They found that patients who are the most in need of treatment benefit the least of it, probably due to inadequate attention skills. However, psychological treatment that targets attention skills is a fairly uncovered area of research.

Posner distinguishes four different levels of attention (Posner, 2016). Focused attention, selective attention, sustained attention, and alternating attention. Since the capacity of a human information selection mechanism is limited, attention needs to be focused and selective. *Focused attention* is the ability to direct attention to stimuli. *Selective attention* is the ability to select one stimulus over another. It is the ability to avoid distractions when focused (Kessels et al., 2012). This can be controlled as a bottom-up process. For example, when involuntary stimuli, like a claxon in traffic, draws attention. Top-down attention implies the capacity to actively focus on stimuli of interest, such as reading this article. Thirdly, certain tasks require one to *sustain* or hold attention over time. One needs to be alert when performing vigilance tasks with a low event rate, like driving a car for hours on a highway. *Alternating attention* is the ability to switch in a sequence between one thing and another. The tempo of alternating attention can vary from calm to rapidly (sometimes referred to as divided attention). When investigating training effects on attention skills, it is important to distinguish between these levels of attention.

If one wants to train attention skills one should focus on the neuropsychological aspects of attention (Silverstein et al., 2001). Research suggests that listening to music stimulates brain plasticity (Pantev and Herzholz, 2011) and leads to activations in multiple brain areas, such as auditory mechanisms, attention, memory storage and retrieval, and sensory–motor integration (Zatorre, 2005). Making music involves the brainstem, limbic systems and frontal lobes (Alluri et al., 2011; Meyer et al., 2014), stimulates the visual- and motor cortex (Collins, 2013), and leads to volume- and activity increases of the corpus callosum (Schlaug et al., 1995; Steele et al., 2013). A growing number of studies suggest that many brain areas involved in attention processes are activated by music (Schmithorst and Holland, 2003; Thaut, 2010; Pantev and Herholz, 2011; Strait and Kraus, 2011; Miendlarzewska and Trost, 2013; Thaut and Gardiner, 2014; Mansouri et al., 2017). An effect study on music therapy and attention showed improvement in learning skills of patients diagnosed with schizophrenia (Ceccato et al., 2006). However, the music therapy interventions in this study were not well-defined. Building on knowledge of three different attention studies (Klein and Jones, 1996; Ceccato et al., 2006; Wolfe and Noguchi, 2009; Thaut and Gardiner, 2014) developed the musical attention control training (MACT). MACT is a protocolled neurological music therapy (NMT) technique targeting music brain mechanisms in structured music making or listening exercises to optimize attention processes. These exercises consist of pre-composed or improvised music. The musical elements cue different musical responses to practice attention skills (Thaut, 2005), such as brainstem reflex, entrainment, and contagion (Juslin, 2019).

A literature review only provided three studies with extreme small sample sizes on the effects of MACT on attention. Abrahams and Van Dooren compared MACT to non-standardized music therapy (NSMT) and treatment as usual (TAU) on attention skills of juveniles in a secure residential facility (N = 6) (Abrahams and Van Dooren, 2018). The participants were randomly allocated to one of various treatment groups. Participants (age: M = 16,5, SD = 0.5) were diagnosed with Attention Deficit (Hyperactivity) Disorder, Oppositional Defiant Disorder and/or Conduct Disorder. Participants were given a six-week training of 45 min weekly. To measure attention the trail making test A and B (TMT) and the Digit Span, forward and backward, were used. The two participants in the MACT group showed a significant increase in selective, sustained and divided attention areas compared to the others.

Pasiali, LaGasse, and Penndid investigated attention skill training in a single group pre- /post-test study. Their aim was to find an effect of MACT on attention skills of adolescents with neurodevelopmental delays (Pasiali et al., 2014). Participants (N = 9) aged 13–20 were diagnosed with minor, mild or severe symptoms of autism. Participants were given eight 45-min sessions spread over 6 weeks' time. Attention was measured with the test of everyday attention for children (TEA-ch). Participants showed significant improvements on selective attention and divided attention.

In an unpublished study, Roefs conducted a randomized controlled trial (RCT) with forensic psychiatric male adults suffering from schizophrenia (Roefs, 2015). He compared music therapy combined with MACT (CM) with improvisation music therapy (IM) for (N = 14) forensic psychiatric patients diagnosed with schizophrenia (ranging in age from 18 to 65). Here too, the TMT A and B, the digit span forward and backward in addition to the parrot digits and letters were used to measure attention. Participants in the CM demonstrated improvement in focused, sustained and alternating attention.

Even though all studies had their limitations, the current literature review led to the hypothesis that MACT could have a positive effect on the development of focused and selective attention as well as sustained and alternating attention skills of psychiatric patients in forensic psychiatry. By conducting a randomized controlled trial, the present study aims to find the effect of MACT on attention skills within a group of adult psychiatric patients with psychotic features who stay in a secure psychiatric setting. The main question is: "What are the effects of MACT on focused, selective, sustained, and alternating attention in psychiatric patients with psychotic features in secure residential care?"

MATERIALS AND METHODS

Design

This study employed a single blind randomized controlled pre-/post-test design and was approved by the Medical Ethics Committee of the University of Amsterdam (registration number 2018-CDE-2968). Julious (2005) state when conducting a pilot study, a sample size of 12 participants per group is a rule of thumb. Prior to the randomization all participants participated in a pre-test assessment. To create a comparable control and experimental group patients were matched (on age, gender and educational level) before being allocated to the experimental group (receiving the MACT training in addition to treatment of usual (TAU)) or the control group (only receiving TAU). The control group was placed on a waiting list for MACT training. Participants of both groups were subjected to a post-test assessment immediately after the sixth session or sixth week (see **Figure 1**). After the post-test assessment the control group was offered to enroll in the MACT training.

Participants

In total 54 patients were found eligible for the MACT treatment program. Inclusion criteria were: adult psychiatric patients (18+ years) with psychotic features in a forensic clinical setting who had severe attention problems, who mastered the Dutch language on at least a basic level. Patients had to be able to leave the unit independently to visit the music therapy room. Exclusion criteria were: acute crisis, florid psychosis or patients who were in a coercive program (i.e., having no permission to leave the unit). There was no exclusion for additional psychiatric disorders, age, gender or educational level.

After informing all eligible patients about the study a total of 15 patients refused to participate. Four left the study before allocation. Three of them were transferred to another psychiatric institution. One committed arson the day before the research started and was deemed to be unsuited to leave the unit. This resulted in a sample of 35 participants (age M = 34.7, SD = 9.6, 69% male) (see **Figure 1** for details). All participants were patients of a secure psychiatric clinic and stayed in one of three units; short-term coercive psychiatry, long-stay secure psychiatry or forensic psychiatry. A total of 35 participants completed the pre-test, compared to 31 who completed the post-test. There were two dropouts in each group.

Procedure

Patients with severe attention problems were referred to participate in the study by their psychiatrists and psychologists. All patients who were enlisted for the treatment were personally invited by one of the three neurologic music therapists who would offer the MACT. The patients received information about the MACT, the research design, the voluntary participation, the possibility to withdraw, and were asked if they had attention problems. Later on, patients who wanted to participate were required to sign an informed consent form.

All patients did a pre-test attention skill assessment in the same week (week 19 of 2018). Attention skills have been shown to differ across age, gender and educational level, and can influence the outcome of treatment (Bates and Lemay, 2004; Tombaugh, 2004). For that reason, prior to randomization, patients were matched on age, gender, psychiatric unit and educational level. Since a third of the patients did not finish high school, the educational level was set on the highest level of education they had attended. Although the sample size of the experimental and control group exceeded the rule of thumb for a pilot study (Julious, 2005), the sample size of this RCT was considered to be too small to secure equivalence of the experimental and control group. Participants were therefore pair-matched after the pre-test assessment. One of the researches entered the patients' variables onto a list and matched similar patients (for example a male patient, born in 1982 who did not finish his lower secondary education was matched with a male patient, born in 1984 who also did not finish his lower secondary education). By flipping a coin, the group was allocated to the conditions. A total of 18 patients (age M = 34.4, SD = 9.4) were assigned to the experimental group and 17 (age M = 35.2, SD = 10.1) to the control group (see **Table 1** for Participants'

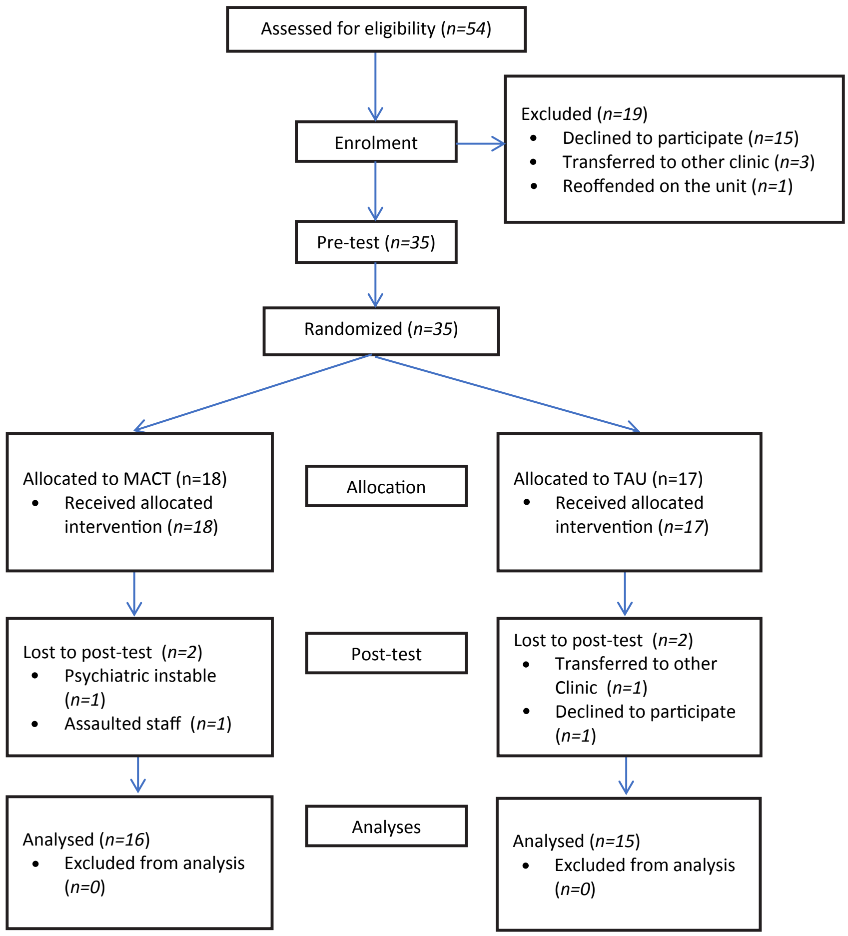

FIGURE 1 | Flow chart of participants.

Characteristics). The experimental and control group turned out to be similar on age (p = 0.768), gender (p = 0.810) and educational level (p = 0.826). Participants were not matched on psychiatric disorders, but visual inspection of **Table 1** suggest that the distribution of psychiatric disorders were similar. The neuropsychological tests were carried out under supervision of independently trained professionals. The data were anonymized and handed over to the researchers. Participants and assessors only learned who would participate in the experimental or control group after every participant had completed the pre-test.

Participants in the experimental group followed the MACT, which started a week after the pre-test. Participants in the control group attended their regular treatment program and received no additional intervention. They started with MACT after the post-test. A total of 69% of the participants had received non-standardized music therapy (NSMT) prior to this study equally distributed over both groups. Therapy goals aimed to introduce music therapy, observation, diminishing negative symptoms of psychosis, increase interaction skills, regulate emotions or increase self-esteem. However, none of the participants received MACT or other neurologic music therapy techniques.

The d2 cancelation Test (Brickenkamp and Zillmer, 1998; Brickenkamp, 2007), the Digit Span Forward and Backward (Wechsler, 2012) and the TMT A and B (Tombaugh, 2004) were used to measure the different levels of attention.

The Intervention: MACT

To allow for replication of the study we will provide the reader with a detailed description of the music therapy intervention as well as the applied standardized assessment tools. Den Heijer (2018) designed a six-week protocol-based (MACT-program) (Thaut and Gardiner, 2014) to meet the needs of psychiatric patients with psychotic features, ensuring that the core of each exercise met the MACT criteria, triggering cognitive areas of attention, neural networks and brain systems and functions (for example, bilateral frontal lobes, brain stem, auditory and visual perception systems). Each session lasted 30 min. The session started with psycho-education about targeted attention processes and defining the proposed musical exercises. Questions patients had, were clarified prior to the start of the musical interventions. The attention skills training was gradually increased in complexity. This kept participants motivated for a longer duration of time.

TABLE 1 | Participants' Characteristics.

	Experimental (*N* = 18)	Control (*N* = 17)
Male/Female	12 (67%)/6 (33%)	12 (71%)/5 (29%)
Age	*M* = 34,39 SD = 9,39	*M* = 35,12 SD = 10,08
Level of education		
No education	1 (6%)	0 (0%)
Primary ed. not completed	0 (0%)	1 (6%)
Primary ed. completed	1 (6%)	1 (6%)
Middle school not completed	1 (6%)	3 (18%)
Middle school completed	8 (44%)	4 (24%)
High school not completed	2 (11%)	1 (6%)
High school completed	0 (0%)	2 (12%)
College not completed	3 (17%)	2 (12%)
College completed Low	2 (11%)	3 (18%)
Psychiatric disorders		
Psychotic disorder	12 (67%)	10 (59%)
Autism	4 (22%)	2 (12%)
Bipolar	0 (0%)	2 (12%)
Drugs abuse	10 (56%)	11 (65%)
BPS	3 (17%)	4 (24%)
PTSD	3 (17%)	1 (6%)
Eating disorder	3 (17%)	2 (12%)
OCD	1 (6%)	0 (0%)
Anxiety	0 (0%)	2 (12%)
Depression	1 (6%)	0 (0%)
Received NS-music therapy	14 (78%)	14 (82%)
Clinic		
FPK	8 (44%)	7 (41%)
LIZ	6 (33%)	7 (41%)
KIB	4 (22%)	3 (18%)

BPS, borderline personality disorder; PTSD, post-traumatic stress disorder, OCD, obsessive compulsive disorder; NS-Music therapy, non-standardized music therapy; FPK, forensische psychiatrische kliniek (forensic psychiatric clinic); LIZ, langdurige intensieve zorg (long-term intensive care); KIB, kortdurende intensieve behandeling (short-term intensive treatment).

The protocol was designed for a closed group with a maximum of six participants. The program had a build-up. It started with musical exercises for focused and selected attention, gradually going to sustained attention, while ending with alternating attention.

The musical equipment used in the exercises were African drums, small percussion, xylophones, metronome, as well as pre-recorded and pre-composed music. Four groups started with MACT-sessions in the same week. The number of participants in the MACT group varied between two to six participants. The protocol was carried out by three experienced and NMT trained music therapists. To meet the institutional requirements a co-therapist was included in each session.

Measures

In this study three different tests to assess different levels of attentions were used. First, the d2 cancelation test was used to measure sustained attention. To conduct the d2 test one uses visual selective attention, speed of information processing and sustained attention (Brickenkamp, 2007). The purpose of the test is to distinguish different characters.[1] Two of the twelve measures of the d2 were used, D2TN and D2CP. D2TN is the total sum of number of characters processed (Bates and Lemay, 2004). The D2CP is the correct number of canceled characters minus the falsely canceled characters, and is considered as a measure of sustained attention. Reliability research done with adults found a good reliability for the D2TN and the D2CP both of $\alpha = 0.98$ (Brickenkamp, 2007).

The second attention test was the Digit Span as a subtest of the WAIS-IV-NL intelligence test (Wechsler, 2012). The digit span forward (DF) task tempts the executive functions and correlates with vigilance (Hale et al., 2002). The DF is used to measure focused attention.[2] The score of the digit span was calculated by the number of correctly named rows. The digit span backward (DB) requires the use of working memory and executive functioning (De Jong and Das-Smaal, 1995), while selecting and maintaining the information additionally requires attention skills. This requires impulse controls and mental flexibility (Hale et al., 2002). Therefore, this test was used to measure selective attention. This test was chosen because, in contrast to the d2 and the TMT A and B, it uses auditory stimuli. For this test a good internal consistency was found of = 0.91 (Wechsler, 2012).

The TMT A and B, developed by Reitan (Reitan, 1958), was the third measure of sustained attention (Reitan, 1958; Benedict et al., 1996; Sánchez-Cubillo et al., 2009).[3] This TMT-A task requires mainly visioperceptual abilities (Benedict et al., 1996) and working memory (Sánchez-Cubillo et al., 2009). TMT-B measures alternating attention, since it reflects primarily working memory and secondarily task-switching ability (Benedict et al., 1996),[4] It requires cognitive alternation, inhibition control, working memory, and attentional shifting (Sánchez-Cubillo et al., 2009). The reliabilities found in clinical groups vary from 0.69 to 0.94 for the TMT-A and 0.66 to 0.86 for the TMT-B (The Goldstein and Watson, 1989).

Beside their validity to assess attention skills, the d2 cancelation test was included to enable comparison with the results of Cornet et al. (2015). The Digit Span and the TMT A and B were used to compare the outcomes of this study with

[1] On an a4-sheet, 14 lines alternate the letter "d" and "p" with one to four dashes. The letter "d" with a total of two dashes must be marked, the letter "p" and letter "d" with more or less than 2 dashes must be ignored. For each line there are 20 s to indicate the correct characters.

[2] In the DF, digit sets are read out loud. The patient has to repeat the numbers. These number sequences build up in length from 2 digits to 9 digits, and stop when the patient makes two errors in a row. In the Digit Span backward (DB), the patients are expected to recall the digits backward (for example, 2-1-7 becomes 7-1-2).

[3] In the TMT-A test patients receive a sheet of paper with 25 numbers, which have to be connected with each other, starting at one and ending at 25. The score is the time patients need to end the test without errors.

[4] The set-up of the TMT-B test is equal to TMT-A, but now numbers and letters must be connected alternated to each other (for example, 1-A-2-B-3-C-4-D etc.).

both previously mentioned studies on the MACT (Roefs, 2015; Abrahams and Van Dooren, 2018).

Analysis

To analyze the data IBM SPSS 23 (George and Mallery, 2016) was used. Mean and standard deviations of variables were calculated. Independent T-tests were used to test whether mean scores of focused and selective attention, sustained attention and alternating attention would increase for the MACT participants compared to the control participants. Effect sizes were computed as Cohens' d, based on means and standard deviations, with a positive sign indicating improvement of the experimental group relative to the control group. Effect sizes around 0.20 are marked as small, effect sizes around 0.50 as medium, effects sizes around 0.80 as large (Cohen, 1988). Because the present research was a pilot study and therefore statistically underpowered, with a small sample size, the p-value was set to $p < 0.10$ (one-tailed significance) in order to be able to detect (trend significant) clinically meaningful effects.

RESULTS

A total of 31 participants completed both the pre- and post-test. Pre- and post-scores of both groups were compared for differences in attention skills.

Three significant effects were discovered at $p < 0.10$. Starting with the D2TN, a medium effect size was found ($t = 1.374$, $p = 0.09$, $d = 0.49$), which means that the experimental group had improved in sustained attention (**Figure 2**). A positive effect was found in the digit span backward ($t = 1.512$, $p = 0.07$, $d = 0.55$), improving on selective attention (**Figure 3**). Third, the experimental group took less time to finish the TMTB compared to the control group ($t = -1.525$, $p = 0.07$, $d = 0.59$), which indicates that the experimental group improved in alternating attention (**Figure 4**). These results suggest that the MACT might have a positive effect on attention skills. No effects were found on focused attention.

Despite all measures of precaution in the paired-match randomization, the experimental group scored better on attention skills than did those in the control at pre-test, as shown in **Table 2**.

The therapists reported an overall high therapy attendance of 87%. Perry, Bannon and Ini (Perry et al., 1999) showed that the average attendance in therapy is 78%, suggesting that motivation for the MACT program was high.

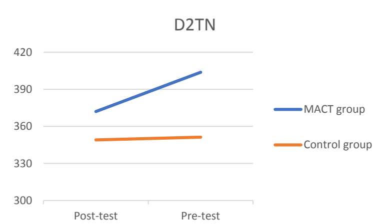

FIGURE 2 | D2TN.

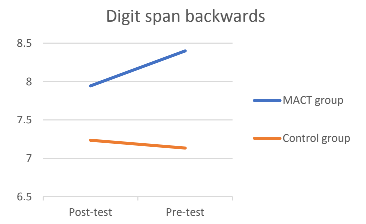

FIGURE 3 | Digit span backward.

FIGURE 4 | TMTB.

DISCUSSION

With regards to the effect of MACT on different levels of attention the experimental group showed better outcomes on selective, sustained and alternating attention compared to the control group, with medium effect sizes at post-test. So, the results indicated that MACT does have a positive effect on three attention levels, selective, sustained and alternating. This suggests that MACT is an effective music therapy program to train attention skills of psychiatric patients with psychotic features in a secure psychiatric facility. The effect of the MACT, improvement on selective, sustained and alternating attention are in line with other studies (Klein and Jones, 1996; Ceccato et al., 2006; Wolfe and Noguchi, 2009; Thaut, 2010; Pasiali et al., 2014; Roefs, 2015; Abrahams and Van Dooren, 2018). No effects were found on focused and specific forms of alternating attention.

This pilot study suggests that an experimental study design testing the effects of MACT on attention skills of psychiatric patients with psychotic features (in a secure psychiatric institution) is feasible, although the program might need modification in order to obtain larger intervention effects. If the results are replicated in future studies, there remain reasons to be careful with implementation. To our knowledge, only one study, carried out by Cornet and others (Cornet et al., 2015), examined the relation between attention skills and treatment outcome, and found that poor attention skills relate to treatment drop out. Adding a new therapy to an existing treatment program brings questions about its additional value in clinical practice that

TABLE 2 | Differences pre and post-test.

	Pre-test					*Post-test*					*post minus pre-test*
	N	***M***	***SD***	***t***	***d***	***N***	***M***	***SD***	***t***	***d***	***d***
D2TN				0.701	0.25				1.374+	0.49	0.24
Test	(*N* = 16)	371.81	89.081			(*N* = 16)	403.88	97.118			
Con	(*N* = 16)	349.31	92.346			(*N* = 15)	351.27	115.803			
D2CP				0.297	0.10				0.792	0.28	0.18
Test	(*N* = 16)	135.94	46.323			(*N* = 16)	148.19	45.809			
Con	(*N* = 16)	131.13	45.425			(*N* = 16)	134.67	49.209			
DF				0.659	0.22				1.013	0.36	0.14
Test	(*N* = 18)	8.50	2.684			(*N* = 16)	8.94	2.265			
Con	(*N* = 17)	7.94	2.331			(*N* = 15)	8.07	2.520			
DB				0.964	0.32				1.512+	0.55	0.22
Test	(*N* = 18)	7.94	2.287			(*N* = 15)	8.40	2.473			
Con	(*N* = 17)	7.24	2.047			(*N* = 15)	7.13	2.100			
TMTA				−1.123	0.38				−0.474	0.17	−0.21
Test	(*N* = 18)	38.22	14.190			(*N* = 16)	34.69	12.333			
Con	(*N* = 17)	44.06	16.528			(*N* = 15)	36.67	10.788			
TMTB				−0.914	0.33				−1.525+	0.59	0.26
Test	(*N* = 16)	96.06	59.013			(*N* = 15)	77.93	40.136			
Con	(*N* = 15)	115.47	59.130			(*N* = 12)	102.92	44.903			

Differences between pre and post-test MACT in test and control group: means, standard deviations and effect-sizes Test, test group (15 < n < 18); Con, control group (12 < n < 17).+ <0.10; D2TN, d2 cancelation test total number of letter (sustained – focussed – attention); D2CP, d2 cancelation test correct total number of letters (sustained – selective – attention); DF, digital span forward test (focussed attention); DB, digital span backward test (selective attention); TMT A, trail making test A (sustained attention); TMT B, trail making test B (alternating attention).

surpasses issues of effectiveness. MACT was added to treatment as usual offered to the three clinics.

Some qualitative date was gathered by asking patients to provide their thoughts and feedback on the program. They expressed their skepticism ("I don't think only six sessions will increase attention skills") or had ideas to modify the musical exercises to make them more challenging (for example, making the rhythms more complex, or playing more difficult melodies on the xylophones). It did not prevent the patients from attending the training. Or as one patient put it; "It was nice to do something, otherwise you're here to waste, but I don't know if my attention skills have improved."

Although a single blind pair matched RCT design was used for this study, some limitations must be acknowledged. The sample was too small for valid generalization and did lack statistical power. Although the direction and magnitude of the effects were similar to earlier studies, still a much larger sample is needed to be able to generalize the present study's findings. This pilot study should be considered as a test of feasibility to examine the effects of MACT on attention of psychiatric patients with psychotic features (in secure psychiatric care). However, the positive trends of the present study warrant further research to test the effects of MACT on different attention processes for this population.

Another limitation of this study is that confounders that could have affected attention skills were not controlled for. For example, methylphenidate is known to boost sustained attention (Dockree et al., 2017), elective compulsory therapy is known for its loss of temporary memory and for disturbing working memory (Datto, 2000), which is a key component of attention (Kessels et al., 2012). However, clients were not screened for those factors. Drug abuse was similarly not controlled for, although 21 participants (60%) had been diagnosed with substance use disorder. Cannabis reduces the function of the attention system, MDMA users are less efficient at focusing, cocaine users show a lack of attention, and heroin users have problems with impulse control and selective processing (Lundqvist, 2005). Thus, future studies should try to incorporate these additional confounding factors in their analysis.

The Hawthorne effect (McCarney et al., 2007; Rapport et al., 2013) cannot be ruled out because the control group did not receive an alternative intervention to control for the effect of getting attention. Similar to the studies conducted by Abrahams and Van Dooren (Abrahams and Van Dooren, 2018) and Roefs (Roefs, 2015), it would be interesting to offer the control group regular music therapy treatment compared to MACT. However, both studies found that control groups receiving another (placebo) form of music therapy did not improve as much on attention skills as did the experimental group receiving MACT.

Finally, although participants in the experimental and control group were paired on similar age, gender, clinical problems and education level, randomization could not prevent that the experimental group showed higher attention skills at pre-test. it should be noticed that the experimental group in general showed better attention scores at pre-test than did the control group, although not significant due to low statistical power.

When results were controlled for pre-test differences, effect sizes were small rather than medium. *Post hoc* ANCOVA's revealed that post-test differences between the experimental and control group were no longer significant after controlling for pre-test differences. So it should be advised to pair on attention skills in addition to the previously named standards.

CONCLUSION

Findings of this pilot study suggest that MACT has a positive effect on attention skills in forensic psychiatry for psychiatric patients with psychotic features. The intervention seems to adequately meet the needs of these patients as evident in the low dropout rate, the good response rate, and the willingness to participate in an RCT. This pleads for replication of this study with a larger sample size. It was calculated with G-power (*power of 0.80 and* α = *5%*) that a sample of $N = 102$ would be needed given a medium effect size. It would be advised to intensify or adapt the MACT training to find larger effects. Compared to musical training, rehearsing multiple times a week has been shown to produce more improvement in music skills, which promotes brain plasticity (Wan and Schlaug, 2010). The duration of someone's music training strengthens neural activation (Pantev and Herzholz, 2011). This means MACT might need broader variation of musical exercises, a prolonged duration and a delivery of multiple times each week. One of the participants suggested additional homework exercises. A possible decrease of treatment dropout through attention improvement would even stronger encourage the implementation of MACT within the treatment of (forensic) psychiatric patients with psychotic features. Cost effectiveness, achieved by a shorter average stay in forensic psychiatry or a greater effectiveness of psychiatric treatment, would be an impetus to implement musical attention control interventions within forensic psychiatric facilities.

ETHICS STATEMENT

The study is approved by the Medical Ethics Committee of the University of Amsterdam (registration number 2018-CDE-2968). Each participant was informed about the content of the study and the possibility to withdraw their consent. Each included participant signed a consent form.

AUTHOR CONTRIBUTIONS

RvA conceptualized and directed this research, recruited participants, collected pre/post measures and facilitated the necessary conditions for the research, collected and analyzed the data, and wrote the first draft of the manuscript. GS supervised the research process. LH contributed to the conception and design of the study. All authors contributed to manuscript revision, read and approved the submitted version.

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REFERENCES

Abrahams, T. P., and Van Dooren, J. C. (2018). Musical attention control training (MACT) in secure residential youth care: a randomised controlled pilot study. *Arts Psychother.* 57, 80–87. doi: 10.1016/j.aip.2017.10.008

Alluri, V., Toiviainen, P., Jääskeläinen, I. P., Glerean, E., Sams, M., and Brattico, E. (2011). Large-scale brain networks emerge from dynamic processing of musical timbre, key and rhythm. *NeuroImage* 59, 3677–3689. doi: 10.1016/j.neuroimage.2011.11.019

Bates, M. E., and Lemay, E. P. (2004). The D2 Test of attention: construct validity and extensions in scoring techniques. *J. Int. Neuropsychol. Soc.* 10, 392–400.

Benedict, R. H., Schretlen, D., Groninger, L., Dobraski, M., and Shpritz, B. (1996). Revision of the brief visuospatial memory test: studies of normal performance, reliability, and validity. *Psychol. Assess.* 8:145. doi: 10.1037//1040-3590.8.2.145

Boonmann, C., Wartna, B. S. J., Bregman, I. M., Schapers, C. E., and Beijersbergen, K. A. (2015). *Recidive na Forensische zorg. Een eerste Stap in de Ontwikkeling van een Recidivemonitor voor de sector Forensische Zorg. Cahier -3*. Den Haag: WODC

Brickenkamp, R. (2007). *D2 Aandachts- en concentratietest Handleiding*. Amsterdam: Hogrefe Uitgevers.

Brickenkamp, R., and Zillmer, E. (1998). *The d2 test of Attention*. Seattle, WA: Hogrefe & Huber.

Broer, J., Koetsier, H., and Mulder, C. L. (2015). Stijgende trend in dwangtoepassing onder de Wet Bopz zet door: implicaties voor de nieuwe Wet verplichte geestelijke gezondheidszorg. *Tijdschrift voor Psychiatrie*. 57, 240–247.

Ceccato, E., Caneva, P., and Lamonaca, D. (2006). Music therapy and cognitive rehabilitation in schizophrenic patients: a controlled study. *Nordic J. Music Ther.* 15, 111–120.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences*, 2nd Edn. Hillsdale, NJ: Erlbaum.

Collins, A. (2013). Music education and the brain what does it take to make a change? *Appl. Res. Music Educ.* 32, 4–10. doi: 10.1016/j.jamda.2017.02.013

Cornet, L. J. M., Van der Laan, P. H., Nijman, H. L. I., Tollenaar, N., and De Kogel, C. H. (2015). Neurobiological factors as predictors of prisoners'. response to a cognitive skills training. *J. Crim. Justice* 43, 122–132. doi: 10.1016/j.jcrimjus.2015.02.003

Datto, C. J. (2000). Side effects of electroconvulsive therapy. *Depress. Anxiety* 12, 130–134. doi: 10.1002/1520-6394(2000)12:3<130::aid-da4>3.0.co;2-c

De Jong, P. F., and Das-Smaal, E. A. (1995). "Het meten van aandacht: Principes en methoden," in *Aandachtsstoornissen: Een Neuropsychologisch Handboek*, ed. P. E. Wiebo Brouwer 231–245.

Den Heijer, J. G. (2018). *Mag ik heel even de aandacht?!' Een bundel met twaalf muziektherapeutische werkvormen ter bevordering van aandachtsvaardigheden bij volwassenen met schizofrenie binnen de forensische psychiatrie*. Inforsa Amsterdam: Internal publication.

Dienst Justitiële Inrichtingen. (2018). Forensische zorg Overzicht behandelinstellingen met verblijf. Available at: https://www.dji.nl/themas-cijfers-en-publicaties/cijfers-en-publicaties/kerncijfers-dji.aspx (accessed October, 2017).

Dijksterhuis, A., and Nordgren, L. F. (2006). A theory of unconscious thought. *Perspect. Psychol. Sci.* 1, 95–109.

Dockree, P. M., Barnes, J. J., Matthews, N., Dean, A. J., Abe, R., Nandam, L. S., et al. (2017). The effects of methylphenidate on the neural signatures of sustained attention. *Biol. Psychiatry* 82, 687–694. doi: 10.1016/j.biopsych.2017.04.016

Eshuis, R. J. J., and Diephuis, B. J. (2017). *Civiele Rechtspraak Onderzoek en Beleid.* Den Haag: Boom Juridische uitgevers.

George, D., and Mallery, P. (2016). *IBM SPSS Statistics 23 Step by Step: A Simple Guide and Reference*. New York, NY: Routledge Press.

Hale, J. B., Hoeppner, J. A. B., and Fiorello, C. A. (2002). Analyzing digit span components for assessment of attention processes. *J. Psychoeduc. Assess.* 20, 128–143. doi: 10.1177/073428290202000202

Heinrichs, R. W., and Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* 12, 426–445. doi: 10.1037/0894-4105.12.3.426

Julious, S. A. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharm. Stat.* 4, 287–291. doi: 10.1002/pst.185

Juslin, P. N. (2019). *Music Emotions Explained*. Oxford: Oxford University Press.

Kavanagh, L., Rowe, D., Hersch, J., Barnett, K. J., and Reznik, R. (2010). Neurocognitive deficits and psychiatric disorders in a NSW prison population. *Int. J. Law Psychiatry* 33, 20–26. doi: 10.1016/j.ijlp.2009.10.004

Kessels, R., Eling, P., Ponds, R., Spikman, J., and van Zandvoort, M. (2012). "Aandacht en executieve functies," in *Klinische neuropsychologie*, eds D. Boelen, L. Fasotti, and J. en Spikman (Amsterdam: Boom), 245–265.

Klein, J. M., and Jones, M. R. (1996). Effects of attentional set and rhythmic complexity on attending. *Atten. Percept. Psychophys.* 58, 34–46. doi: 10.3758/bf03205473

Large, M. M., and Nielssen, O. (2011). Violence in first-episode psychosis: a systematic review and meta-analysis. *Schizophrenia Res.* 125, 209–220. doi: 10.1016/j.schres.2010.11.026

Lundqvist, T. (2005). Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacol. Biochem. Behav.* 81, 319–330. doi: 10.1016/j.pbb.2005.02.017

Mansouri, F. A., Acevedo, N., Illipparampil, R., Fehring, D. J., Fitzgerald, P. B., and Jaberzadeh, S. (2017). Interactive effects of music and prefrontal cortex stimulation in modulating response inhibition. *Sci. Rep.* 7, 1–13. doi: 10.1038/s41598-017-18119-x

McCarney, R., Warner, J., Iliffe, S., Van Haselen, R., Griffin, M., and Fisher, P. (2007). The Hawthorne Effect: a randomised, controlled trial. *BMC Med. Res. Methodol.* 7:30. doi: 10.1186/1471-2288-7-30

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C., and Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med.* 2:13. doi: 10.1186/1741-7015-2-13

Meyer, G., Spray, A., Fairlie, J., and Uomini, N. (2014). Inferring common cognitive mechanisms from brain blood-flow lateralisation data: a new methodology for fTCD analysis. *Front. Psychol.* 5:552. doi: 10.3389/fpsyg.2014.00552

Miendlarzewska, E. A., and Trost, W. J. (2013). How musical training affects cognitive development: rhythm, reward and other modulating variables. *Front. Neurosci.*. 7:729. doi: 10.3389/fnins.2013.00279

Nagtegaal, M. H., Goethals, K., and Meynen, G. (2016). De tbs-maatregel: kosten en baten in perspectief. *Tijdschrift voor Psychiatrie* 10, 739–745.

Pantev, C., and Herholz, S. C. (2011). Plasticity of the human auditory cortex related to musical training. *Neurosci. Biobehav. Rev.* 35, 2140–2154. doi: 10.1016/j.neubiorev.2011.06.010

Pantev, C., and Herzholz, S. C. (2011). Plasticity of the human auditory cortex related to musical training. *Neurosci. Biobehav. Rev.* 35, 2140–2154. doi: 10.1016/j.neubiorev.2011.06.010

Pasiali, V., LaGasse, A. B., and Penn, S. L. (2014). The effect of musical attention control training (MACT) on attention skills of adolescents with neurodevelopmental delays: a pilot study. *J. Music Ther.* 51, 333–354. doi: 10.1093/jmt/thu030

Perry, C., Banon, E., and Ianni, F. (1999). Effectiveness of psychotherapy for personality disorders. *Am. J. Psychiatry* 156, 1312–1321.

Petersen, S. E., and Posner, M. I. (2012). The attention system of the human brain: 20years after. *Ann. Rev. Neurosci.* 35, 73–89. doi: 10.1146/annurev-neuro-062111-150525

Pompili, M., Amador, X. F., Girardi, P., Harkavy-Friedman, J., Harrow, M., Montross, L. P., et al. (2007). Suicide risk in schizophrenia: learning from the past to change the future. *Ann. Gen. Psychiatry* 6:10.

Posner, M. I. (2016). Orienting of attention: then and now. *Q. J. Exp. Psychol.* 69, 1864–1875. doi: 10.1080/17470218.2014.937446

Rapport, M. D., Orban, S. A., Kofler, M. J., and Friedman, L. M. (2013). Do programs designed to train working memory, other executive functions, and attention benefit children with ADHD? A meta-analytic review of cognitive, academic, and behavioral outcomes. *Clin. Psychol. Rev.* 33, 1237–1252. doi: 10.1016/j.cpr.2013.08.005

Reitan, R. M. (1958). Validity of the trail making test as an indicator of organic brain damage. *Percept. Motor Skills* 8, 271–276. doi: 10.2466/pms.1958.8.3.271

Roefs, G. (2015). Neurologische muziektherapie en schizofrenie. Available at: http://kenvak.nl/wp-content/uploads/2015/04/2015-06-26-Gerben-Roefs-Eindpresentatie-Neurologische-Muziektherapie-bij-Schizofrenie.pdf. (accessed June 19, 2015).

Sánchez-Cubillo, I., Perianez, J. A., Adrover-Roig, D., Rodriguez-Sanchez, J. M., Rios-Lago, M., Tirapu, J. E. E. A., et al. (2009). Construct validity of the trail making test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J. Int. Neuropsychol. Soc.* 15, 438–450. doi: 10.1017/S1355617709090626

Schlaug, G., Jäncke, L., Huang, Y., Staiger, J. F., and Steinmetz, H. (1995). Increased corpus callosum size in musicians. *Neuropsychologia* 33, 1047–1055. doi: 10.1016/0028-3932(95)00045-5

Schmithorst, V. J., and Holland, S. K. (2003). The effect of musical training on music processing: a functional magnetic resonance imaging study in humans. *Neurosci. Lett.* 348, 65–68. doi: 10.1016/s0304-3940(03)00714-6

Shiffrin, R. M., and Schneider, W. (1977). Controlled and automatic human information processing: II. perceptual learning, automatic attending, and a general theory. *Psychol. Rev.* 84, 127–190. doi: 10.1037//0033-295x.84.2.127

Silverstein, S. M., Menditto, A. A., and Stuve, P. (2001). Shaping attention span: an operant conditioning procedure to improve neurocognition and functioning in schizophrenia. *Schizophrenia Bull.* 27, 247–257. doi: 10.1093/oxfordjournals.schbul.a006871

Steele, C. J., Bailey, J. A., Zatorre, R. J., and Penhune, V. B. (2013). Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. *J. Neurosci.* 33, 1282–1290. doi: 10.1523/JNEUROSCI.3578-12.2013

Strait, D. L., and Kraus, N. (2011). Can you hear me now? musical training shapes functional brain networks for selective auditory attention and hearing speech in noise. *Front. Psychol.* 2, 1–10. doi: 10.3389/fpsyg.2011.00113

Thaut, M. H. (2005). *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications*. New York, NY: Routledge.

Thaut, M. H. (2010). Neurologic music therapy in cognitive rehabilitation. *Music Percept.* 27, 281–285. doi: 10.1525/mp.2010.27.4.281

Thaut, M. H., and Gardiner, J. C. (2014). "Musical attention control training,". in *Handbook of Neurologic Music Therapy*. eds M. H. Thaut, and V. Hoemberg. New York, NY: Oxford University Press.

Goldstein, G., and Watson, J. R. (1989). Test-retest reliability of the Halstead-Reitan battery and the WAIS in a neuropsychiatric population. *Clin. Neuropsychol.* 3, 265–273.

Tombaugh, T. N. (2004). Trail making test A and B: normative data stratified by age and education. *Arch Clin. Neuropsychol.* 19, 203–214. doi: 10.1016/s0887-6177(03)00039-8

Vancampfort, D., Rosenbaum, S., Schuch, F. B., Ward, P. B., Probst, M., and Stubbs, B. (2016). Prevalence and predictors of treatment dropout from physical activity interventions in schizophrenia: a meta-analysis. *Gen. Hosp. Psychiatry* 39, 15–23. doi: 10.1016/j.genhosppsych.2015.11.008

Wan, C. Y., and Schlaug, G. (2010). Music making as a tool for promoting brain plasticity across the life span. *Neuroscientist* 16, 566–577. doi: 10.1177/1073858410377805

Wechsler, D. (2012). *Wechsler Adult Intelligence Scale- Fourth Edition Nederlandse bewerking*. Amsterdam: Printpartners Ipskamp, Enschede.

Wolfe, D. E., and Noguchi, L. K. (2009). The use of music with young children to improve sustained attention during a vigilance task in the presence of auditory distractions. *J. Music Ther.* 46, 69–83.

Zatorre, R. (2005). Music, the food of neuroscience? *Nature* 434, 312–315. doi: 10.1038/434312a

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Music to One's Ears: Familiarity and Music Engagement in People With Parkinson's Disease

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Parkinson's disease (PD) is a complex diagnosis commonly associated with motor dysfunction, but known to comprise cognitive, psychiatric, and mood disturbances as well. Music has been successfully used to address motor and non-motor symptoms of PD. Still, little is known about the nature of an individual with PD's experience and relationship with music on conceptual and emotional levels, which may factor into their engagement in music-based techniques to ameliorate impairments. Two surveys were administered to 19 individuals with PD and 15 individuals without PD in order to gauge their subjective impressions and valuations of music. Participants completed The Brief Music Experience Questionnaire (BMEQ), a standard self-report measure pertaining to the role of music in one's life, prior to performing a perception task which involved listening to and making sound adjustments to three music recordings. Following the perception task, a custom Exit Survey was administered to evaluate the experience of listening to and engaging with the music in the perception task. In all six dimensions of the BMEQ, examining aspects of music experience including commitment to music, self-reported musical aptitude, social uplift, affective reactions, positive psychotropic effects, and reactive musical behavior (RMB, pertaining to actions or behaviors in response to music), the mean and the median were greater for the control group than for the PD group, but the difference was only statistically significant in the RMB dimension. On the Exit Survey, both groups assessed recent, specific, and interactive music listening more positively than the imagined, hypothetical or general music experiences addressed on the BMEQ. Additionally, familiarity had a greater effect on listening pleasure for participants with PD than those without PD. We conclude that people with PD may perceive less of an automatic connection between music and activity than their healthy peers. Additionally, they may receive more pleasure and value from music than they anticipate. Taken together, our results suggest that people with PD may require encouragement to participate as well as empowerment to choose familiar selections in order to better access music-based interventions and the benefits they can offer.

Keywords: neuromusic, Brief Music Experience Questionnaire, neurologic music therapy, Rhythmic Auditory Stimulation, Parkinson's disease therapy

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INTRODUCTION

Parkinson's disease (PD) is characterized by degeneration of dopaminergic neurons and reduced innervation of the substantia nigra and the basal ganglia, neural structures that are responsible for generating the internal rhythm required for executing walking movements (Merchant et al., 2013; Dalla Bella et al., 2015). Gait disorders such as start hesitation, freezing of gait, and festination (small, rapid steps), along with postural instability, severely decrease independence and increase the risk of falls in PD (Clair et al., 2011; Grabli et al., 2012). Bradykinesia (slowness) and muscle rigidity, prominent motor symptoms of PD, also affect the muscles of the vocal apparatus, leading to speech dysfunctions such as slowness, breathiness, harshness, and limitations in pitch and loudness (Holmes et al., 2000; Pinto et al., 2004). PD can also impair cognition and lead to emotional disturbances such as depression and anhedonia, a lowered ability to experience pleasure (Loas et al., 2012).

Music has long been a part of the landscape in the treatment of PD. Applications of music and its elements have addressed the wide-ranging symptoms and functional deficits caused by PD, and can complement or exceed benefits achieved through other forms of treatment (Pacchetti et al., 2000; Nombela et al., 2013; Dalla Bella et al., 2015; Rodger and Craig, 2016). Music is processed diffusely throughout the brain, where networks for the processing of music and its components such as melody, pattern, meter, and tempo overlap with networks that govern other human functions (Thaut, 2008). For example, neural activity in rhythm perception is closely related to that of movement regulation, involving cortical and subcortical regions such as the premotor cortex, supplementary motor area, cerebellum, and the basal ganglia (Zatorre et al., 2007; Raglio, 2015). As many of these same areas are compromised in PD (Nombela et al., 2013), the ability of music to activate key motor regions during rhythm perception can serve an important compensatory purpose. Music can increase regional cerebral blood flow (Blood and Zatorre, 2001) and stimulate the release of dopamine (Salimpoor et al., 2011), a neurochemical depleted in PD, which also regulates motivation and goal-directed behaviors (Chanda and Levitin, 2013).

Internal cueing of movement timing is disturbed by malfunctioning basal ganglia – cortical circuitry in people with PD (Herrojo Ruiz et al., 2014). However, external auditory cuing in the form of metronome pulses or rhythmic music can enable affected individuals to initiate steps and maintain gait movements (Benoit et al., 2014; Mainka, 2015) or can train sequences of action related to everyday tasks (Pohl et al., 2013). In music with a clear beat, the steady temporal input serves as a continuous reference, creating a rhythmic template that influences the motor system's ability to coordinate and execute movement (Nombela et al., 2013). As the pattern of regular external cues generates temporal expectations, the temporal-motor system begins to act on those expectations, predicting subsequent beats and priming movement in anticipation of them (Nombela et al., 2013; Benoit et al., 2014). In the absence of a healthy basal ganglia timing system, the cerebellar–thalamic–cortical network seems to be recruited to mediate the entrainment process, or synchronization of movement to sound (Thaut, 2008; Nombela et al., 2013; Benoit et al., 2014; Raglio, 2015). In addition, cueing through a neurologic music therapy technique known as Rhythmic Auditory Stimulation (RAS) has been shown to help normalize multiple gait parameters including velocity, cadence, and stride length (Thaut et al., 1996; McIntosh et al., 1997; Arias and Cudeiro, 2010) even on individuals with mild cognitive impairment (Rochester et al., 2009).

Research has shown that music that is familiar is more likely than unfamiliar music to lead to accurate tempo matching and functional strides with RAS (Leow et al., 2015). Familiarity influences emotional arousal; this level of arousal is strongly related to the degree of pleasure experienced by the music listener (van den Bosch et al., 2013). Predictions and expectations of auditory events are made and satisfied when listening to familiar music, resulting in dopamine release in the striatal system (Salimpoor et al., 2011), as well as activation of emotion-related regions (Pereira et al., 2011). Familiar, preferred music can optimize motivation for therapeutic training programs and promote emotional engagement (Mainka, 2015). For example, music therapy has been shown to mitigate speech impairment in PD by facilitating synchronization of articulatory muscle patterns to rhythm, and training respiratory support and control through singing and other vocal exercises. These types of programs are often provided in a group singing or choir context, allowing for rewarding social interaction and improving quality of life (Yinger and LaPointe, 2012; Buetow et al., 2014; Stegemöller et al., 2016). Cognitive abilities have also been improved through music-based training in this population (Pohl et al., 2013).

In addition to experiencing physical challenges, depression is common in people with PD (Frisina et al., 2008; Reijnders et al., 2008), and mood disorders may manifest even before motor symptoms appear (Raglio, 2015). Depression is considered a core symptom of PD, diminishing quality of life (Global Parkinson's Disease Survey Steering Committee, 2002). Some researchers believe depression in PD is mediated by the degeneration of the neurotransmission of dopamine, among other neurochemicals (Sawabini and Watts, 2004). The ability of music to induce neurochemical and physiological changes may have particular relevance in the treatment of people with PD, not only for its effects on movement, but also to address mood disturbances (Koelsch, 2010; Bega et al., 2014). Enjoyable music recruits the reward-motivational circuitry involved in survival behaviors, with activations in areas including the ventral striatum and its nucleus accumbens (Blood and Zatorre, 2001). Music listening has been shown to trigger the release of dopamine in the striatal system (Salimpoor et al., 2011). Therefore, dopaminergic activity may be mediating the affective response to music through mesolimbic structures relevant to PD.

Earlier research shows that people with PD and their healthy counterparts are equally able to detect out-of-key tones, rhythmic changes, and differences in meter (Lima et al., 2013). In addition, through experimentation we have shown that individuals with PD are able to perceive and correct distortions introduced into different musical pieces, although they are slightly less able to eliminate distortions than healthy peers (Muratori et al., 2015;

Pinkhasov et al., 2015; Schedel et al., 2016). In the current study, we were interested in seeing if individuals with PD experience music in the same way as those without PD. To do this we analyzed survey responses to a broad range of statements about personal music experiences and reactions to music in general and specific to listening to three musical pieces. We hypothesized the two populations would have equal familiarity with musical selections. However, due to the frequency of depressive symptoms in people with PD, we expected that participants with PD would return more negative survey ratings than those without PD, with specific differences in responses to involvement in musical behaviors and enjoyment resulting from listening to music.

MATERIALS AND METHODS

Nineteen individuals with PD (11 male, aged 52–79 years, $\bar{x}$ = 67 years, Hoehn and Yahr I–III) and fifteen healthy peers (7 male, aged 51–89 years, $\bar{x}$ = 66 years) participated in this study. Participants were recruited by word of mouth and via flyers with information sent to local movement disorder neurologists. Interested persons called the principal investigator (LM) and were screened for eligibility as either a person with PD or a peer without PD. Eligibility included (1) adequate visual and auditory acuity and motor control to perform the study tasks; (2) willingness and ability to sign an informed consent and comply with the study protocol; and for participants with PD; (3) clinical PD as determined by a neurologist; any disease duration and disease level according to the Hoehn and Yahr scale (Hoehn and Yahr, 1967); (4) no history of a secondary neurological or medical problem that has a known effect on vision, auditory, or cognitive functioning; and (5) stable neurological function and medications for at least 30 days prior to study entry. This study was carried out in accordance with the Committee on Research Involving Human Subjects, Institutional Review Board (IRB) of Stony Brook University. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the IRB prior to initiating any data collection. Testing occurred at Stony Brook University's Rehabilitation Research and Movement Performance (RRAMP) Laboratory.

Upon arrival at the lab, participants were surveyed regarding their musical experience through a computerized version of the Brief Music Experience Questionnaire (BMEQ) (Werner et al., 2006) using Qualtrics software (Qualtrics, Provo, UT, United States). Completion of the BMEQ was immediately followed by listening to excerpts of three pieces of music representing a range of genres and textures: Billie Holiday's "Love me or leave me" (Donaldson and Kahn, 1928/1941/1996, track 14), The Beatles' "Here comes the sun" (Harrison, 1969, track 7), and Haydn's "Finale – Allegro con spiritu" (Haydn, 1795/2008, track 8) from the 103rd Symphony. The Beatles song is in the genre of rock and roll. Its homophonic setting features prominent male vocals and acoustic guitar lines, with other components of a rock band providing harmonic support, and a tempo of 129 beats per minute (bpm). Haydn's work is an example of classical instrumental music in a densely layered orchestral setting, at 145 bpm. The Billie Holiday song is from the jazz genre, with an instrumental ensemble backing up an expressive female vocal line. It has the slowest tempo of the pieces, at 90 bpm. We wanted to give participants a variety of musical affects to draw from, and provide different auditory backdrops against which the distortions would be detected. Each song was first played as it was originally recorded. Then (as part of a separate study – see Muratori et al., 2015; Schedel et al., 2016) three different kinds of distortions were overlaid onto each recording with Ableton Live Software (Ableton, Berlin) to create nine different musical conditions. Distortions consisted of Beat Repeat (a captured sound repeated in a loop for a jittery, shuddering effect); Timbral Shift (a high-frequency whooshing or warbling sound produced by a frequency shifter); and White Noise Generator (static). Each condition was repeated three times for a total of 27 trials. For more detail about the distortions, please refer to our prior publications (Muratori et al., 2015; Schedel et al., 2016). The procedure consisted of approximately 20 min of listening time per song; the song was distorted for about 5 min of this time. Rather than passively listening to music, the participants were required to actively listen to, interact with, and evaluate the effects of their responses on the music, resulting in a profound exposure to each musical selection. Immediately after the active listening, participants completed a pencil-and-paper Exit Survey, a custom measurement tool created by the researchers for purposes of this study, rating their familiarity with and enjoyment of the music heard. The results of the BMEQ and Exit Survey are reported here with a discussion of considerations for the use of music as an intervention in PD.

Measures

The Music Experience Questionnaire (MEQ) was developed to measure the relationship between music experience and aspects of personality, including clinically relevant behavior (Werner et al., 2006, 2009). The developers of this self-report measurement tool suggested that such a questionnaire may be useful in the clinical setting to identify individuals who are likely to respond to music-based intervention techniques, and recommended that future MEQ-related studies factor in music preference and listening choices (Werner et al., 2009). Respondents' choices on a five-point rating system represent their level of agreement with 141 survey statements, from 1 (Very untrue) to 5 (Very true). Statements on a range of music experience topics are intended to be relevant to non-musicians as well as musicians, and are grouped into six specific categories (also referred to as scales or dimensions) of music experience outlined by Werner et al. (2009) that focus on types of responses to and involvement in music: "Commitment to Music" (CM), "Social Uplift" (SU), "Affective Reactions" (AR), "Reactive Musical Behavior" (RMB), "Innovative Musical Aptitude" (IMA), and "Positive Psychotropic Effects" (PPE), as shown in **Table 1**. We used a condensed version of the MEQ, the BMEQ, which comprises 53 items falling within these categories.

TABLE 1 | Brief Music Experience Questionnaire (BMEQ) dimensions.

Abbreviations	Dimension	Description
AR	Affective Reactions	Affective and spiritual reactions to music
CM	Commitment to Music	The centrality of pursuit of musical experiences in the person's life
IMA	Innovative Musical Aptitude	Self-reports of musical performance ability as well as the ability to generate musical themes and works
PPE	Positive Psychotropic Effects	Calming, energizing, integrating reactions
RMB	Reactive Musical Behavior	Motile reactions including humming and swaying along with music
SU	Social Uplift	The experience of being stirred and uplifted in a group-oriented manner by music

Adapted from Werner et al. (2006).

Our Exit Survey listed the music played by title and performer or composer, to aid in identification and recall. The headings "The Beatles (Here Comes the Sun)," "Billie Holiday (Love Me or Leave Me)," and "Haydn (Symphony)" were followed by rows for indicating familiarity and enjoyment. As the BMEQ utilized a five-point rating system, we used the same system to express ratings of these variables. Guidelines were printed under the numbers to illustrate the direction of response strength. The familiarity scale ranged from "Never heard it before" to "Very familiar," and the esthetic response scale ranged from "I hate it" to "I love it." The participants circled the number, from 1 to 5, that represented their level of familiarity with and listening enjoyment of each of the three musical selections. The participants had the option to re-listen to any of the songs to ensure that they were attributing their reactions to the correct piece. Participants offered their ratings at the conclusion of the entire set of listening trials.

Data Analysis

Descriptive statistics were computed for all variables and used for further analysis. Data was analyzed using Statistical Package for the Social Sciences software (SPSS, version 20, IBM, NY, United States). For the BMEQ, reverse-coded question scores were re-ordered so that all questions could be evaluated using a scale with a consistent direction. To determine differences between participants with and without PD, BMEQ and Exit Survey data was examined using Mann–Whitney *U* tests with a $p < 0.05$ significance level. The non-parametric Mann–Whitney test was chosen because response datasets did not, in general, conform to a normal data distribution. Mean responses for each participant were used as *U* test input in order to focus on the variance between subjects. BMEQ data was further divided to examine the influence of the six dimensions within the survey. As previous literature has shown an influence of familiarity on music enjoyment (Meyer, 1994; Pereira et al., 2011; van den Bosch et al., 2013), the Exit Survey data was analyzed using Spearman's rho correlation testing to determine if participants with PD and control participants were equally impacted by the songs tested.

RESULTS

Data analysis revealed minor variation between populations, and one instance of statistical significance when examining responses at the level of each of the six scales that make up the BMEQ, though on this survey as a whole there was no response difference between populations ($p > 0.05$ across categories). These scales categorize reactions to and experiences of music that underlie the perceived role of music in one's life, as outlined in **Table 1**.

There were greater positive responses by control participants to 43 out of 53 survey statements, or 81% of the questionnaire, with responses from the participants with PD lagging behind on each of the six scales, throughout the various contexts of music experience explored in the BMEQ (**Figure 1A**). Yet, a significant difference between groups was found in only the RMB dimension, in which individuals with PD reported lower responses than their non-PD peers (RMB PD median = 3.0, Control median = 4.1, $U = 80$, $Z = -2.17$, $p < 0.05$, $r = 0.37$). Note that these differences were seen throughout the RMB dimension questions rather than just resulting from a single divergent response (see **Figure 1B**). **Figures 1C,D** show that mean responses for the PD group also trailed the control group for questions throughout the IMA and PPE scales, though the difference in median response did not prove to be statistically significant in the Mann–Whitney *U* test (see **Table 2**).

Unlike the BMEQ, the custom Exit Survey evaluated responses as they related to the specific recent experience of listening to the three musical pieces in this experiment through ratings on two parameters: familiarity and enjoyment. Most participants reported familiarity with and enjoyment of the selected pieces with overall $\bar{x}$ scores of 3.8 and 4.2 on the respective 5 point scales. However, similar to the BMEQ, the Exit Survey showed a moderate effect size with results that were lower for participants with PD, indicating those with PD were less familiar (PD median = 3.67, Control median = 4.33, $U = 78$, $Z = -2.28$, $p < 0.05$, $r = 0.39$) and enjoyed the music less (PD median = 4.0, Control median = 4.3, $U = 85$, $Z = -2.10$, $p < 0.05$, $r = 0.36$) than their healthy peers (see **Table 3**). Examining the influence of familiarity on enjoyment, bivariate correlation analysis demonstrated an overall correlation between familiarity and enjoyment (Spearman's rho = 0.581, $p < 0.001$) with a stronger effect for those with PD (Spearman's rho = 0.654, $p < 0.001$) than for control participants (Spearman's rho = 0.458, $p = 0.002$; see **Figures 2A,B**).

DISCUSSION

Differences in responses on the BMEQ between the two populations surveyed were subtle but consistent. On the majority of questions, ratings from participants with PD were lower than controls on a broad range of items pertaining to musical responsiveness, consciousness, ability, and overall experience.

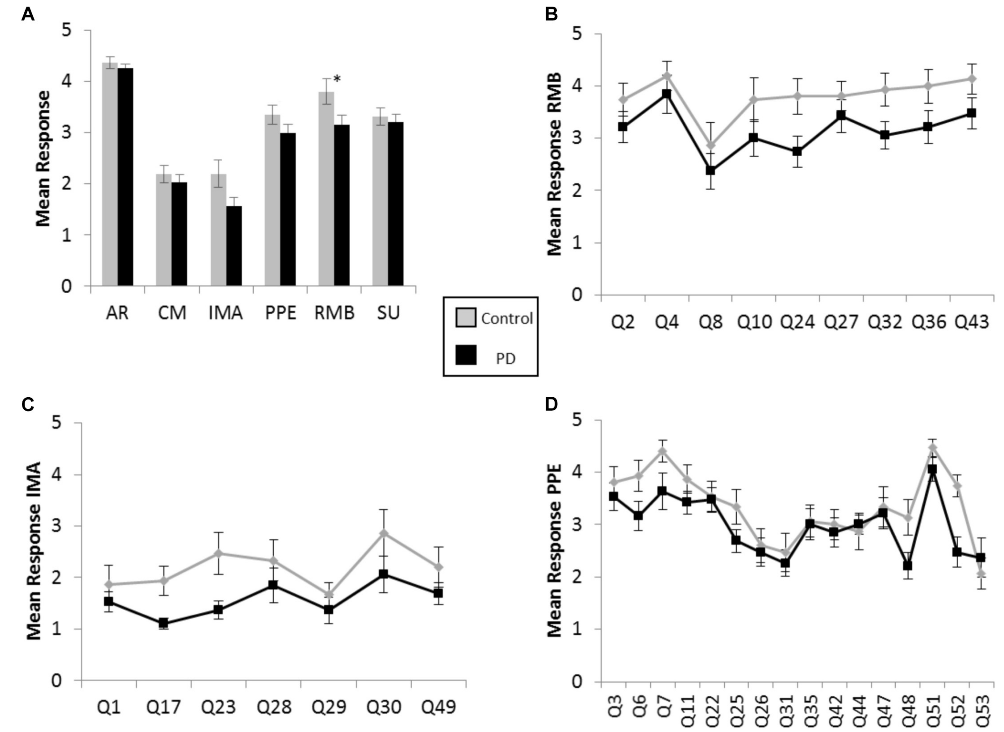

FIGURE 1 | Brief Music Experience Questionnaire (BMEQ) ratings by participants with and without PD. **(A)** Overall group means of six music experience scales of the BMEQ showing the categories: Affective Reactions (AR), Commitment to Music (CM), Innovative Musical Aptitude (IMA), Positive Psychotropic Effects (PPE), Reactive Musical Behavior (RMB), and Social Uplift (SU) as rated on a 5-point scale (*y* axis) by participants with (Black) and without (Gray) PD. Error bars indicate the standard error of the means. Asterisks (*) indicate significance between groups at $p < 0.05$ as determined by Mann–Whitney *U* test. Individual question means for **(B)** RMB, **(C)** IMA, and **(D)** PPE for participants with and without PD. Q numbers (*x* axis) refer to the questions/items on the BMEQ that constitute the corresponding category. Data points represent mean responses for each participant group to that question.

Responses from healthy participants were skewed toward the high end of the five-point scale denoting more positive responses to or agreement with the statements, whereas responses from those with PD veered more toward the low end, even if just slightly in most dimensions. However, only in items dealing with motor/behavior responses to music, represented in the RMB

TABLE 2 | Two sample Mann–Whitney *U* test results for the domains of the BMEQ.

Scale	PD median	Control median	*U* statistic	z score	*p* value	Effect size
AR Affective Reactions	4.30	4.40	118.0	−0.86	0.41	0.15
PPE Positive Psychotropic Effects	3.19	3.44	104.5	−1.32	0.19	0.23
CM Commitment to Music	1.86	2.29	117.5	−0.87	0.391	0.15
IMA Innovative Musical Aptitude	1.29	2.14	92.5	−1.75	0.083	0.30
RMB Reactive Musical Behavior	3.00	4.11	80.0	−2.17	0.030*	0.37
SU Social Uplift	3.25	3.50	129.0	−0.47	0.656	0.08

Asterisk (*) indicates statistically significant difference between groups at $p < 0.05$. For each participant, mean responses were calculated over all questions in the domain and used as input to the analysis ($N = 34$). Effect size $r = Z/sqrt(N)$.

TABLE 3 | Two sample Mann–Whitney *U* test results for the Exit Survey.

Scale	PD median	Control median	*U* statistic	z score	*p* value	Effect size
Familiarity	3.67	4.333	77.5	−2.28	0.023*	0.39
Enjoyment	4.00	4.333	84.5	−2.10	0.043*	0.36

Asterisk (*) indicates statistically significant difference between groups at $p < 0.05$. For each participant, mean responses over the three Exit Survey songs were used as input to the analysis ($N = 34$). Effect size $r = Z/sqrt(N)$.

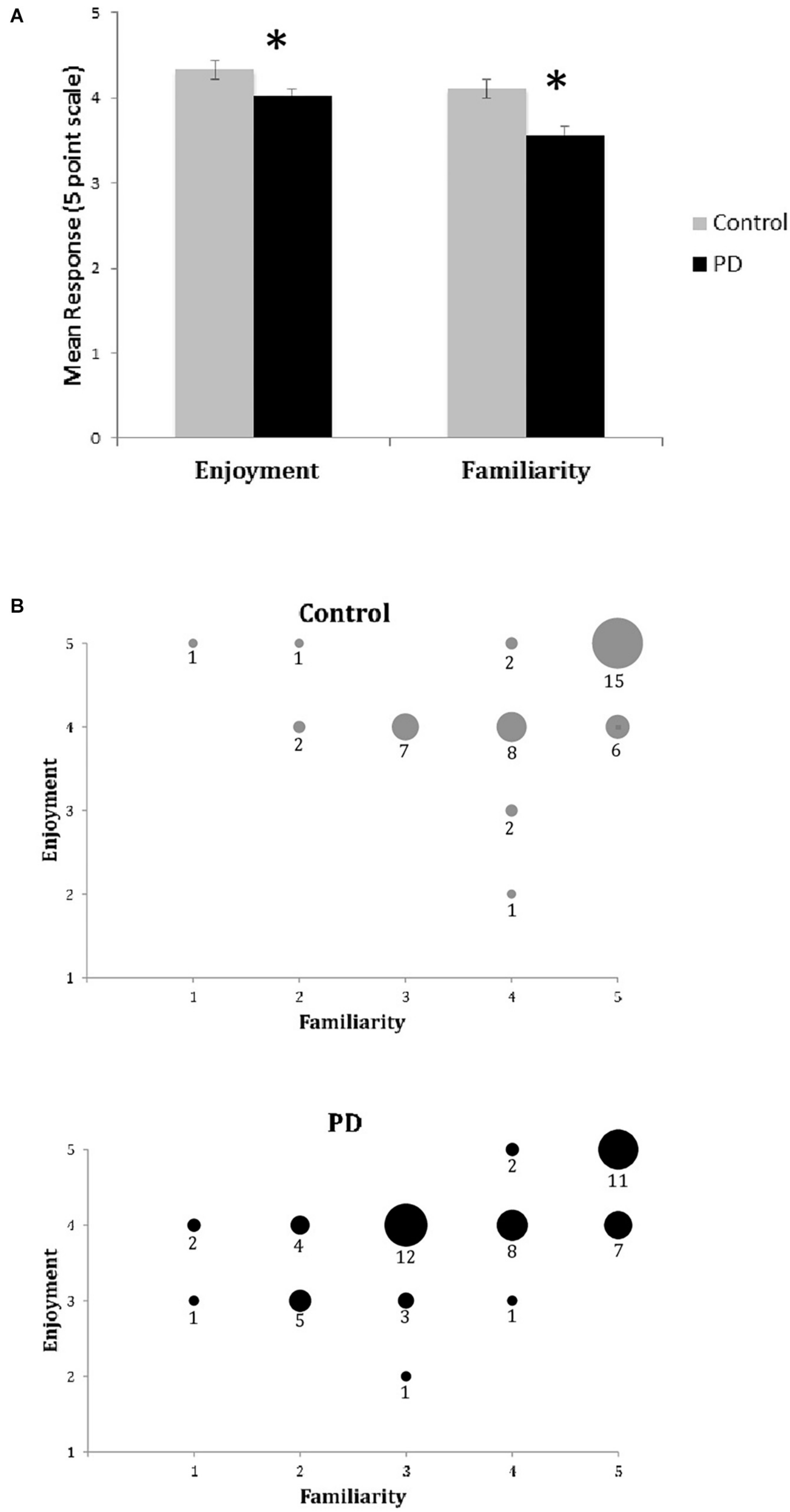

FIGURE 2 | Exit Survey results of music enjoyment and familiarity. **(A)** Mean responses (±SEM) for enjoyment and familiarity on the Exit Survey for healthy controls (Gray) and participants with PD (Black). Asterisks (*) indicates significance at $p < 0.05$ as determined by Mann–Whitney U test. There were significant between group differences for both enjoyment and familiarity. **(B)** Enjoyment plotted against familiarity for control (top) and PD (bottom) groups. Responses for all songs and all participants are included in dataset. Size of circle and numbers below indicate the number of participants from each group who responded at that coordinate for the three songs.

category of BMEQ survey questions, was the difference between groups significant. PD causes disturbances in the motor and vocal systems that support these types of musical responses. Whereas healthy people may feel stimulated or even compelled to sing or dance along to music under certain circumstances, members of our PD group reported they saw little influence on such activities from music. The generation of motor responses related to anticipation of reward appears to be mediated by the release in the ventral striatum of dopamine, which is depleted in PD (Elliott et al., 2004). When diminished dopaminergic activity interrupts the normal circuit of anticipation, movement and reward in PD, individuals may not feel moved to move. Our data suggests that people with PD perceive the motor impairments caused by the disease as pervading their physical responses to music.

Depression and anhedonia, more common in PD than the broader population (Frisina et al., 2008; Loas et al., 2012), may translate to a reduction in behaviors and activities that seek, explore, express, and result in pleasure. Although we did not evaluate participants for these conditions, it is possible that depression in some participants with PD resulted in lower scores.

Meaningfulness, esthetics, emotional response to and valence of music are covered in the BMEQ's AR scale, which returned the smallest average difference between groups and had the most positive responses of all the categories. AR casts music as a general concept as well as a stimulus capable of evoking subjective, affective/spiritual reactions. In AR, the PD group's impressions of music's power to mediate responses in the emotional realm may be seen as suppressed compared to controls, but to a noticeably lesser degree than on the scale dealing with physical/behavioral responses and capacities (RMB), or even creative/expressive and calming/energizing effects (IMA and PPE, respectively). This is somewhat surprising as AR has been correlated with the Center for Epidemiological Studies Depression Scale in previous studies (see Werner et al., 2009) and a stronger distinction between groups was expected in our hypothesis based on an increased likelihood of depression in the PD group. Although it is certainly possible that our sample did not exhibit depression overall, an alternate suggestion is that for people with PD, the ability to relate and respond to music on an emotional level may exceed their estimation of its capability to influence other aspects of their lives.

Our Exit Survey was concerned solely with listening data, and in particular with familiarity and enjoyment ratings of discrete works listened to in the immediate past (the Exit Survey was completed just after the listening trials). Importantly, all participants had repeated exposure to each of the three songs as part of the active listening trials. In a study by Madison and Schiölde (2017), novel musical examples that were initially less liked by listeners increased in enjoyment ratings after multiple presentations, demonstrating increased enjoyment with increased familiarity. In our study, control participants reported higher pleasure rankings on the Exit Survey than participants with PD. We did not explore whether the distortions, which were added to the original recordings for brief periods as part of a separate study (Muratori et al., 2015; Schedel et al., 2016), may have affected pleasure or familiarity valuations by either or both groups of participants. However, it is possible that the distorted sounds had different effects on each group and perhaps biased the findings. Uluyol et al. (2016) reported that individuals with PD have more high frequency hearing loss and greater severity of tinnitus than peers without PD. In addition, central auditory processing deficits in PD may have influenced perceptions of distortions making them less impactful in our participants with PD (Folmer et al., 2017). As those with PD may not have heard the full range of distorted sounds or may have processed the distortions less completely, reports of more enjoyable experiences on the Exit Survey may reflect this difference.

The three pieces of music were chosen in advance by the researchers without knowing what preferences and dislikes or emotional associations with the music the participants might have had. The use of existing, available music gave us the ability to consider the effects of familiarity, but also brought with it the possible influence of episodic musical associations (Sloboda, 1999). The experience of hearing certain music connects the listener with previous events that the person associates with the music, and the people, places, and emotions that played a part in them. These memories may be extramusical, distinctly individualized, and highly charged, emotionally. Therefore, the specific selections may have affected the listening experiences in ways that we were not able to predict ahead of time or evaluate in the data.

While we had hypothesized all participants would have similar previous exposure to the musical selections, those without PD also had unexpected higher rates of familiarity with the musical selections, with greater listening enjoyment during the task. Not surprisingly, the Beatles selection was well known to all the participants, but the Haydn and Billie Holiday pieces were both more familiar to the control participants than to those with PD. While the overall relationship between familiarity and enjoyment was not surprising given previous studies (e.g., van den Bosch et al., 2013) the strength of this relationship was greater for the participants with PD. Listening proximity may have been a factor that prompted a different and more positive interpretation and valuation of the listening experience, as both respondent groups reported higher levels of emotional engagement in the immediate post-experimental survey (Exit Survey) compared to the pre-test survey of hypothetical or imagined music listening and consumption (BMEQ). Immediacy and familiarity may be necessary for people with PD to cross the threshold from indifference to arousal, excitement and uplift from music, which may mean that they will be more likely to seek out and benefit from the therapeutic effects of applications of music.

Results demonstrated that following a recent specific music listening exercise, music was viewed more positively (measured on the Exit Survey) compared to general experiences of music on the earlier-administered BMEQ. We believe that the task of actively engaging with the music in listening trials versus abstractly thinking about music may explain this difference. Unlike passive listening (such as hearing background music), active listening involves listening *for* as much as listening *to* the music. The active listener mentally tracks the music through time, maintaining attention and engaging cognitive processes beyond the simple perception of sound (Gregory, 2002). Attentive music listening is linked with psychophysiological arousal, and a strong positive correlation exists between arousal and pleasure ratings (Salimpoor et al., 2009). Particularly relevant to people with PD, this arousal effect can influence motivational processing, and, indeed, therapeutic applications of music have been shown to increase motivation in people with poor ability to internally generate feelings of anticipation, motivation, and drive (Pacchetti et al., 2000). In addition, it is possible that the motor aspect of the listening task (moving controls on an iPad) contributed to all participants attending to the music with more intensity that would have been achieved without the movement element. A sustained active music listening intervention with movement features has been shown to help maintain attention skills for people with diagnoses, like PD, that affect cognitive processing (Gregory, 2002). In the movement task associated with our study, manipulating the slider and adjusting the sound may have mimicked the experience of playing an instrument, a motor-attentional operation that combines stimulation of both auditory and tactile pathways for a more integrated sensory response (Pacchetti et al., 2000).

We saw that familiar music in particular can catalyze a pleasure response in people with PD, consistent with findings in the general population by Pereira et al. (2011) and van den Bosch et al. (2013). Music responses that operate below the conscious level may have been at play, causing a distinction between contextual music experiences and imagined music listening, with additional valence generated by familiarity. In therapeutic applications, music can stimulate both conscious and automatic processes to alleviate symptoms and improve quality of life (Pacchetti et al., 2000; Clair et al., 2011). Some reactions to music occur without conscious awareness or intent, such as RAS entrainment effects, arousal and motivational benefits and physiological changes. As we have seen, even though the qualities of certain aspects of music, such as its ability to elicit an affective response, may be viewed quite similarly by individuals with PD and their unafflicted peers, music listening experiences vary with personal perceptions. This has implications for clinical work when music is used in interventions with persons with PD. Familiarity and preference of music should be considered. Furthermore, while survey assessments or other quantitative evaluation tools may be useful in identifying candidates for music therapy and the kinds of music to which they would most favorably respond (Werner et al., 2009), it is important to note the limitations of these tools in capturing subjective, experiential information. Future studies incorporating qualitative methods could greatly enhance our understanding of how people with and without PD experience and appreciate music.

One limitation of the present study is that the investigators were not blinded as to whether the participant had PD. Note that the surveys were completed by the participant on a computer (BMEQ) or with pencil-and-paper (Exit survey), and there was limited interaction with the investigators during the completion of these surveys. Furthermore, the quantitative nature of these surveys leaves little room for subjective interpretation by the investigators during analysis. We cannot, however, rule out the possibility that the investigators could have unintentionally influenced the results. The effect of participant-investigator interaction on the musical experience would be an interesting topic for future research, and may provide useful insights into the effectiveness of music therapy. For instance, one might ask whether the clinician's music preference affects the person's response to music therapy.

Another limitation of the present study is that we examine how people with PD respond to only one type of musical experience: listening. Other avenues of research could investigate whether responses differ between different types of musical experience, such as dancing or music-making.

CONCLUSION

Many elements factor into an individual's musical preferences, enjoyment and consciousness; music enjoyment is a highly personal human reaction, based on an individualized framework shaped by emotions and subjective experience. In PD, there are disease processes that affect emotional state and enjoyment, and may influence an individual's anticipation and expectations of music experiences. Past evidence has shown that people with PD can benefit from the rhythm and structure of music to train and enhance movement, speech abilities, cognitive function, and emotional well-being, and that familiarity may improve music therapy outcomes. Our data suggests that of the various parameters of music experience, the active, physical response is most keenly felt to be reduced in PD. It also appears that persons with PD may have a diminished perception of their ability to derive value or pleasure from music, but their capacity for enjoyment can exceed the expectation. As people with PD may underrate the value of music in their lives, they may need and benefit from encouragement to actively engage in music, to access its power to assist with movement and communication and to improve mood, motivation, and quality of life. Our analysis clearly suggests a particular dependence of enjoyment on music familiarity in PD, endorsing the use of client-preferred familiar music in music therapy applications for individuals with this disease.

ETHICS STATEMENT

This study was carried out in accordance with the Committee on Research Involving Human Subjects, Institutional Review Board (IRB) of Stony Brook University with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the IRB prior to initiating any data collection.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception, analysis, and interpretation of data of this work. IM, LM, MS, JL, and TP were involved in the acquisition of data. IM, MS, and LM provided the original drafts and all authors revised or provided the critical content to the paper prior to giving final approval of the manuscript. The authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

Arias, P., and Cudeiro, J. (2010). Effect of rhythmic auditory stimulation on gait in parkinsonian patients with and without freezing of gait. *PLoS One* 5:e9675. doi: 10.1371/journal.pone.0009675

Bega, D., Gonzalez-Latapi, P., Zadikoff, C., and Simuni, T. (2014). A review of the clinical evidence for complementary and alternative therapies in Parkinson's disease. *Curr. Treat. Options Neurol.* 16:314. doi: 10.1258/mi.2012.012001

Benoit, C., Dalla Bella, S., Farrugia, N., Obrig, H., Mainka, S., and Kotz, S. (2014). Musically cued gait-training improves both perceptual and motor timing in Parkinson's disease. *Front. Hum. Neurosci.* 8:494. doi: 10.3389/fnhum.2014.00494

Blood, A., and Zatorre, R. (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc. Natl. Acad. Sci. U.S.A.* 98, 11818–11823. doi: 10.1073/pnas.191355898

Buetow, S., Talmage, A., McCann, C., Fogg, L., and Purdy, S. (2014). Effects of singing on voice, respiratory control and quality of life in persons with Parkinson's disease. *Disabil. Rehabil.* 36, 430–433. doi: 10.3109/09638288.2016.1152610

Chanda, M., and Levitin, D. (2013). The neurochemistry of music. *Trends Cogn. Sci.* 17, 179–193. doi: 10.1016/j.tics.2013.02.007

Clair, A., Lyons, K., and Hamburg, J. (2011). A feasibility study of the effects of music and movement of physical function, quality of life, depression, and anxiety in patients with Parkinson's disease. *Music Med.* 4, 49–55. doi: 10.1177/1943862111425680

Dalla Bella, S., Benoit, C., Farrugia, N., Schwartze, M., and Kotz, S. (2015). Effects of musically cued gait training in Parkinson's disease: beyond a motor benefit. *Ann. N. Y. Acad. Sci.* 1337, 77–85. doi: 10.1111/nyas.12651

Donaldson and Kahn (1928/1941/1996). *Love Me or Leave Me [Recorded by Billie Holiday, 1941]. On Love Me or Leave Me: 20 Classics From the First Lady of Jazz [CD]*. London: Hallmark Recordings doi: 10.1111/nyas.12651

Elliott, R., Newman, J., Longe, O., and William Deakin, J. (2004). Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. *Neuroimage* 21, 984–990. doi: 10.1016/j.neuroimage.2003.10.010

Folmer, R. L., Vachhani, J. J., Theodoroff, S. M., Ellinger, R., and Riggins, A. (2017). Auditory processing abilities of Parkinson's disease patients. *BioMed Res. Int.* 2618587. doi: 10.1155/2017/2618587

Frisina, P., Borod, J., Foldi, N., and Tenenbaum, H. (2008). Depression in Parkinson's disease: health risks, etiology, and treatment options. *Neuropsychiatr. Dis. Treat.* 4, 81–91.

Global Parkinson's Disease Survey Steering Committee (2002). Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov. Disord.* 17, 60–67. doi: 10.1002/mds.10010

Grabli, D., Karachi, C., Welter, M.-L., Lau, B., Hirsch, E., Vidailhet, M., et al. (2012). Normal and pathological gait: what we learn from Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 83, 979–985. doi: 10.1136/jnnp-2012-302263

Gregory, D. (2002). Music listening for maintaining attention of older adults with cognitive impairments. *J. Music Ther.* 39, 244–264. doi: 10.1093/jmt/39.4.244

Harrison, G. (1969). *Here Comes the Sun [Recorded by The Beatles]. On Abbey Road [mp3]*. London: Apple.

Haydn, F. J. (1795/2008). *Finale - Allegro con spiritu" from Symphony 103 [Recorded by Royal Philharmonic Orchestra]. On Haydn: Symphonies* 101 & 103 [CD]. London: Royal Philharmonic Masterworks.

Herrojo Ruiz, M., Rusconi, M., Brücke, C., Haynes, J. D., Schönecker, T., and Kühn, A. A. (2014). Encoding of sequence boundaries in the subthalamic nucleus of patients with Parkinson's disease. *Brain* 137, 2715–2730. doi: 10.1093/brain/awu191

Hoehn, M., and Yahr, M. (1967). Parkinsonism: onset, progression and mortality. *Neurology* 17, 427–442.

Holmes, R., Oates, J., Phyland, D., and Hughes, A. (2000). Voice characteristics in the progression of Parkinson's disease. *Int. J. Lang. Commun. Disord.* 35, 407–418. doi: 10.1080/136828200410654

Koelsch, S. (2010). Towards a neural basis of music-evoked emotions. *Trends Cogn. Sci.* 14, 131–137. doi: 10.1016/j.tics.2010.01.002

Leow, L., Rinchon, V., and Grahn, J. (2015). Familiar music increases walking speed in rhythmic auditory cueing. *Ann. N. Y. Acad. Sci.* 1337, 53–61. doi: 10.1111/nyas.12658

Lima, C. F., Garrett, C., and Castro, S. L. (2013). Not all sounds sound the same: Parkinson's disease affects differently emotion processing in music and in speech prosody. *J. Clin. Exp. Neuropsychol.* 35, 373–392. doi: 10.1080/13803395.2013.776518

Loas, G., Krystkowiak, P., and Godefroy, O. (2012). Anhedonia in Parkinson's disease: an overview. *J. Neuropsychiatry Clin. Neurosci.* 24, 444–451.

Madison, G., and Schiölde, G. (2017). Repeated listening increases the liking for music regardless of its complexity: implications for the appreciation and aesthetics of music. *Front. Neurosci.* 11:147. doi: 10.3389/fnins.2017.00147

Mainka, S. (2015). Music stimulates muscles, mind, and feelings in one go. *Front. Psychol.* 6:1547. doi: 10.3389/fpsyg.2015.01547

McIntosh, G., Brown, S., Rice, R., and Thaut, M. (1997). Rhythmic auditory-motor facilitation of gait patterns in patients with Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 62, 22–26. doi: 10.1136/jnnp.62.1.22

Merchant, H., Harrington, D. L., and Meck, W. H. (2013). Neural basis of the perception and estimation of time. *Annu. Rev. Neurosci.* 36, 313–336. doi: 10.1146/annurev-neuro-062012-170349

Meyer, L. (1994). *Music, the Arts, and Ideas: Patterns and Predictions in Twentieth-century Culture*. Chicago: University of Chicago Press.

Muratori, L., Schedel, M., Weymouth, D., Pinkhasov, T., Loomis, J., Morris, I. B., et al. (2015). "Sonification of gait to create real-time auditory feedback for people with Parkinson's disease," in *Proceedings of the 11th International Symposium on Computer Music Multidisciplinary Research*, Plymouth.

Nombela, C., Hughes, L., Owen, A., and Grahn, J. (2013). Into the groove: can rhythm influence Parkinson's disease? *Neurosci. Biobehav. Rev.* 37, 2564–2570. doi: 10.1016/j.neubiorev.2013.08.003

Pacchetti, C., Mancini, F., Aglieri, R., Fundaro, C., Martignoni, E., and Nappi, G. (2000). Active music therapy in Parkinson's disease: an integrative method for motor and emotional rehabilitation. *Psychosom. Med.* 62, 386–393. doi: 10.1097/00006842-200005000-00012

Pereira, C. S., Teixeira, J., Figueiredo, P., Xavier, J., Castro, S. L., and Brattico, E. (2011). Music and emotions in the brain: familiarity matters. *PLoS One* 6:e27241. doi: 10.1371/journal.pone.0027241

Pinkhasov, T., Vasudevan, E., Schedel, M., Weymouth, D., Loomis, J., Morris, I. B., et al. (2015). *"Neuroscience Meeting Planner"* in Program No. 582.09, (Washington, DC: Society for Neuroscience).

Pinto, S., Ozsancak, O., Tripoliti, E., Thobois, S., Limousin-Dowsey, P., and Auzou, P. (2004). Treatments for dysarthria in Parkinson's disease. *Lancet Neurol.* 3, 547–556. doi: 10.1016/s1474-4422(04)00854-3

Pohl, P., Dizdar, N., and Hallert, E. (2013). The ronnie gardiner rhythm and music method – a feasibility study in parkinson's disease. *Disabil. Rehabil.* 35, 2197–2204. doi: 10.3109/09638288.2013.774060

Raglio, A. (2015). Music therapy interventions in Parkinson's disease: the state-of-the-art. *Front. Neurol.* 6:185. doi: 10.3389/fneur.2015.00185

Reijnders, J., Ehrt, U., Weber, W., Aarsland, D., and Leentjens, A. (2008). A systematic review of prevalence studies of depression in Parkinson's disease. *Mov. Disord.* 23, 183–189. doi: 10.1002/mds.21803

Rochester, L., Burn, D., Woods, G., Godwin, J., and Nieuwboer, A. (2009). Does auditory rhythmical cueing improve gait in people with Parkinson's disease and cognitive impairment? A feasibility study. *Mov. Disord.* 24, 839–845. doi: 10.1002/mds.22400

Rodger, M., and Craig, C. (2016). Beyond the metronome: auditory events and music may afford more than just interval durations as gait cues in Parkinson's disease. *Front. Neurosci.* 10:272. doi: 10.3389/fnins.2016.00272

Salimpoor, V., Benovoy, M., Longo, G., Cooperstock, J., and Zatorre, R. (2009). The rewarding aspects of music listening are related to degree of emotional arousal. *PLoS One* 4:e7487. doi: 10.1371/journal.pone.0007487

Salimpoor, V. N., Benovoy, M., Larcher, K., Dagher, A., and Zatorre, R. J. (2011). Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat. Neurosci.* 14, 257–262. doi: 10.1038/nn.2726

Sawabini, K., and Watts, R. (2004). Treatment of depression in Parkinson's disease. *Parkinsonism Relat. Disord.* 10, S37–S41.

Schedel, M., Muratori, L., Pinkhasov, T., Loomis, J., Morris, I. B., and Vasudevan, E. (2016). "Interactive sonification of gait: realtime biofeedback for people with Parkinson's disease," in *Poster at the ISon 2016, Interactive Sonification Workshop*, (Bielefeld: CITEC).

Sloboda, J. (1999). "Music: where cognition and emotion meet," in *Proceedings of the XII National Conference from Australian Society for Music Education*, (Sydney NSW: University of Sydney),

Stegemöller, E., Radig, H., Hibbing, P., Wingate, J., and Sapienza, C. (2016). Effects of singing on voice, respiratory control and quality of life in persons with Parkinson's disease. *Disabil. Rehabil.* 39, 594–600. doi: 10.3109/09638288.2016.1152610

Thaut, M. (2008). *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications*. New York, NY: Routledge.

Thaut, M., McIntosh, G., Rice, R., Miller, R., Rathbun, J., and Brault, J. (1996). Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov. Disord.* 11, 193–200.

Uluyol, S., Kilicaslan, S., Baydar, C., and Sener, U. (2016). Hearing impairment and tinnitus severity in Parkinson's disease. *Turk. J. Geriatr.* 19, 228–231. doi: 10.1159/000478267

van den Bosch, I., Salimpoor, V., and Zatorre, R. (2013). Familiarity mediates the relationship between emotional arousal and pleasure during music listening. *Front. Hum. Neurosci.* 7:534. doi: 10.3389/fnhum.2013.00534

Werner, P., Swope, A., and Heide, F. (2006). The music experience questionnaire: development and correlates. *J. Psychol.* 140, 329–345. doi: 10.3200/jrlp.140.4.329-345

Werner, P., Swope, A., and Heide, F. (2009). Ethnicity, music experience and depression. *J. Music Ther.* 46, 339–358. doi: 10.1093/jmt/46.4.339

Yinger, O., and LaPointe, L. (2012). The effects of participation in a group music therapy voice protocol (G-MTVP) on the speech of individuals with Parkinson's disease. *Music Ther.Perspect.* 30, 25–31. doi: 10.1093/mtp/30.1.25

Zatorre, R., Chen, J., and Penhune, V. (2007). When the brain plays music: auditory–motor interactions in music perception and production. *Nat. Rev. Neurosci.* 8, 547–558. doi: 10.1038/nrn2152

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Musical Sonification of Arm Movements in Stroke Rehabilitation Yields Limited Benefits

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Neurologic music therapy in rehabilitation of stroke patients has been shown to be a promising supplement to the often strenuous conventional rehabilitation strategies. The aim of this study was threefold: (i) replicate results from a previous study with a sample from one clinic (henceforth called Site 1; $N = 12$) using an already established recording system, and (ii) conceptually replicate previous findings with a less costly hand-tracking system in Site 2 ($N = 30$), and (iii) compare both sub-studies' outcomes to estimate the efficiency of neurologic music therapy. Stroke patients in both sites were randomly assigned to treatment or control groups and received daily training of guided sequential upper limb movements additional to their standard stroke rehabilitation protocol. Treatment groups received sonification (i.e., changes in musical pitch) of their movements when they moved their affected hand up and down to reproduce a sequence of the first six notes of a C major scale. Controls received the same movement protocol, however, without auditory feedback. Sensors at the upper arm and the forearm (Xsens) or an optic sensor device (Leapmotion) allowed to measure kinematics of movements and movement smoothness. Behavioral measures pre and post intervention included the Fugl-Meyer assessment (FMA) and the Stroke Impact Scale (SIS) and movement data. Bayesian regression did not show evidence supporting an additional effect of sonification on clinical mobility assessments. However, combined movement data from both sites showed slight improvements in movement smoothness for the treatment group, and an advantage for one of the two motion capturing systems. Exploratory analyses of EEG-EMG phase coherence during movement of the paretic arm in a subset of patients suggested increases in cortico-muscular phase coherence specifically in the ipsilesional hemisphere after sonification therapy, but not after standard rehabilitation therapy. Our findings show that musical sonification is a viable treatment supplement to current neurorehabilitation methods, with limited clinical benefits. However, given patients' enthusiasm during training and the low hardware price of one of the systems it may be considered as an add-on home-based neurorehabilitation therapy.

Keywords: sonification, stroke, neurorehabilitation, neuroplasticity, music-supported therapy, neurologic music therapy, auditory-motor coupling

INTRODUCTION

Stroke survivors frequently suffer from severe disabilities. Stroke may lead to impairments in motor and sensory systems, emotion regulation, language perception, and cognitive functions (Morris and Taub, 2008). Impaired arm function caused by gross-motor disability is also a common consequence of stroke immensely affecting quality of life in a considerable number of patients. In this case, regaining control over body movements is one of the crucial components in post-stroke recovery. There is an urgent need for effective motor rehabilitation approaches to improve quality of life in stroke survivors. Different therapeutic approaches such as Constraint Induced Movement Therapy (CIMT), mental practice, robot-aided therapy, electromyographic biofeedback, and repetitive task training have been applied to improve arm function after stroke (Langhorne et al., 2009). Of note, in a recent review it has been suggested that neurologic music therapy might be more effective than conventional physiotherapy (for a recent review see Sihvonen et al., 2017).

Motivational factors seem to play an important role for the beneficial effects of neurologic music therapy. From the patients' informal descriptions of their experience with music-supported training, it appears that this is frequently highly enjoyable and a highlight of their rehabilitation process, regardless of the form of auditory stimulation, be it piano tones, or sonification of movement with other timbres [for a review see Altenmüller and Stewart (2018)]. However, effects of music supported therapy in stroke rehabilitation are not always consistent. In a recent review, seven controlled studies that evaluated the efficacy of music as an add-on therapy in stroke rehabilitation were identified (Sihvonen et al., 2017). In these studies, training of finger dexterity of the paretic hand was done using either a piano-keyboard, or, for wrist movements, drum-pads tuned to a C major scale. Superiority of the music group over fine motor training without music and over conventional physiotherapy was evident in one study after intervention comprising five 30-min sessions per week for 3 weeks (Schneider et al., 2010). The beneficial effect seen in the music group could be specifically attributed to the musical component of the training rather than the motor training *per se*, since patients practicing with mute instruments remained inferior to the music group. Here, the Fugl-Meyer Assessment (FMA) was applied before and after 20 sessions of either music supported therapy on a keyboard or equivalent therapy without sound. FMA scores of the motor functions of the upper limb improved by 16 in the music group and by 5 in the control group, both improvements being statistically significant although to a lesser degree in the control group ($p = 0.02$ vs. $p = 0.04$; Tong et al. (2015)).

With regard to the neurophysiological mechanisms of neurological music therapy, it was demonstrated that patients undergoing music supported therapy not only regained their motor abilities at a faster rate but also improved in timing, precision and smoothness of fine motor skills as well as showing increases in neuronal connectivity between sensorimotor and auditory cortices as assessed by means of EEG-EEG-coherence (Altenmüller et al., 2009; Schneider et al., 2010).

These findings are corroborated by a case study of a patient who underwent music supported training 20 months after suffering a stroke. Along with the clinical improvement, functional magnetic resonance imaging (fMRI) demonstrated activation of motor and premotor areas, when listening to simple piano tunes, thus providing additional evidence for the establishment of an auditory-sensorimotor co-representation due to the training procedure (Rojo et al., 2011). Likewise, in a larger group of 20 chronic stroke patients, increases in motor cortex excitability following 4 weeks of music-supported therapy were demonstrated using transcranial magnetic stimulation (TMS), which were accompanied by marked improvements of fine motor skills (Amengual et al., 2013).

In addition to functional reorganization of the auditory-sensorimotor network, recent findings have reported changes in cognition and emotion after music-supported therapy in chronic stroke patients. Fujioka et al. (2018) demonstrated in a 10-week-long randomized controlled trial (RCT), including 14 patients with music supported therapy and 14 patients receiving conventional physiotherapy, that both groups only showed minor improvements. However, the music group performed significantly better in the trail making test, indicating an improvement in cognitive flexibility, and furthermore showed enhanced social and communal participation in the Stroke Impairment Scale and in PANAS (Positive and Negative Affect Schedule, Watson et al., 1988), lending support to the prosocial and motivational effects of music. In another RCT with an intervention of only 4 weeks, Grau-Sánchez et al. (2018) demonstrated no superiority in fine motor skills in the music group as compared to a control group, but instead an increase in general quality of life as assessed by the Profile of Mood states and the stroke specific quality of live questionnaire. Despite growing evidence, the neurophysiological mechanisms of neurological music therapy remain poorly understood.

Most of the existing studies on music-supported therapy have focused on rehabilitation of fine motor functions of the hand.

Much less evidence exists on post-stroke rehabilitation of gross motor functions of the upper limbs. In a previous study we thus developed a movement sonification therapy in order to train upper arm and shoulder functions (Scholz et al., 2015). Gross movements of the arm were transformed into discrete sounds, providing a continuous feedback in a melodic way, tuned to a major scale (i.e., patients could use movements of their paretic arms as a musical instrument). In this way, sound perception substituted for defective proprioception. In a first pilot study in subacute stroke patients we were able to demonstrate that musical sonification therapy reduced joint pain in the Fugl-Meyer pain subscale (difference between groups: −10; $d = 1.96$) and improved smoothness of movements ($d = 1.16$) in comparison to movement therapy without sound (Scholz et al., 2016). Here, we extend these findings by comparing the effects of the established musical sonification setup (Scholz et al., 2016) with a newly developed, less expensive sonification device in a group of subacute stroke patients with upper limb motor impairments. The only apparent differences between both data acquisition methods were the improved sound quality and the loss of need to strap sensors to patient limbs. In order to further elucidate the neurophysiological underpinnings of musical sonification therapy we simultaneously recorded EEG and EMG data from a subset of patients to analyze cortico-muscular phase coherence during upper limb movements (Chen et al., 2018; Pan et al., 2018). According to previous studies (Pan et al., 2018) we hypothesized that cortico-muscular phase coherence increases in the ipsilesional hemisphere after musical sonification therapy.

MATERIALS AND METHODS

Patients

Patient inclusion criteria were acute or subacute unilateral stroke on one hemisphere, and decided on by the admitting physician based on the clinical picture of the patients. No other screening tools or cut-offs were used. Exclusion criteria were reports of aphasia, additional neurological, psychiatric or cognitive deficits. Moreover, patients needed to be able to perform gross motor arm movements without the assistance of their unaffected side's limb.

For Site 1, one patient was enrolled at ZAR Tübingen, Germany (center for outpatient rehabilitation), and 11 patients were enrolled at M&I Clinics Hohenurach, Bad Urach, Germany. At BDH Clinic Hessisch-Oldendorf, Germany, henceforth called Site 2, 30 patients were enrolled. Two patients at Site 2 were excluded due to data loss or loss to follow-up, respectively.

Patients were alternatingly assigned to either control or treatment group in the order of enrollment at Site 1, and pseudo-randomly assigned at Site 2 to the experimental or to the control group by the supervisor of the study who was not the experimenter. Both treatment groups received conventional physiotherapy plus a musical sonification training. The control groups also received conventional physiotherapy and an additional sham sonification movement training with exactly the same movements required as in the sonification group, but with no sound being played back. All patients were German native speakers. See **Table 1** and **Figure 1** for patient characteristics and group differences.

This study was carried out in accordance with the recommendations of the Ethics Review Board of the Hannover Medical School and the Ethics Committee of the Medical Faculty of Eberhard Karls University of Tübingen. The protocol was approved by the Ethics Review Board of the Hannover Medical School (Approval No. 1767-2013) and the Ethics Committee of the Medical Faculty of Eberhard Karls University of Tübingen (Protocol No. 597/2013BO2). All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Experimental Setup

Training took place as regular one-on-one sessions (see *training days* in **Table 1**), in which patients sat in front of a table with a wooden frame on top. The frame consisted of a 51 × 51 cm board at the bottom that was subdivided into nine equally spaced numbered fields (**Figure 2A**) to simplify instructions where in the horizontal plane a task had to be carried out. Vertical bars (length: 51 cm) were attached in three corners of the board, all subdivided by clearly visible markings into six equally spaced intervals. Each interval was labeled with a musical note-pitch name of the C major scale from c' (at the bottom) to a' (top). Tasks increased in complexity throughout each session and consisted of up-and-down movements of the hand at one position in the *x-z* plane. Up-and-down movement instructions for each task were shown separately as a sequence of musical note pitches on a sheet behind the frame. The tasks consisted of four upward and downward legato C major scales, restricted to the first six notes (i.e., c′-d′-e′-f′-g′-a′ and g′-f′-e′-d′-c′) at each of the positions 1, 2, 7, and 9 (**Figure 2A**) as well as musical intervals from c′ to d′, from c′ to e′, from c′ to f′, from c′ to g′, and from c′ to a′. This exercise was also repeated four times at positions 1, 2, 3, 7, and 9. The final goal of the training was to teach patients to play several simple nursery rhymes or other familiar tunes only by moving their affected arm in the three-dimensional sonification space. Patients always moved their impaired arms by themselves without the aid of neither their unimpaired arm nor the experimenter.

Patients at Site 1 wore Xsens inertial sensors (model X-MB-XB3; **Figure 2B**)[1] at the wrist and upper arm that transmitted acceleration, rotation, and gravity data via Bluetooth® to a computer with custom-made software that inferred the current coordinates of the hand relative to the dimensions of the wooden frame and mapped the thus determined position to a predefined sound.

At Site 2, a Leapmotion controller (**Figure 2C**)[2] was located at the edge of the front of the board. The controller consists of three infrared light emitters and two infrared cameras and tracks hand movements in three dimensions. The controller transferred the coordinates of the patient's palm centroid within the predefined space to a custom-made computer program on a computer. There the coordinates were mapped to the corresponding

[1] www.xsens.com

[2] www.leapmotion.com

TABLE 1 | Patient characteristics.

	Site 1		Site 2	
	Treatment	**Control**	**Treatment**	**Control**
N	7	5	14	14
Male	6	3	10	11
Age, M ± SD; range, years	65.30 ± 12.70; 50–84	66.40 ± 6.90; 59–76	68.71 ± 11.76; 48–92	70.21 ± 14.29; 42–88
Right arm affected	3	1	5	6
Right-handed	7	5	14	14
Days after stroke median (range)	27 (16–40)	21 (18–27)	36.5 (12–144)	26 (5–510)
Training days, median (range)	15 (11–15)	15 (13–15)	22 (7–40)	16.5 (9–46)
Barthel index, M ± SD	45.70 ± 23.20	42.00 ± 20.20	39.64 ± 17.27	36.43 ± 17.87
Fugl-Meyer Assessment: median (range)				
FM.A-D,	39 (13–50)	44 (25–48)	52.5 (20–65)	55.5 (14–65)
FM.H,	12 (10–12)	12 (8–12)	12 (2–12)	12 (8–12)
FM.I,	24 (23–24)	24 (24–24)	24 (12–24)	24 (18–24)
FM.J,	23 (22–24)	24 (22–24)	24 (12–24)	24 (18–24)
Lesion type:				
Ischemic/hemorrhagic	7/0	5/0	12/2	9/5
Lesion site:				
Left cortical	1			
– Frontal				
– Fronto-temporal with participation gyrus pre- and post-centralis				1
– Occipital				1
– Parietal			1	1
– Temporal				2
– A. Cerebri media flow area		1	2	1
Left subcortical				
– Capsula interna			1	
– Basal ganglia			1	
Left pons	2			
Right cortical	1			
– Frontal			2	2
– Fronto-parietal				4
– Occipital			1	1
– Parietal			1	
– Parietooccipital			3	
– Temporal				
– A. Cerebri media flow area	1			1
Right subcortical				
– Capsula interna	1			
– Basal ganglia		1	1	
Right pons	1	3	1	

Total number N of patients per group are given per site; age at the begin of the study, the number of patients affected by stroke in the right arm, and the number of right-handed patients are provided; the number of training sessions patients were subjected to and the patients' mean Barthel index prior to study commencement are also supplied. Scoring on Fugl-Meyer subscales as well as lesion types and lesion sites are specified.

sound parameters which were subsequently played back to the patient in real-time.

Note pitches ranged from c′ = 226.6 Hz at the bottom to a′ = 440 Hz at the top. On the *x* axis, sound varied in brightness via a variation in sound synthesis (Site 1; Synthesis ToolKit, Cook and Scavone, 1999) or of the sound samples used (Site 2) with three different timbres (from dull = clarinet sound on the left side of the patient, to saxophone in the middle, and a bowed instrument = bright at the right). Loudness of sounds was mapped along the *z* axis, so that a proximal hand position resulted in a louder sound than a more distal one. Regular training sessions lasted approximately 30 min.

Evaluation of Motor Functions and Stroke Impact

Evaluation of the patient rehabilitation process was conducted by administering several clinical motor function tests and a psychological questionnaire pre and post training.

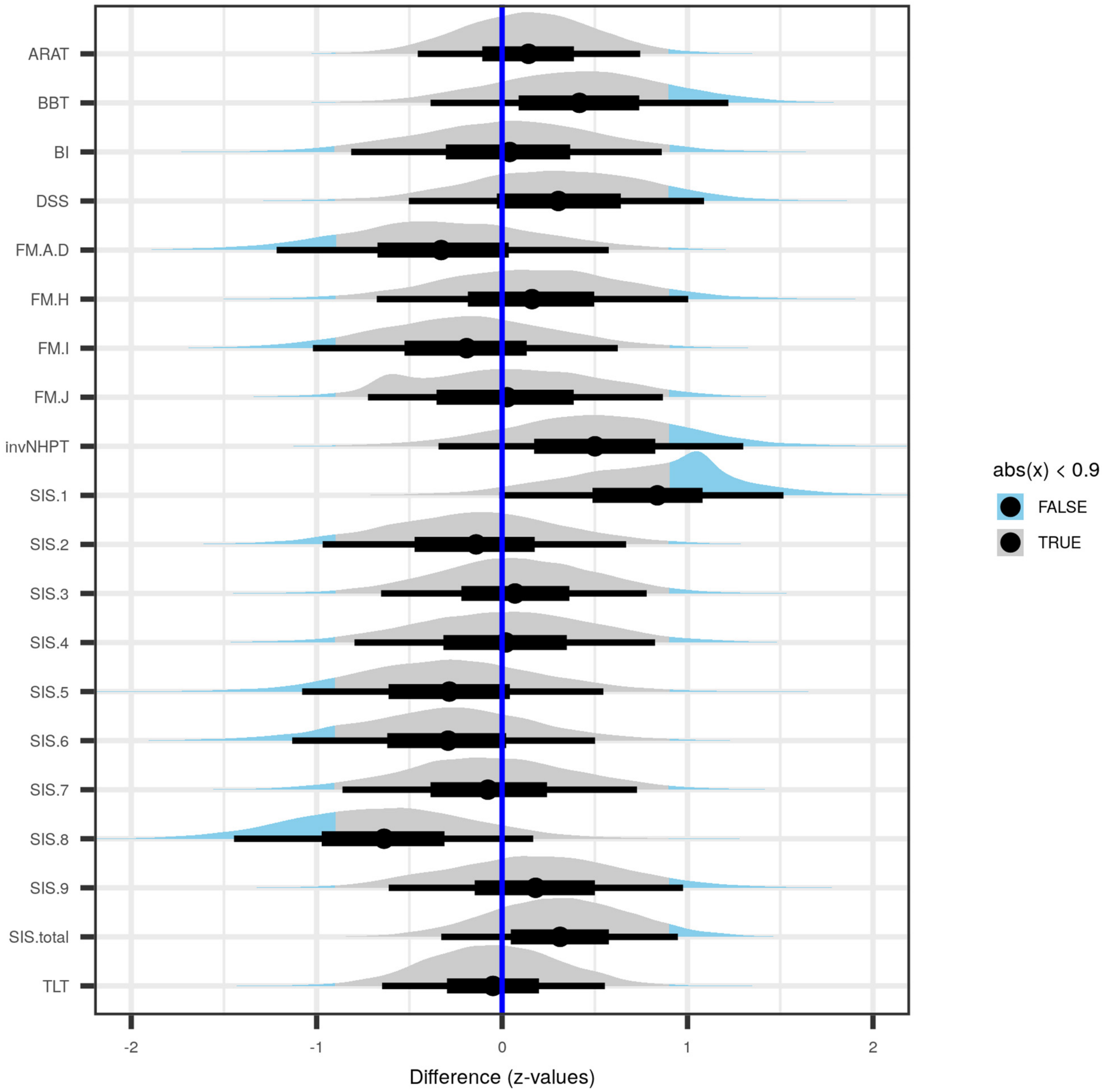

FIGURE 1 | Posterior distributions of differences between treatment and control groups of the tested variables, each along with median point estimate (dot), 50 percent uncertainty interval (thick black horizontal bar), and 90 percent uncertainty interval (thin black horizontal bar). The part of a given distribution further than 0.9 standard deviations away from zero is shown in light blue instead of in gray. Point estimates >0 represent higher initial scores in the treatment group, while values <0 imply larger initial scores in the control group. ARAT, Action Research Arm Test; BBT, Box and Block Test; BI, Barthel Index prior to begin of rehabilitation; DSS, number of days elapsed between ocurrence of stroke and commencement of rehabilitation; FM.A-D, Fugl-Meyer test subscales A–D, covering reflexes, volitional movements, wrist and hand function and the coordination of the upper extremity; FM.H, tactile sensation in the affected and non-affected extremity; FM.I, passive joint motion; FM.J, passive movement joint pain; invNHPT, (inverted) Nine-Hole Peg Test; SIS.1, physical problems as a result of the stroke; SIS.2, memory and thinking abilities; SIS.3, mood and emotions; SIS.4, communicational skills in speaking, reading and writing; SIS.5, impairment of daily activities; SIS.6, mobility; SIS.7, remaining function of the affected hand; SIS.8, impairment of social activities; SIS.9, self-rating of how far stroke recovery has progressed; TLT, Thumb Localizing Test; SIS.total, total sum score over Stroke Impact Scale subscales. See "Materials and Methods" section for details.

The clinical motor function tests consisted of six major sections:

(a) The upper extremity part of the FMA, still considered the gold standard for the evaluation of motor recovery after stroke (Crow and Harmeling-van der Wel, 2008; Woodbury et al., 2008). The FMA includes four main subsections

- FM.A-D: reflexes, volitional movements, wrist and hand function and the coordination of the upper extremity

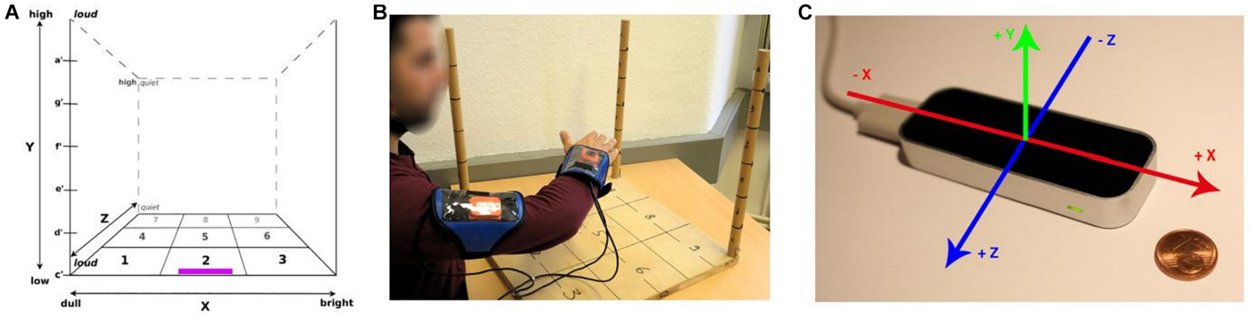

FIGURE 2 | Experimental setup. **(A)** three-dimensional space (the Leapmotion controller at Site 2 was placed on the board at the position marked in purple), with axis labels describing qualitative sound changes when the hand was moved relative to the frame (and hence, the body). **(B)** Xsens sensors as used at Site 1, attached to wrist and upper arm of patient. **(C)** Leapmotion controller as used at Site 2, with the space axes superimposed. Panel **(A)** taken from Scholz et al. (2016).

- FM.H: tactile sensation in the affected and non-affected extremity
- In FM.I: passive joint motion
- FM.J: passive movement joint pain

(b) The Box and Block Test (BBT) assesses unilateral gross manual dexterity (Mathiowetz et al., 1985; Canny et al., 2009; Chen et al., 2009)
(c) The Nine-Hole Peg Test measures finger dexterity (Grice et al., 2003). For modeling purposes and to simplify presentation of data, the obtained scores were inverted (invNHPT)
(d) The Stroke Impact Scale (SIS; Duncan et al., 2003; Lin et al., 2010) evaluates health status following a stroke, including sub-scales for emotional well-being, memory, thinking and social participation. The consecutively numbered subscales are

  (1) physical problems as a result of the stroke
  (2) memory and thinking abilities
  (3) mood and emotions
  (4) communicational skills in speaking, reading and writing
  (5) impairment of daily activities
  (6) mobility
  (7) remaining function of the affected hand
  (8) impairment of social activities
  (9) self-rating of how far stroke recovery has progressed

(e) Thumb Localizing Test (TLT; Hirayama et al., 1999)
(f) The Action Research Arm Test (ARAT; Lyle, 1981)

Additionally, the Barthel Index (BI; Mahoney and Barthel, 1965) prior to intervention, and the number of days between the occurence of the stroke and beginning of the intervention (Days Since Stroke–DSS) were collected. Administration of the motor assessment test battery and the questionnaire pre and post intervention took approximately 1 h to complete.

EMG and EEG Recordings

At Site 1, electrophysiological data were acquired from two subjects who underwent music therapy (both left hemispheric stroke, trained on right arm) and two subjects who underwent control therapy (one left hemispheric stroke, trained on right arm; one right hemispheric stroke, trained on left arm), before and after therapy. Subjects were instructed to conduct one hundred self-paced elevations of their paretic and non-paretic arm, respectively, in separate blocks of trials, and at a frequency of around one elevation per 5 s. Specifically, subjects were asked to elevate their arm from c' to d' in the *y*-axis at position 1 (right arm) and position 3 (left arm), respectively, in the three-dimensional training space (cf. **Figures 1A,B**), along with training of upward C major scale movements during therapy. EMG (from deltoid muscles) and 20-channel EEG were recorded using a Neurofax EEG-9200 system (Nihon Kohden, Japan). The position of the EEG electrodes followed the International 10–20 system (Seeck et al., 2017), and EEG data were referenced to A1 and A2 (linked earlobes). Biosignals were recorded at a sampling frequency of 200 Hz. Electrode impedances were regularly checked and kept below 10 kΩ throughout the experiment.

Movement Smoothness

Movement trajectories from the patients' first task (four C major scales at position 1) on each training day were manually identified and separated into upward and downward strokes for offline calculation of movement smoothness. Following Osu et al. (2011), in each of these strokes the three-dimensional curvature κ^2 for each time point was determined:

$$\kappa^2 = \frac{\left(\dot{x}^2 + \dot{y}^2 + \dot{z}^2\right)\left(\ddot{x}^2 + \ddot{y}^2 + \ddot{z}^2\right) - \left(\dot{x}\ddot{x} + \dot{y}\ddot{y} + \dot{z}\ddot{z}\right)^2}{\left(\dot{x}^2 + \dot{y}^2 + \dot{z}^2\right)}$$

The median of the negative natural log from the κ^2 vector of each stroke was taken as a measure of its movement smoothness.

Data Analysis

EEG and EMG data which were analyzed using MATLAB (version R2017b, The MathWorks) with EEGLAB (version 13.5.4b; Delorme and Makeig, 2004) and Fieldtrip (Oostenveld et al., 2011) toolboxes. The programming language R (version 3.5.1; R Core Team, 2018) in conjunction with RStudio Server (version 1.2.1080; RStudio Team, 2018) was used for all other data preprocessing and analyses.

To account for small samples, unbalanced group sizes, and a decreasing number of data points over time (see "Results" section on data loss) we opted for Bayesian multilevel regression modeling to analyze the motor test outcomes and movement smoothness data. Modeling was carried out with the R package brms (Bürkner, 2018). In Bayesian regression, small samples can be bridled by using informative priors, while the growing uncertainty about the distribution of estimated parameters due to the diminishing number of data points over time, e.g., caused by data loss or dropout, is reflected by increasingly wider credible intervals, acknowledging the growing uncertainty. Multilevel modeling (MLM) also helps keeping the lid on small clusters by partial pooling, which basically leads to shrinkage of lower level estimates toward higher level estimates. If, for instance the highest level of a MLM is the grouping into treatment and controls, then group averages can be estimated based on the grand-average. A far-off group estimate is then shrunk toward the grand-average, and the more so, the fewer data points this extreme estimate contains (Gelman et al., 2012).

Motor Test Batteries and the Stroke Impact Scale

Simple Bayesian regressions were carried out for all motor test battery subscales prior to intervention, with *Treatment* (0|1) as predictor, to determine any differences between the two groups prior to intervention. Pre-intervention scores of outcome variables were z-transformed to increase computational stability, and priors were chosen to be informative with heavy tails to allow for extreme values (central Student's t distribution: $df = 3$; $scale = 1$; left-bounded at zero for variance parameters).

Posterior distributions of pre-intervention differences between treatment and control groups in the motor test batteries, the SIS scores, and the number of days between stroke and begin of the intervention are shown in **Figure 1**. Almost all of the difference-distributions substantially overlap with zero, with the notable exceptions *SIS.1*, which was larger in the treatment group, while *SIS.8* was larger in the control group.

Movement Smoothness

Increasingly complex multilevel models were built using the joint data sets from both sites in order to examine and better understand the underlying data-generating processes. All models included z-transformed movement smoothness (zero mean and unit *SD*) as outcome. The most simple model used patient group as population-level predictor, while further models included an increasing number of explanatory variables, eventually modeling correlated varying coefficients (see **Table 2**). All priors were chosen to be informative; slopes were modeled to be student t-distributed with $df = 3$, located at zero, and with scale set to 3, and left-bounded at zero for variance components; priors placed on varying parameter correlation matrices were LKJcorr, with $\eta = 2$. Prediction accuracy between models was compared using Pareto-smoothed importance sampling leave-one-out cross-validation (Vehtari et al., 2017), an approximation to leave-one-out cross-validation.

EMG and EEG

EMG event markers for movement onset were set manually by visual inspection and using an individually adjusted threshold of 30–110 μV according to individual noise levels. Post therapy EMG data from one subject who underwent control therapy was too noisy to allow for reliable identification of movement onsets; this subject was excluded from further analysis. Data of the remaining three subjects (two left hemispheric stroke patients with music therapy, one right hemispheric stroke patient with control therapy) were analyzed using MATLAB (R2017b, MathWorks) and the Fieldtrip open-source toolbox (Oostenveld et al., 2011), with customized scripts. Trials were visually inspected and noisy trials were removed from further analysis. For the patients with music therapy, 96 epochs before (pre) and 98 epochs after (post) therapy, and 98 epochs for both pre and post therapy measurements, respectively, were considered; for the patient with control therapy, 85 trials for both pre and post therapy measurements were considered. Data were first detrended and band-pass filtered between 2 and 80 Hz. Subsequently, data were filtered with a 1–80 Hz 3rd order Butterworth zero phase band pass filter and a 49–51 Hz notch filter. As a measure of cortico-muscular phase coherence the Weighted Phase Lag Index (WPLI) was computed between EEG and EMG channels, following previous reports (Stam et al., 2007; Vinck et al., 2011). As phase coherences were found significant (Rosenberg et al., 1989) in channels of the sensorimotor area (i.e., electrodes C3 and C4, respectively) pre and post therapy with a 95% confidence probability only in the low beta (14–20 Hz) frequency band, further analyses were restricted to the low beta band.

A cluster-based permutation analysis (Maris et al., 2007) was performed to test for significant differences between beta band cortico-muscular phase coherence pre vs. post therapy. Cluster statistics were evaluated at the single subject level, considering each trial as a unity of observation. The minimum number of neighboring channels to form a cluster was 2. A positive cluster was defined as WPLI Post > WPLI Pre, a negative cluster as WPLI Post < WPLI Pre. The significance level was set at $p < 0.05$.

RESULTS

Motor Test Batteries and the Stroke Impact Scale

Post-treatment differences in motor test batteries and the SIS are depicted in **Figure 3**, while **Supplementary Table S1** lists posterior point estimates along with credible intervals, separately for both sites. All difference point estimates lay close to zero, and most had very wide credible intervals, the latter pointing to large heterogeneity of the data which impeded more precise estimation given the sample.

Movement Smoothness

Smoothness assessing models did not converge for data from Site 1 alone, most likely due to a combination of pronounced heterogeneity and small sample size. A considerable amount of smoothness data at site 2 was lost due to a combination of

TABLE 2 | Parameter estimates of models used to explain movement smoothness over time in treatment and control groups, using two different motion capturing systems.

Number	Model	Term	estimate	std.error	conf.low	conf.high
1	MedianLC ∼ Group.c + (1 | IDanon)	Intercept	−0.17	0.13	−0.39	0.05
		Group.c	0.49	0.26	0.04	0.91
2	MedianLC ∼ Group.c × Session.c + (1 | IDanon)	Intercept	−0.17	0.13	−0.39	0.05
		Group.c	0.49	0.26	0.05	0.90
		Group.c:Session.c	0.00	0.03	−0.04	0.05
		Session.c	0.01	0.01	−0.02	0.03
3	MedianLC ∼ Group.c × Session.c + (Session.c | IDanon)	Intercept	−0.15	0.14	−0.38	0.07
		Group.c	0.50	0.26	0.07	0.92
		Group.c:Session.c	0.01	0.03	−0.04	0.06
		Session.c	0.01	0.02	−0.02	0.04
4	MedianLC ∼ Group.c × Session.c + pre.z + (Session.c + pre.z | IDanon)	Intercept	−0.10	0.10	−0.27	0.05
		Group.c	0.23	0.19	−0.09	0.55
		Group.c:Session.c	0.00	0.03	−0.05	0.04
		Session.c	0.01	0.01	−0.01	0.04
		pre.z	0.56	0.12	0.36	0.77
5	MedianLC ∼ Group.c × Session.c + pre.z + MoCap.c + (Session.c + pre.z | IDanon)	Intercept	−0.10	0.09	−0.25	0.06
		Group.c	0.21	0.19	−0.09	0.52
		Group.c:Session.c	0.00	0.03	−0.05	0.04
		Session.c	0.00	0.02	−0.02	0.03
		pre.z	0.54	0.12	0.34	0.74
		MoCap.c	−0.34	0.20	−0.66	−0.03

Models grow in complexity from top to bottom of the table. The outcome variable in every model is the median negative natural logarithm of movement curvature (term MedianLC in the Model column). To account for repeated measurements, each model incorporates an individual varying intercept for each patient (term | IDanon). The term Group.c represents the estimated average of the two groups. Model 2 also incorporated training sessions the patients partook (Session.c); model 3 added an interaction between Group.c and Session.c. Model 4 allowed the session slope of each individual to correlate with their intercept: (Session.c | IDanon). Models 5 and 6 also accounted for standardized pre-treatment movement smoothness (pre.z) and the type of motion capturing system (MoCap.c), respectively. The column std.error lists the standard error, while columns conf.low and conf.high contain the 90 percent credible interval bounds of the point estimate.

human and technical error. While patients adhered to the regular training schedule with a median of 22 (treatment group) and 16.5 (control group) training sessions (see also *training days* in **Table 1**), the data available for analysis only had a median (range) of 2.5 (1,7) sessions. We therefor decided to pool the movement data from both sites.

In the combined smoothness data set, the most simple model estimated a substantial average smoothness increase for both groups [approx. 0.5 (CI: 0, 0.9) standard deviations], but with a wide credible interval (model #1 in **Figure 4** and **Table 2**). The subsequent addition of *Session*, and the interaction *Group:Session* (model #2) as regression input, as well as modeling the correlation between an individual's intercepts and their session slopes (model #3) did not considerably change the estimate of the average group effect. Both the effect of *Session*, and the interaction *Group:Session* were estimated to be close to zero, with 90%-credible intervals substantially overlapping with zero, indicative of non-relevant smoothness changes across sessions. However, the addition of pre-treatment smoothness as a covariate (model #4) led to a decent decrease in the estimated average group effect. Adding the type of motion capture device employed at a given site (*MoCap*, #5) did not further change the group estimate, nor did it lead to an increase in predictive accuracy (**Supplementary Table S2**). Regardless, the effect of *MoCap* was not negligible. This last result led us to *post hoc* model the interaction *Group:MoCap* (#6), which was estimated to be very close to zero. The unexpected effect of *MoCap* led to further exploration of the interaction *Pre smoothness:MoCap* which was estimated to be close to zero (#7).

While in non-Bayesian regression adjusted R^2 serves as a measure against overfitting, prior probabilities in Bayesian models and shrinkage in MLM jointly serve the same purpose, together with estimated leave one out cross-validation of the posterior log-likelihood (PSIS-LOO-CV; Vehtari et al., 2017). The latter is also used to find the best fitting model by identifying the expected log predictive density (elpd) differences between models. See **Supplementary Table S2**. **Figure 5** shows conditional plots of the population-level effects for model #5, placing the parameter estimates from **Figure 4** into context of the data.

The best-fitting model (#5) estimated an average movement smoothness increase for *Group* of 0.21 [−0.09, 0.52]; see **Table 2**.

Cortico-Muscular Phase Coherence

Exploratory analyses of beta-band EEG-EMG phase coherence as measured with WPLI during movement of the paretic arm showed a positive EEG cluster in the left (lesioned) hemisphere (channels: Fp1, Fp2, F3, C3, P3, F7, T3, T5) for patient 1 with music therapy, and a positive cluster in the left (lesioned) hemisphere (channels: F7, T3, T5, P3, O1, Pz) and a negative right

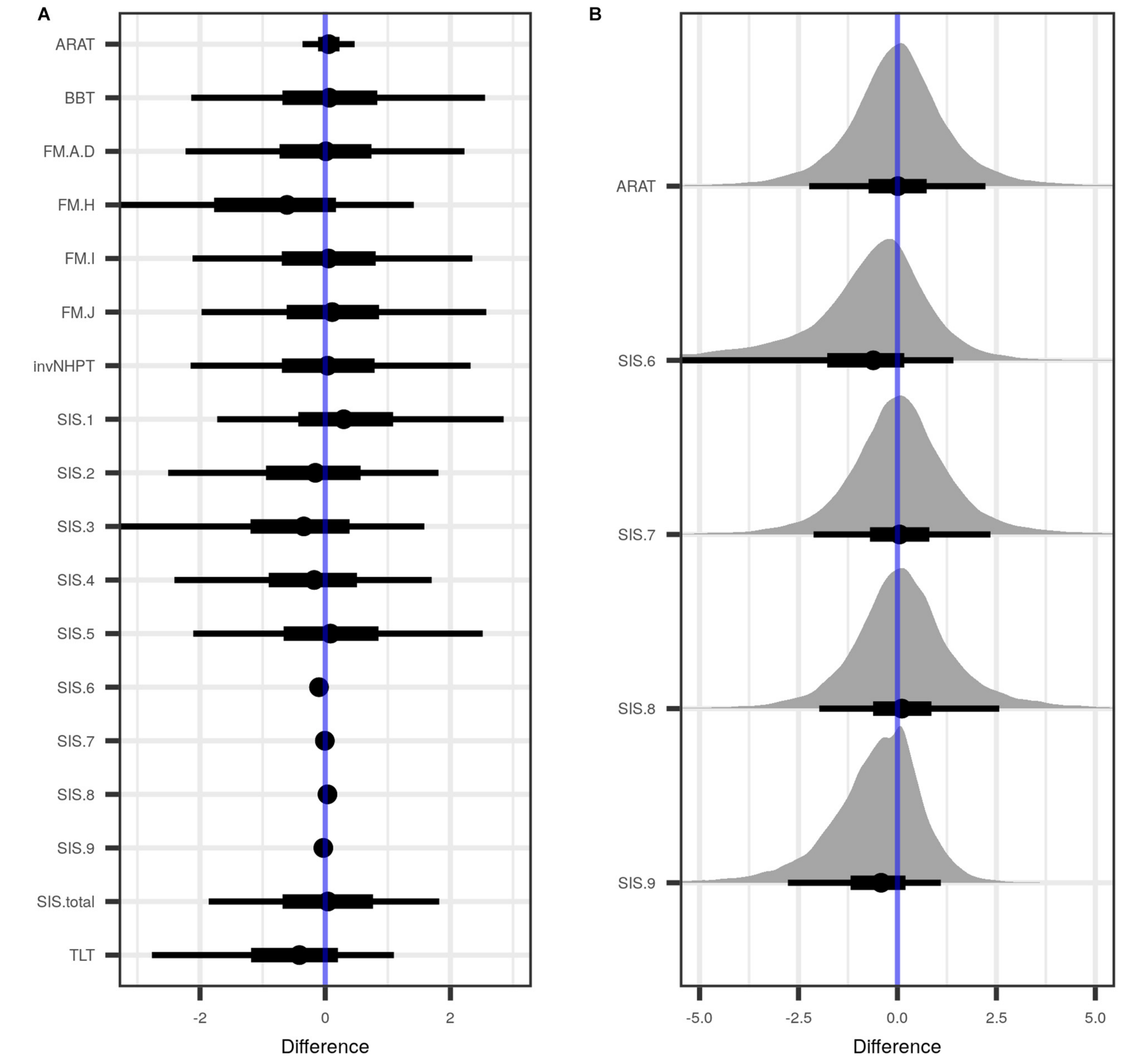

FIGURE 3 | Estimated differences between treatment and control group, when data from both sites were combined and pre-treatment values were taken into account. **(A)** Shown are the posterior distributions of differences between treatment and control groups of the tested variables, with median point estimate (dot), 50 percent uncertainty interval (thick black horizontal bar), and 90 percent uncertainty interval (thin black horizontal bar). **(B)** A close-up of those variables in A with a point estimate close to zero. ARAT, Action Research Arm Test; BBT, Box and Block Test; FM.A-D, Fugl-Meyer test subscales A–D, covering reflexes, volitional movements, wrist and hand function and the coordination of the upper extremity; FM.H, tactile sensation in the affected and non-affected extremity; FM.I, passive joint motion; FM.J, passive movement joint pain; invNHPT, (inverted) Nine-Hole Peg Test; SIS.1 (Stroke Impact Scale, subscale 1), physical problems as a result of the stroke; SIS.2, memory and thinking abilities; SIS.3, mood and emotions; SIS.4, communicational skills in speaking, reading and writing; SIS.5, impairment of daily activities; SIS.6, mobility; SIS.7, remaining function of the affected hand; SIS.8, impairment of social activities; SIS.9, self-rating of how far stroke recovery has progressed; TLT, Thumb Localizing Test; SIS.total, total sum score over SIS. See "Materials and Methods" section for details.

posterior cluster (channels: O2, T6, T4) for patient 2 with music therapy (**Figure 6**). These findings indicate increased cortico-muscular phase coherence post vs. pre musical sonification therapy in the ipsilesional hemisphere during movement of the paretic arm. In contrast, for the patient with control therapy, who had suffered a right hemispheric stroke, a positive frontal cluster (channels: Fp1, Fp2, F3, Fz, F4, F8) and a negative posterior cluster (channels: Pz, P4, T6, O1, O2) with bilateral topography were found in post vs. pre therapy comparisons. Of note, for movements with the non-paretic arm no significant cluster was found in either patient (data not shown), indicating similar cortico-muscular phase coherences (i.e., WPLI values) at the two

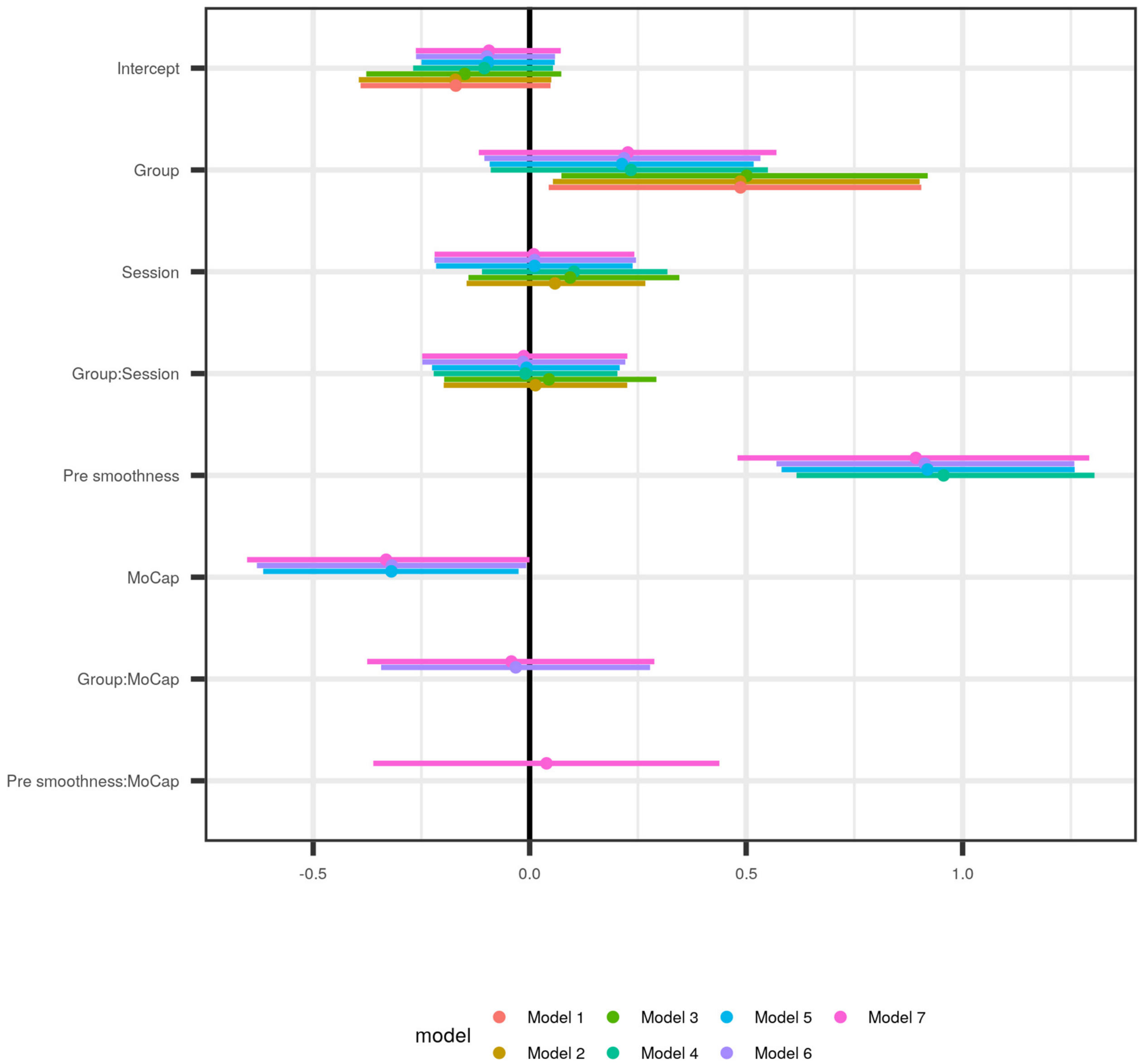

FIGURE 4 | Comparison of population parameters as estimated by models of increasing complexity, starting with the most simple one (#1), which modeled the outcome as the result of Group, and hence only has two parameters (Intercept and Group; see **Table 2** for a numerical representation of the data). Model 2 additionally employed the time factor (Session) as explanatory variable, and its interaction with Group, and thus has two further parameter estimates, and so forth. The first three models do not change considerably, only the addition of pre-intervention movement smoothness pre smoothness as covariate in model 4 moves the Group estimate closer to zero. In model 5, with the motion capturing system added as covariate (MoCap), the Group estimate does not change much although the MoCap effect is noticeable.

measurement time points during movement of the non-trained arm in all patients.

DISCUSSION

Summarizing the effects of rehabilitation of the upper limb after stroke, it is unclear whether musical sonification training is efficient. Bayesian regression of several motor test batteries and the Stroke Impairment Scale did not provide evidence supporting an additional effect of the treatment. However, MLM revealed that movement smoothness of the treatment group was greater, albeit with the credible interval overlapping zero (**Figures 4**, **5**). This suggests a small effect, if any, of musical sonification training on movement smoothness. Adding pre-treatment smoothness as covariate to the model (model 4) decreased the *Group* effect estimate substantially. This suggests that the heterogeneity of the pre-treatment movement smoothness in the sample considerably influenced the accuracy with which the improvement could be estimated. When the type

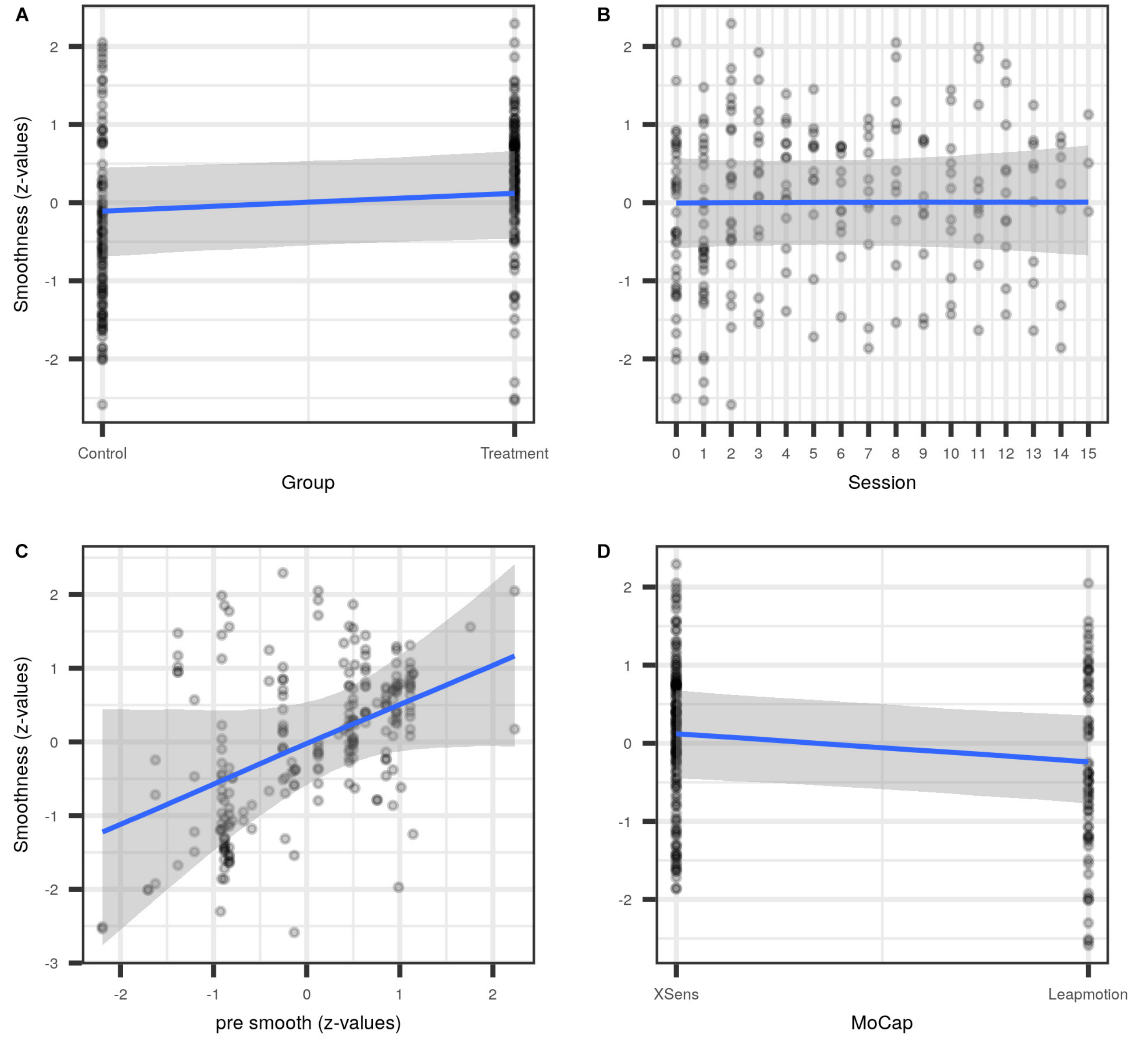

FIGURE 5 | Conditional plots for model #5. Population effects for the covariates Group **(A)**, medianized session **(B)**, standardized pre-intervention smoothness pre smooth **(C)**, and the motion capturing system MoCap **(D)**.

of motion capturing system was added to the model as predictor (model 5), it captured a substantial amount of variation. This last point may be explained in several, not mutually exclusive ways. It is possible that the samples at both sites either differed in more respects than had been anticipated, and this difference was not apparent in the pre-treatment screening (**Figure 2**). Or, differential handling of patients at the two sites may have led to differing success of the supplementary rehabilitation. A third possible explanation, and one corroborated by our data, would be the differing temporo-spatial resolution of the two motion capturing systems (**Figure 5D**), resulting in the Leapmotion sensor finding movements of comparable groups "rougher" then would the Xsens system.

Exploratory analyses of EEG-EMG coherence during movement of the paretic arm in a subset of our patients suggested increased beta-band cortico-muscular phase coherence specifically in the lesioned hemisphere after musical sonification therapy, but not after motor training without sonification (cf. **Figure 6**). Of note, cortico-muscular phase coherence during movement of the non-paretic arm did not change after either training. These findings are in line with previous results showing an increase in beta-band cortico-muscular phase coherence in the lesioned hemisphere after 4 weeks of electrical stimulation of the median nerve combined with hand function training, but not after hand function training alone (Pan et al., 2018). Whether increases in beta-band cortico-muscular phase coherence indeed

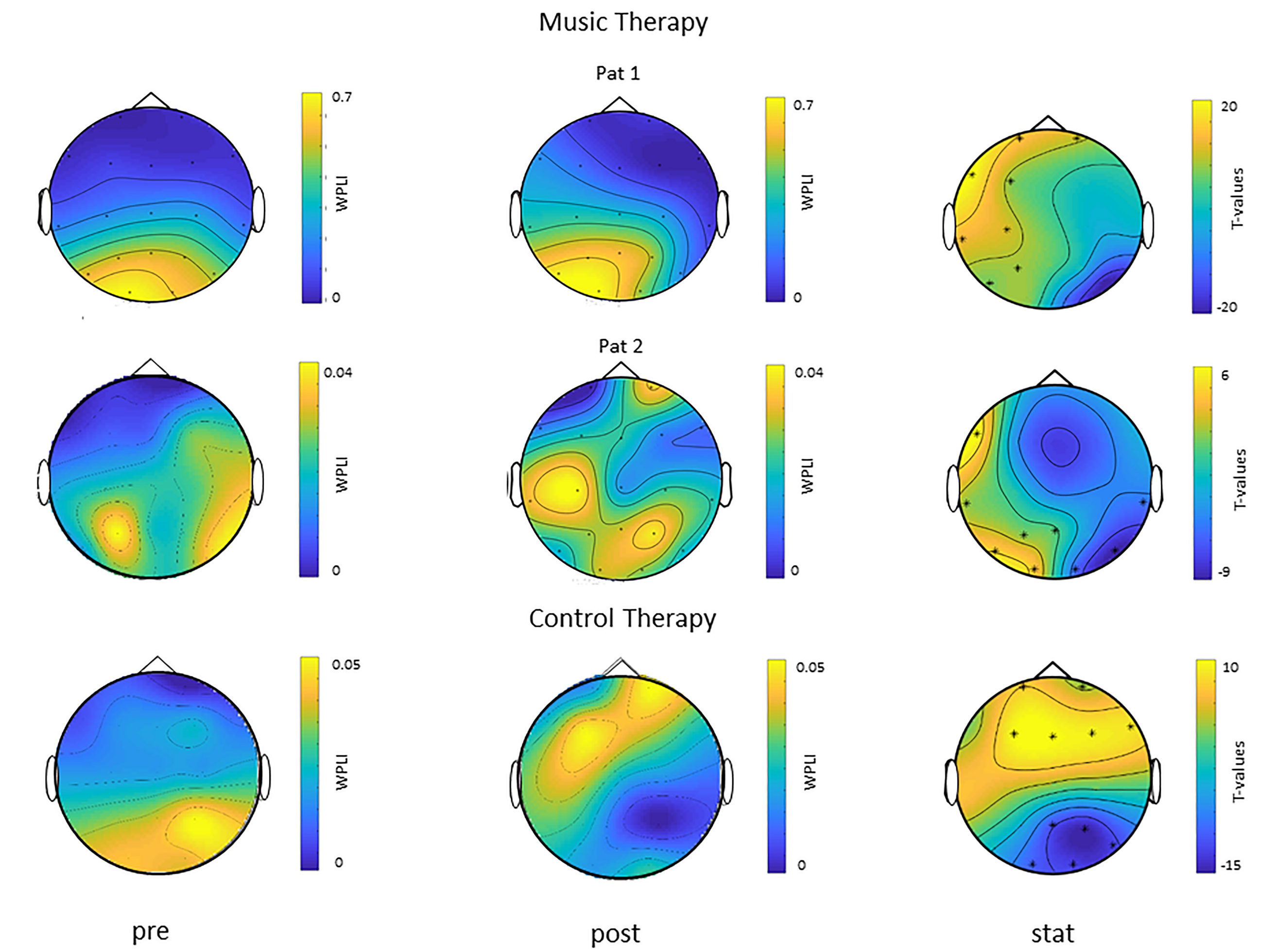

FIGURE 6 | Modulation of cortico-muscular phase coherence during movement of the paretic arm (single subject data). Topoplots of WPLI as a measure of cortico-muscular phase coherence before (pre) and after (post) therapy in two patients with music therapy (Pat 1 and Pat 2, both left hemispheric stroke, right arm trained, upper two rows) and one patient with control therapy (right hemispheric stroke, left arm trained, lower row) are shown in the left and middle column, respectively. T-statistic maps (stat) of cluster-based analyses of differences in WPLI post vs. pre therapy are shown in the right column. Channels belonging to significant clusters are marked with asterisks. Note left hemispheric (i.e., ipsilesional) cortico-muscular phase coherence increases during movements of the paretic right arm in the two patients with music therapy, while the patient with control therapy showed a rather bilateral topography of cortico-muscular phase coherence modulations during movements of the paretic left arm.

underlie clinical improvements of motor function of the upper limb after musical sonification therapy, and how these changes link to functional reorganization of the auditory-sensorimotor (Altenmüller et al., 2009; Schneider et al., 2010; Fujioka et al., 2012) or other (e.g., fronto-parietal) cerebral networks needs to be investigated in future studies.

Several other mechanisms have been implicated in the effects of music-supported therapy of motor function post-stroke. From the patients' informal descriptions of their experience with music-supported training, it appears that this was highly enjoyable and a highlight of their rehabilitation process, regardless of the form of auditory stimulation. Thus, as already explored in earlier articles, motivational and emotional factors might have contributed to the improvement of the training program (as reported in Särkämö et al., 2008). In addition, the role of the auditory feedback in music-supported therapy needs further investigation. Up to now it has not been clarified whether auditory feedback *per se* (e.g., simple beep tones) can have a similar effect on fine motor post-stroke rehabilitation, or whether explicit musical parameters such as a sophisticated pitch and time structure are prerequisites for the success of the training. This has to be addressed in a study comparing the effects of musical feedback compared to simple acoustic feedback. With respect to the latter, according to a study by Thaut et al. (2002), simple rhythmic cueing with a metronome significantly improves the spatio-temporal precision of reaching movements in stroke patients.

Finally, it is not clear whether timing regularity and predictability is crucial for the beneficial effect of music supported therapy. Although it has been argued that the effectiveness of this therapy relies on the fact that the patient's brain receives a time-locked auditory feedback with each movement, new results challenge this viewpoint. In a recent study, 15 patients in early stroke rehabilitation with no previous musical background were studied (van Vugt et al., 2016). They learned to play simple finger exercises and familiar children's songs on the piano. Participants were assigned to one of two groups: in the normal group, the keyboard emitted a tone immediately at keystroke, in the delay group, the tone was randomly delayed. To assess recovery, standard clinical tests such as the nine-hole-pegboard test and index finger tapping speed and regularity were used. Surprisingly, patients in the delay group improved in the nine-hole-pegboard test, whereas patients in the normal group did not. The normal group showed reduced depression whereas the delay group did not. Thus, music supported therapy even with a randomly delayed keyboard can improve motor recovery after stroke, possibly because patients in the delayed feedback group implicitly learn to be independent of the auditory feedback and therefore outperform those in the normal condition when auditory feedback is not available.

In summary, musical sonification therapy for rehabilitation of motor impairments of the upper limbs is a viable treatment option, yet with limited clinical effects in subacute stroke patients. Given the patients' enthusiasm during training and the low hardware price for one of the sonification devices it may be considered as an add-on, home-based neurorehabilitation therapy. Future research should address the long-term sustainability of improvements and strive to optimize length and number of training sessions, according to patients needs and preference. Most probably, a client-tailored treatment algorithm considering severity of impairment, psychological status and motivational drive would be most efficient.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The study was approved by the Ethics Review Board of the Hannover Medical School (Approval No. 1767-2013) and the Ethics Committee of the Medical Faculty of Eberhard Karls University of Tübingen (Protocol No. 597/2013BO2).

AUTHOR CONTRIBUTIONS

NN and DS share the first authorship for this publication. MG and SS did the data collection and -analysis for Site 2 (Hessisch Oldendorf). JS, PB, and FM-D did the data collection and -analysis for Site 1 (Tübingen). JDR coordinated and contributed to the new audiodesign at Site 2. UZ is senior author and PI for Site 1. JR and EA are senior authors and PIs for Site 2.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.01378/full#supplementary-material

REFERENCES

Altenmüller, E., Marco-Pallares, J., Münte, T. F., and Schneider, S. (2009). Neural reorganization underlies improvement in stroke-induced motor dysfunction by music-supported therapy. *Ann. N. Y. Acad. Sci.* 1169, 395–405. doi: 10.1111/j.1749-6632.2009.04580.x

Altenmüller, E., and Stewart, L. (2018). "Music supported therapy in neurorehabilitation," in *Oxford Textbook of Neurorehabilitation*, eds V. Dietz, and N. Ward (Oxford: Oxford University Press), (in press).

Amengual, J. L., Rojo, N., Veciana de Las Heras, M., Marco-Pallarés, J., Grau-Sánchez, J., Schneider, S., et al. (2013). Sensorimotor plasticity after music-supported therapy in chronic stroke patients revealed by transcranial magnetic stimulation. *PLoS One* 8:e61883. doi: 10.1371/journal.pone.0061883

Bürkner, P. C. (2018). Advanced Bayesian multilevel modeling with the R package brms. *R J.* 10, 395–411.

Canny, M. L., Thompson, J. M., and Wheeler, M. J. (2009). Reliability of the box and block test of manual dexterity for use with patients with fibromyalgia. *Am. J. Occup. Ther.* 63, 506–510. doi: 10.5014/ajot.63.4.506

Chen, H.-M., Chen, C. C., Hsueh, I.-P., Huang, S.-L., and Hsieh, C.-L. (2009). Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke. *Neurorehabil. Neural Repair* 23, 435–440. doi: 10.1177/1545968308331146

Chen, X., Xie, P., Zhang, Y., Chen, Y., Cheng, S., and Zhang, L. (2018). Abnormal functional corticomuscular coupling after stroke. *Neuroimage Clin.* 19, 147–159. doi: 10.1016/j.nicl.2018.04.004

Cook, P. R., and Scavone, G. (1999). "The synthesis toolkit in C++ (STK)," in *Proceedings of the International Computer Music Conference*, Berlin.

Crow, J. L., and Harmeling-van der Wel, B. C. (2008). Hierarchical properties of the motor function sections of the fugl-meyer assessment scale for people after stroke: a retrospective study. *Phys. Ther.* 88, 1554–1567. doi: 10.2522/ptj.20070186

Delorme, A., and Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21. doi: 10.1016/j.jneumeth.2003.10.009

Duncan, P. W., Bode, R. K., Lai, S. M., and Perera, S. (2003). Rasch analysis of a new stroke-specific outcome scale: the stroke impact scale. *Arch. Phys. Med. Rehabil.* 84, 950–963. doi: 10.1016/s0003-9993(03)00035-2

Fujioka, T., Dawson, D. R., Wright, R., Honjo, K., Chen, J. L., Chen, J. J., et al. (2018). The effects of music-supported therapy on motor, cognitive, and psychosocial functions in chronic stroke. *Ann. N. Y. Acad. Sci.* doi: 10.1111/nyas.13706 [Epub ahead of print].

Fujioka, T., Ween, J. E., Jamali, S., Stuss, D. T., and Ross, B. (2012). Changes in neuromagnetic beta-band oscillation after music-supported stroke rehabilitation. *Ann. N. Y. Acad. Sci.* 1252, 294–304. doi: 10.1111/j.1749-6632.2011.06436.x

Gelman, A., Hill, J., and Yajima, M. (2012). Why we (usually) don't have to worry about multiple comparisons. *J. Res. Educ. Eff.* 5, 189–211. doi: 10.1080/19345747.2011.618213

Grau-Sánchez, J., Duarte, E., Ramos-Escobar, N., Sierpowska, J., Rueda, N., Redón, S., et al. (2018). Music-supported therapy in the rehabilitation of subacute stroke patients: a randomized controlled trial. *Ann. N. Y. Acad. Sci.* doi: 10.1016/j.rehab.2018.05.438 [Epub ahead of print].

Grice, K. O., Vogel, K. A., Le, V., Mitchell, A., Muniz, S., and Vollmer, M. N. (2003). Adult norms for a commercially available nine hole peg test for finger dexterity. *Am. J. Occup. Ther.* 57, 570–573. doi: 10.5014/ajot.57.5.570

Hirayama, K., Fukutake, T., and Kawamura, M. (1999). "Thumb localizing test" for detecting a lesion in the posterior column–medial lemniscal system. *J. Neurol. Sci.* 167, 45–49. doi: 10.1016/s0022-510x(99)00136-7

Langhorne, P., Coupar, F., and Pollock, A. (2009). Motor recovery after stroke: a systematic review. *Lancet Neurol.* 8, 741–754. doi: 10.1016/S1474-4422(09)70150-4

Lin, K.-C., Fu, T., Wu, C.-Y., Hsieh, Y.-W., Chen, C.-L., and Lee, P.-C. (2010). Psychometric comparisons of the stroke impact scale 3.0 and stroke-specific quality of life scale. *Q. Life Res.* 19, 435–443. doi: 10.1007/s11136-010-9597-5

Lyle, R. C. (1981). A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int. J. Rehabil. Res.* 4, 483–492. doi: 10.1097/00004356-198112000

Mahoney, D., and Barthel, F. I. W. (1965). Functional evaluation: the barthel index: a simple index of independence useful in scoring improvement in the rehabilitation of the chronically ill. *Md. State Med. J.* 14, 61–65.

Maris, E., Schoffelen, J.-M., and Fries, P. (2007). Nonparametric statistical testing of coherence differences. *J. Neurosci. Methods* 163, 161–175. doi: 10.1016/j.jneumeth.2007.02.011

Mathiowetz, V., Volland, G., Kashman, N., and Weber, K. (1985). Adult norms for the box and block test of manual dexterity. *Am. J. Occup. Ther.* 39, 386–391. doi: 10.5014/ajot.39.6.386

Morris, D. M., and Taub, E. (2008). "The use of constraint-induced movement therapy (ci therapy) to promote motor recovery following stroke," in *Cognitive Neurorehabilitation. Evidence and Application*, eds D. T. Stuss, G. Winocur, and I. H. Robertson (Cambridge: Cambridge University Press), 401–413.

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). FieldTrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput. Intell. Neurosci.* 2011:156869. doi: 10.1155/2011/156869

Osu, R., Ota, K., Fujiwara, T., Otaka, Y., Kawato, M., and Liu, M. (2011). Quantifying the quality of hand movement in stroke patients through three-dimensional curvature. *J. Neuroeng. Rehabil.* 8:62. doi: 10.1186/1743-0003-8-62

Pan, L.-L. H., Yang, W.-W., Kao, C.-L., Tsai, M.-W., Wei, S.-H., Fregni, F., et al. (2018). Effects of 8-week sensory electrical stimulation combined with motor training on eeg-emg coherence and motor function in individuals with stroke. *Sci. Rep.* 8:9217. doi: 10.1038/s41598-018-27553-4

R Core Team, (2018). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Rojo, N., Amengual, J., Juncadella, M., Rubio, F., Camara, E., Marco-Pallares, J., et al. (2011). Music-supported therapy induces plasticity in the sensorimotor cortex in chronic stroke: a single-case study using multimodal imaging (fMRI-tms). *Brain Injury* 25, 787–793. doi: 10.3109/02699052.2011.576305

Rosenberg, J. R., Amjad, A. M., Breeze, P., Brillinger, D. R., and Halliday, D. M. (1989). The fourier approach to the identification of functional coupling between neuronal spike trains. *Prog. Biophys. Mol. Biol.* 53, 1–31. doi: 10.1016/0079-6107(89)90004-7

RStudio Team, (2018). *RStudio: Integrated Development Environment for R*. Boston, MA: RStudio, Inc.

Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., et al. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain* 131, 866–876. doi: 10.1093/brain/awn013

Schneider, S., Münte, T., Rodriguez-Fornells, M., Sailer, A., and Altenmüller, E. (2010). Music-supported training is more efficient than functional motor training for recovery of fine motor skills in stroke patients. *Music Percept.* 27, 271–280. doi: 10.1525/mp.2010.27.4.271

Scholz, D. S., Rohde, S., Großbach, M., Rollnik, J., and Altenmüller, E. (2015). Moving with music for stroke rehabilitation: a sonification feasibility study. *Ann. N. Y. Acad. Sci.* 1337, 69–76. doi: 10.1111/nyas.12691

Scholz, D. S., Rohde, S., Nikmaram, N., Brückner, H.-P., Grossbach, M., Rollnik, J. D., et al. (2016). Sonification of arm movements in stroke rehabilitation – a novel approach in neurologic music therapy. *Front. Neurol.* 7:106. doi: 10.3389/fneur.2016.00106

Seeck, M., Koessler, L., Bast, T., Leijten, F., Michel, C., Baumgartner, C., et al. (2017). The standardized eeg electrode array of the ifcn. *Clin. Neurophysiol.* 128, 2070–2077. doi: 10.1016/j.clinph.2017.06.254

Sihvonen, A. J., Särkämö, T., Leo, V., Tervaniemi, M., Altenmüller, E., and Soinila, S. (2017). Music-based interventions in neurological rehabilitation. *Lancet Neurol.* 16, 648–660. doi: 10.1016/S1474-4422(17)30168-0

Stam, C. J., Nolte, G., and Daffertshofer, A. (2007). Phase lag index: assessment of functional connectivity from multi channel eeg and meg with diminished bias from common sources. *Hum. Brain Map.* 28, 1178–1193. doi: 10.1002/hbm.20346

Thaut, M. H., Kenyon, G. P., Hurt, C. P., McIntosh, G. C., and Hoemberg, V. (2002). Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. *Neuropsychologia* 40, 1073–1081. doi: 10.1016/s0028-3932(01)00141-5

Tong, Y., Forreider, B., Sun, X., Geng, X., Zhang, W., Du, H., et al. (2015). Music-supported therapy (mst) in improving post-stroke patients' upper-limb motor function: a randomised controlled pilot study. *Neurol. Res.* 37, 434–440. doi: 10.1179/1743132815Y.0000000034

van Vugt, F. T., Kafczyk, T., Kuhn, W., Rollnik, J. D., Tillmann, B., and Altenmüller, E. (2016). The role of auditory feedback in music-supported stroke rehabilitation: a single-blinded randomised controlled intervention. *Restor. Neurol. Neurosci.* 34, 297–311. doi: 10.3233/RNN-150588

Vehtari, A., Gelman, A., and Gabry, J. (2017). Practical bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat. Comput.* 27, 1413–1432. doi: 10.1007/s11222-016-9696-4

Vinck, M., Oostenveld, R., Wingerden, M., van Battaglia, F., and Pennartz, C. M. A. (2011). An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage* 55, 1548–1565. doi: 10.1016/j.neuroimage.2011.01.055

Watson, D., Clark, L. A., and Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the panas scales. *J. Pers. Soc. Psychol.* 54, 1063–1070. doi: 10.1037//0022-3514.54.6.1063

Woodbury, M. L., Velozo, C. A., Richards, L. G., Duncan, P. W., Studenski, S., and Lai, S.-M. (2008). Longitudinal stability of the fugl-meyer assessment of the upper extremity. *Arch. Phys. Med. Rehabil.* 89, 1563–1569. doi: 10.1016/j.apmr.2007.12.041

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Rhythmic Auditory Stimulation as an Adjuvant Therapy Improved Post-stroke Motor Functions of the Upper Extremity: A Randomized Controlled Pilot Study

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Objectives: To explore whether rhythmic auditory stimulation (RAS) could improve motor functions of post-stroke hemiparetic upper extremity.

Design: A prospective, randomized controlled, assessor-blinded pilot study.

Methods: Thirty stroke patients were randomly distributed into the RAS group (n = 15) and the control group (n = 15). Both groups received regular therapies. The RAS group received additional 30 min of RAS training, while the control group received additional 30 min of regular therapies for 5 days per week for 4 weeks. The Fugl-Meyer Assessment—Upper Extremity (FMA-UE), Wolf Motor Function Test (WMFT), and Barthel Index (BI) were used. The co-activation interval and co-contraction index were calculated from surface electromyography (sEMG) recordings on the affected biceps and triceps during elbow flexion and extension. Assessments were performed before and after the treatments.

Results: Significant improvements in motor functions were observed within both groups ($p < 0.05$ in the FMA-UE, WMFT, and BI, respectively), as well as between groups after the treatments (higher scores in the RAS group, all $p < 0.05$ except for $p = 0.052$ in the FMA-UE; group × time interaction, all $p < 0.05$). Statistical significance was found in the co-activation interval between groups after the treatments (lower in the RAS group; $p = 0.022$ during elbow extension; $p = 0.001$ during elbow flexion; group × time interaction, $p < 0.05$ only during elbow extension). No statistical significance was found in the co-contraction index between groups; an inversed pattern of changes was observed between groups supported by relatively higher increments in the triceps recruitments to the biceps.

Conclusion: Using RAS in task-oriented exercises was effective in moderating co-contraction, facilitating task-oriented movements of the hemiparetic upper extremity, and improving ADLs among those who had emerging isolated joint movements.

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The effects were evident on sEMG possibly by adjusting the balance of recruitments between the agonist and the antagonist.

Clinical Trial Registration: The study was registered at the Chinese Clinical Trial Registry (No. 1900026665).

Keywords: rhythmic auditory stimulation, stroke, motor function, upper extremity, surface EMG

INTRODUCTION

Stroke commonly results in impairments on limbs' functions (Hu et al., 2019), leaving patients with various levels of dependence (WHO, 2014; Zerna et al., 2019). Motor function of the upper extremity is one of the cardinal determinants of functional independence and quality of life (Kokotilo et al., 2009; Pollock et al., 2014). It has been a challenge to restore due to the complicated involvement of multiple motor domains (i.e., weakness, spasticity, incoordination, and synergistic movements) in the arm and hand after stroke (Padua et al., 2019), yet the intricacy of neural wiring and plasticity remains unclear. Task-oriented movement therapy was considered beneficial in the restoration of upper extremity functions (Boffa et al., 2019) as it emphasizes on movements highly relevant to daily activities, which theoretically facilitates neural plasticity toward a practical formation and has been routinely incorporated in the current rehabilitative practice. However, patients, even with substantial functional recovery, still struggle with the trajectory and the efficiency of using the affected arm. There is a clinical need for further exploration of potential therapeutic modalities to maximize motor functions of the paretic upper extremity.

The RAS, as a type of neurologic music therapy, was found to be effective in improving motor functions, especially gait, in persons with neurological disorders (Schaffert et al., 2019). Numerous studies have shown that RAS improved gait velocity, stride length, and cadence after stroke, as well as balance and sit-to-stand and walk sequencing (Thaut et al., 2007; Hayden et al., 2009; Cha et al., 2014; Suh et al., 2014). There are comparatively fewer studies focusing on its application and efficacy on upper extremity motor functions (Yoo and Kim, 2016; Ghai, 2018). Despite the scarcity of the study and the heterogeneity in the available studies, the pooled data in a meta-analysis favored RAS on post-stroke upper extremity motor functions (Yoo and Kim, 2016). The beneficial effects manifested in strength, range of motion, synchrony, coordination, and functional motor performance (Whitall et al., 2000; Malcolm et al., 2009; Ghai, 2018). The major deficiencies in these studies were small sample size and without control subjects.

The proposed theory on RAS's therapeutic effects include the regulation of spatiotemporal and force parameters with specification of the dynamics of a movement and reduction of variability via the rhythmic cues, thus achieving the optimal movement pattern with repetitive exercise (Thaut et al., 2002; Thaut et al., 2009; Kim et al., 2014). Also, the rhythmic auditory cues may help with motor priming, facilitate movement anticipation and preparation, and potentially bypass damaged areas through the activation of alternative pathways (Yoo and Kim, 2016). Part of the auditory-motor coupling was proposed to locate in the RS pathway. It was suggested, theoretically, that this type of cues would activate RS pathway and result in synergistic activation, thus being more helpful in gross motor strength in patients with less spasticity but severe paresis, rather than those with more spasticity and spastic co-contraction (Li, 2017). In the study, the sEMG was used to further explore the changes of neuromuscular activities under the rhythmic auditory cues, as previously used in the gait analysis after RAS therapy, to provide new evidence on its neuromuscular modulation effects (Schreiber et al., 2016).

Therefore, the aim of this study was to explore the effects and mechanisms of RAS on the hemiparetic upper extremity motor functions after stroke, using clinical scales for functional evaluations and sEMG as an objective measurement of the underlying neuromuscular changes.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized controlled study. The sample size of 30 subjects was considered sufficient to manifest statistical significance based on previous study protocols (Hsieh et al., 2009; Schreiber et al., 2016) and a sample size calculation based on an effect size of 0.97, a significance level of 0.05, and 80% power. It was derived from two previous studies in which the effect sizes were 0.83 and 1.12 on the FMA, respectively (Whitall et al., 2000; van Delden et al., 2013). Considering approximately 10% dropout rate, the sample size was determined as 32 subjects. Eligible stroke patients were recruited and assigned a number orderly on a pre-established random number list in the Microsoft Excel software. The numbers on the list were rearranged in an ascending order, with the first 16 numbers on the sequence being assigned to the RAS group while the latter 16 numbers being assigned to the control group. The study was reviewed and approved by the Ethics Committee of Huashan Hospital, Fudan University. The study was registered at the Chinese Clinical Trial Registry (No. 1900026665).

Abbreviations: ADL, activities of daily living; BI, Barthel Index; CID, clinical important difference; FMA-UE, Fugl-Meyer Assessment—Upper Extremity; MMSE, Mini-Mental State Examination; RAS, rhythmic auditory stimulation; RMS, root mean square; RS, reticulospinal; sEMG, surface electromyography; WMFT, Wolf Motor Function Test.

Participants

The inclusion criteria were (I) confirmed diagnosis of stroke with evidence on MRI or CT; (II) having motor impairments in the upper extremity with a Brunnstrom Stages IV–VI; (III) first-time stroke with or without previous lacunar infarction which resulted in no functional consequences; (IV) 40–80 years old; (V) vital signs stable; and (VI) inpatient rehabilitation status. The exclusion criteria were (I) having Parkinson's disease or other neurological conditions causing motor dysfunction; (II) having cognitive (MMSE < 24) or auditory (tuning-fork test) impairment; (III) having cancer or severe cardiopulmonary diseases; (IV) participating in other research projects; (V) unable to follow commands; and (VI) having pacemaker placement. All participants signed the informed consent and participated under their free will.

Interventions

All participants received regular therapies, including 30 min of individualized physical therapy and 30 min of individualized occupational therapy per day, 5 days per week for 4 weeks. The patients in the RAS group received additional 30 min of RAS therapy every day, while the patients in the control group received additional 15 min of regular physical therapy and 15 min of regular occupational therapy every day, which were also provided 5 days per week for 4 weeks.

Regular Therapies

The regular physical therapy included strength exercise (e.g., isotonic movements with weights and repetitions), gait exercise, balance exercise, and coordination exercise (e.g., side walking exercise and heel-to-toe walking exercise). The regular occupational therapy included forced use of the affected upper extremity in ADL activities, fine motor exercise of the hand (e.g., grasp a cylindrical object or a small bead and move to the target area), and sensory integration (e.g., mold with plasticine or squeeze soft ball).

RAS Therapy

The RAS therapy was performed by practicing movements of certain tasks with auditory cues at a gradually increased rhythm, as delineated in **Table 1**. Two categories of tasks were chosen. Task Numbers 1–9 without usage of instruments (Category I) were provided during the first 2 weeks; Task Numbers 10–14 with usage of certain instruments (Category II) were performed during the latter 2 weeks. The process of proceeding RAS therapy is described as below. First, to identify the applicable tempo (beats per minute, bpm) at the beginning of the study, the participants were required to perform each movement for 5 rounds at their own pace without the auditory cues. The trial was recorded and analyzed by a metronome software (Pro Metronome, 2014 EUMLab, Xanin Technology Limited Liability Company, China) to obtain the baseline tempo for each movement. For example, for the 3rd movement listed in **Table 1**, the participant was required to touch the target line (5 cm in width) back and forth by flexing and extending the shoulder. The metronome software recorded and calculated the average tempo of the movement, which was considered as the baseline. When the participant was able to keep up with a tempo and finish touching the target lines for 5 rounds, the tempo would be increased by 5% as the next level of training. No more than 5% increase was allowed in a day. Repetitive exercise with a specific tempo was implemented under supervision and instruction of an experienced therapist until the next level could be reached. The tempos at the beginning and at the end of the study were recorded, of which the means and the increments were calculated and listed in **Table 1**.

Clinical Assessments

The assessments included (I) the Fugl-Meyer Assessment of the affected upper extremity (FMA-UE), (II) the WMFT of the affected upper extremity, (III) the BI, and (IV) the sEMG recordings of the biceps and the triceps on the affected side. The assessments were performed before and after all the treatments. The assessors were blind to patient allocation.

Assessments of Upper Extremity Motor Function and ADL

The Fugl-Meyer Assessment (upper extremity) is a scale with high validity to assess motor functions of the upper extremity (Page et al., 2012). In the FMA-UE, 33 items were listed with a total score of 66. Unable to complete a required action or no muscle reflex was scored as 0; partially able to complete the action was scored as 1; adequately complete the action was scored as 2. A higher score indicates better functionality.

The WMFT is used to assess the task-oriented function of the upper extremity. In the WMFT, 15 items were listed with a six-grade scale, from 0, meaning no attempt from the tested arm, to 5, meaning being able to perform the task with a relatively normal movement. A higher score indicates better functionality.

The BI is a commonly used scale to evaluate the ability of ADLs. In the BI, 12 items were listed with a total score of 100. A higher score indicates better functionality.

Parameters of sEMG

The sEMG signals were recorded through disposable AgCl electrodes by the 8-channel wireless sEMG system (Myo MUSCLE, Noraxon, USA Inc., Scottsdale, AZ, United States) (Mackala et al., 2013; Kim et al., 2014). The electrodes were placed on the affected biceps and the triceps. The participant sat on an armless chair in a quiet room and rested the affected upper extremity on the body side, as the starting position. The participant was instructed to touch the nose and the most front part of the knee back and forth with the index finger for five times. No audio cue was provided during the assessment. The raw sEMG signal was processed based on RMS (peak %) algorithm. The time window was set at 50 ms. The movement stage of the sEMG was determined based on the simultaneous sEMG recording and real-time video of the joint movement in the sEMG system. The peak normalization was used in this study rather than the maximum voluntary contraction since the paretic limb was tested (Kim et al., 2011). The parameters used in this study were the co-activation interval and the co-contraction index, reflecting the appropriateness of the activation and coordination between the muscles (Thaut et al., 1991; Rosa et al., 2013). The co-activation interval is a ratio of the time of co-activation of

TABLE 1 | The rhythmic auditory stimulation protocol.

Number	Movement	Specification*	Tempo 1 (bpm)[#]	Tempo 2 (bpm)[§]	Increment of the tempo
Category I:					
(1)	Shrug bilateral shoulder	Shrug and relax	40 ± 2	60 ± 3	50%
(2)	Shrug affected side	Shrug and relax	40 ± 1	60 ± 1	50%
(3)	Shoulder flexion/extension to touch the target line	With elbow extension	53 ± 4	80 ± 4	51%
(4)	Shoulder abduction/adduction to touch the target line	With elbow extension	54 ± 3	79 ± 4	46%
(5)	Elbow flexion/extension to touch the nose and the knee back and forth	Use index fingers to touch	51 ± 4	79 ± 4	55%
(6)	Reach back and forth on a desk	Elbow extension/flexion combined with shoulder flexion/extension	52 ± 4	79 ± 4	52%
(7)	Forearm pronation/supination	Palm contact desk when pronation; Opisthenar contact desk when supination;	64 ± 2	88 ± 4	38%
(8)	Wrist flexion/extension	Without compensatory action	65 ± 1	98 ± 4	51%
(9)	Shoulder horizontal abduction/adduction to touch the target line	With elbow extension (1 action per 2 beats)	69 ± 2	87 ± 4	26%
Category II:					
(10)	Hold a cup to move	Use it to touch mouth and put it back on the desk	52 ± 4	70 ± 4	35%
(11)	Hold a large block to move	Put the block in the target scope	64 ± 2	79 ± 2	23%
(12)	Hold a little block to move	Put the block in the target scope	59 ± 1	70 ± 2	19%
(13)	Hold a large ball to move	Put the ball in the target scope	64 ± 2	79 ± 2	23%
(14)	Hold a little ball to move	Put the ball in the target scope	59 ± 1	71 ± 2	20%

*Category I (Numbers 1–9, tasks without usage of instruments) contains the training items for the first 2 weeks; Category II (Numbers 10–14, tasks with usage of instruments) contains the training items for the latter 2 weeks. *One action per beat, except for those indicated otherwise in the specification. [#]The average tempo obtained at the baseline; [§] the average tempo achieved at the end of the study. bpm, beats per minute.*

the agonist and the antagonist to the total activation time during elbow flexion and extension. The co-contraction index is a ratio of the RMS of the antagonist to the RMS of the agonist. The RMS of the individual muscle groups was also recorded and presented.

Statistical Analysis

Data analysis was performed by SPSS 22.0 (IBM Corp., Armonk, NY, United States). For the categorical data, chi-square test, or Fisher's exact test when sample size was below 5, was performed. For the normally distributed continuous data with equal variance, independent t-test for comparisons between groups and paired sample t-test for comparisons within the group before and after the treat were used. The mix model analysis of covariance (ANOVA) was used to explore time × group interaction. The significance level was set at $p < 0.05$ (2-tailed). G*Power Version 3.1.9.2 (program written by Franz Faul, Universität Kiel; Germany) was used to calculate the sample size and the effect size.

RESULTS

Demographics

Thirty-two patients were initially enrolled in the study, including 16 patients in the RAS group and 16 patients in the control group based on the randomization. One participant in each group was excluded due to unexpected discharge before the pre-treatment assessment. A total of 15 patients in each group completed the study, as shown in **Figure 1**. Most patients were male, were in their 60s, had ischemic stroke within 6 months, and classified as Brunnstrom Stage IV on enrollment. All patients were right-handed. Primary stroke area was basal ganglia in both groups. No statistical difference was found in the demographics between the two groups (**Table 2**).

Among the Category I tasks, the tempo for most of the items advanced around 50% at the end of the study, except for movements involving shoulder horizontal abduction/adduction and forearm pronation/supination. Among the Category II tasks, the tempo for most of the items advanced around 20% (**Table 1**).

Motor Functions of the Hemiparetic Upper Extremity

Motor function assessment, using the FMA-UE, showed improvement after the treatments in both groups, with 20% increase in the RAS group (p = 0.000) and 12.5% increase in the control group (p = 0.000). There was no statistical difference between groups before the treatments (p = 0.542). No statistical difference reached between groups after the treatments (p = 0.052). However, the ANOVA analysis revealed significant effect of treatment over time [group × time interaction:

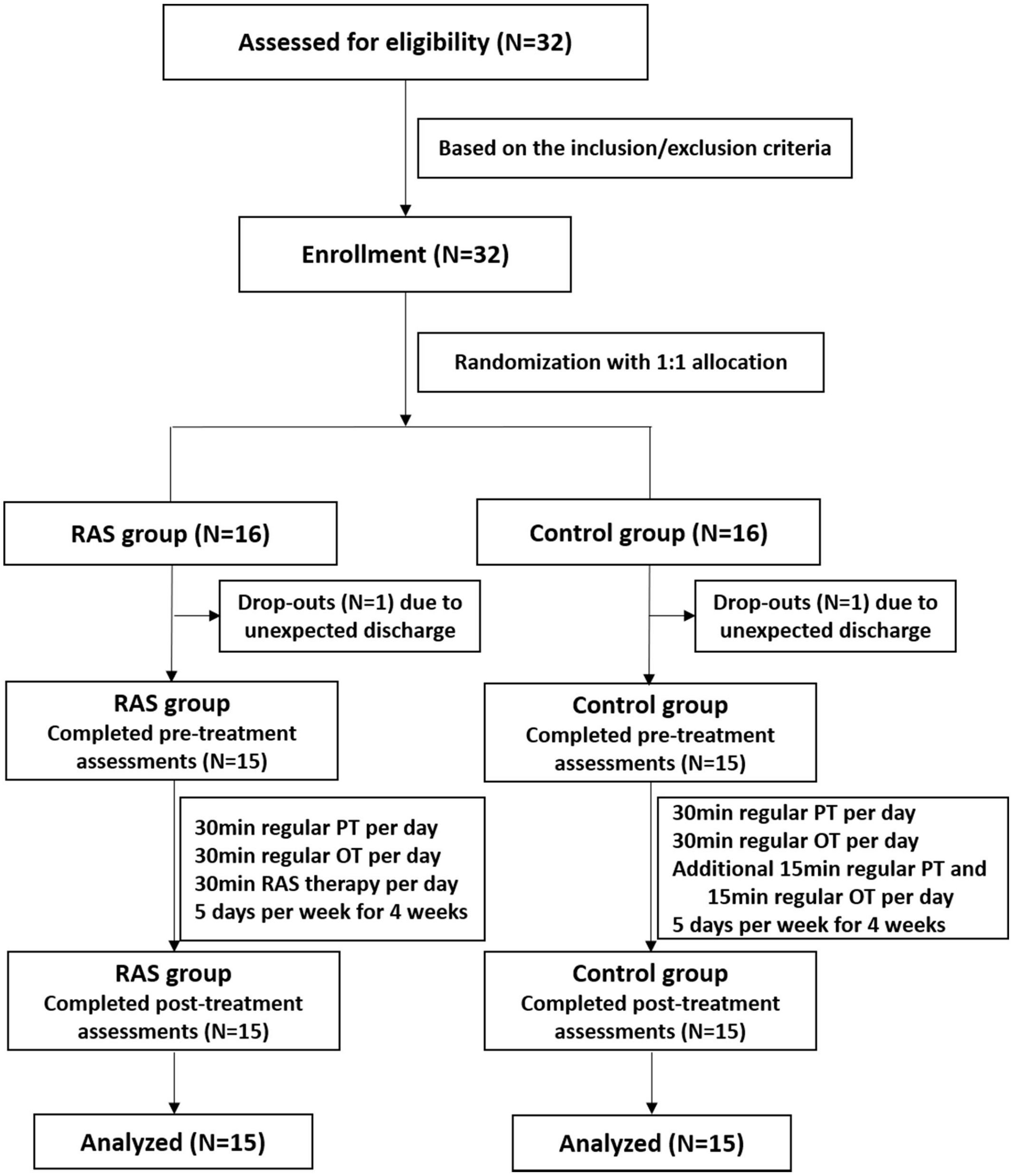

FIGURE 1 | The flow diagram of the study.

$F(1,28) = 7.717$, $p = 0.010$]. The score was higher in the RAS group than that of the control group after the treatments with an effect size of 0.52.

Task-oriented movement, using the WMFT, showed improvement after the treatments in both groups, with 32% increase in the RAS group ($p = 0.000$) and 16% increase in the control group ($p = 0.000$). There was no statistical difference between groups before the treatments ($p = 0.591$). There was statistical difference between groups after the treatments (49.53 ± 10.56 in the RAS group vs. 42.67 ± 10.20 in the control group, $p = 0.041$; effect size, 0.72). The ANOVA analysis also revealed significant effect of treatment over time [group × time interaction: $F(1,28) = 14.526$, $p = 0.001$]. The results are presented in **Table 3**.

Activities and Participation

The ADLs, using the BI, showed significant improvement after the treatments in both groups, with 31% increase in the RAS group ($p = 0.000$) and 17% increase in the control group ($p = 0.000$). There was no statistical difference between groups before the treatments ($p = 0.916$). Statistical difference was found between groups after the treatments (80.33 ± 8.96 in the RAS group vs. 69.67 ± 7.19 in the control group, $p = 0.001$; effect size 0.91). The ANOVA analysis also revealed significant effect of

TABLE 2 | The demographics of the participants.

	RAS group (n = 15)	Control group (n = 15)	P-value
Age (years)	66.67 ± 13.59	64.40 ± 13.41	0.821
Gender (male:female)	13:2	10:5	0.195
Type (ischemic:hemorrhagic)	10:5	12:3	0.409
Brunnstrom stage (IV:V:VI)	9:4:2	10:3:2	0.907
Handedness (left:right)	0:15	0:15	1.000
Damage hemisphere (left:right)	7:8	8:7	0.833
Time (months)	5.00 ± 7.55	3.77 ± 9.00	0.137
Intracranial lesion (number,%)			0.707
Frontal temporal lobe	1 (7%)	/	
Frontal lobe	/	1 (7%)	
Corona radiate	1 (7%)	/	
Capsula externa	1 (7%)	/	
Thalamus	2 (13%)	1 (7%)	
Basal ganglia	9 (59%)	8 (52%)	
Brainstem	1 (7%)	3 (20%)	
Paraventricular	/	1 (7%)	
Cerebellum	/	1 (7%)	

RAS, rhythmic auditory stimulation.

treatment over time [group × time interaction: $F(1,28) = 23.197$, $p = 0.000$]. The results are presented in **Table 3**.

Surface EMG Features of the Biceps and the Triceps During Elbow Flexion and Extension

Co-activation Interval

The results are presented in **Table 4**. During elbow extension, no statistical difference was found between the two groups before the treatments ($p = 0.468$). Statistical significance was found between groups after the treatments (26.70 ± 13.59 in the RAS group vs. 51.58 ± 21.46 in the control group, $p = 0.022$; effect size, 0.64). There was a 48% reduction in the co-activation interval in the RAS group before and after the treatments ($p = 0.031$), but no significant reduction in the control group ($p = 0.562$). The ANOVA analysis revealed significant effect of treatment over time [group × time interaction: $F(1,28) = 11.539$, $p = 0.002$].

During elbow flexion, similarly, no statistical difference was found between the two groups before the treatments ($p = 0.944$). Statistical significance was found between groups after the treatments (14.80 ± 7.79 in the RAS group vs. 28.66 ± 20.82 in the control group, $p = 0.001$). There was a 44% reduction in the co-activation interval in the RAS group before and after the treatments ($p = 0.000$), while a 9% reduction in the control group ($p = 0.930$). The ANOVA analysis revealed no significant effect of treatment over time [group × time interaction: $F(1,28) = 1.091$, $p = 0.305$].

TABLE 3 | Motor functions and activity of daily living assessments.

	RAS group		Control group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
FMA-UE	50.40 ± 9.97	59.73 ± 6.23*	48.27 ± 8.93	54.07 ± 8.85*
WMFT	38.27 ± 8.75	49.53 ± 10.56*#	36.60 ± 8.00	42.67 ± 10.20*
BI	60.67 ± 10.33	80.33 ± 8.96*#	60.33 ± 6.40	69.67 ± 7.19*

**p* < 0.05 between pre- and post-treatment in the same group; #*p* < 0.05 between groups with the same scale after the treatments. RAS, rhythmic auditory stimulation; FMA-UE, Fugl-Meyer Assessment—Upper extremity; WMFT, Wolf Motor Function Test; BI, Barthel Index.*

TABLE 4 | Surface EMG features of the biceps and the triceps during elbow flexion and extension.

	RAS group		Control group	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Co-activation interval (%)				
Elbow extension	51.54 ± 15.62	26.70 ± 13.59*	52.02 ± 21.03	51.58 ± 21.46#
Elbow flexion	26.81 ± 18.25	14.80 ± 7.79*	32.23 ± 21.95	28.66 ± 20.82#
RMS during elbow extension				
Biceps	32.05 ± 11.53	34.87 ± 9.18	32.40 ± 10.83	38.07 ± 11.05
Triceps	36.79 ± 10.32	40.07 ± 10.83	38.87 ± 10.89	38.67 ± 9.88
Co-contraction index (%)	94.27 ± 46.01	92.02 ± 30.46	85.93 ± 29.75	103.67 ± 38.33
RMS during elbow flexion				
Biceps	43.15 ± 11.01	44.03 ± 10.07	46.39 ± 6.86	47.00 ± 4.66
Triceps	41.29 ± 14.07	46.33 ± 13.18	46.69 ± 11.56	40.47 ± 13.83
Co-contraction index (%)	101.86 ± 42.53	112.83 ± 49.57	102.28 ± 34.01	86.68 ± 30.24

**p* < 0.05 between pre- and post-treatment in the same group; #*p* < 0.05 between groups with the same movement after the treatments. RAS, rhythmic auditory stimulation; RMS, root mean square. Co-contraction index during elbow extension was calculated as the RMS of the antagonist (biceps)/the RMS of the agonist (triceps); co-contraction index during elbow flexion was calculated as the RMS of the antagonist (triceps)/the RMS of the agonist (biceps).*

Co-contraction Index

No statistical difference was found between groups before or after the treatments, or in the individual group before and after the treatments. In the RAS group, during elbow flexion, the co-contraction index increased after the treatments (from 101.86 to 112.83%), while it decreased during elbow extension (from 94.27 to 92.02%). In the control group, an inversed pattern was observed, where during elbow flexion, the co-contraction index decreased after the treatments (from 102.28 to 86.68%), while it increased during elbow extension (from 85.93 to 103.67%). During elbow flexion, the ANOVA analysis revealed no significant effect of treatment over time [group × time interaction: $F(1,28) = 1.887$, $p = 0.180$], or during elbow extension [group × time interaction: $F(1,28) = 2.001$, $p = 0.168$]. The results are presented in **Table 4**.

RMS of the Biceps and the Triceps During Elbow Flexion and Extension

The RMS of the biceps and the triceps during elbow flexion and extension was obtained as an indirect parameter of muscle recruitment. No statistical difference was found before and after the treatments in both groups. The results are presented in **Table 4**.

DISCUSSION

The study showed the potential benefits of using RAS as an adjuvant therapy among those who have achieved relatively higher functional levels on the hemiparetic upper extremity, when compared with a control group that only received regular therapies. Our results provided confirmatory evidence on the benefits of clinical application of RAS for post-stroke upper extremity motor restoration and proposed the potential underlying higher increments in the triceps recruitments to the biceps on sEMG.

Upper Extremity Functional Improvements After RAS Therapy

The participants in the study were required to achieve Brunnstrom IV or above as most of the tasks in our RAS protocol required isolated joint movements. Theoretically, with the decreasing spasticity and the emerging isolated movements, the patients gradually regain the liberty and functional abilities of the limb (Naghdi et al., 2010). However, movement is not only about tone and strength; it is also about preparation, coordination, accuracy, stability, and efficiency, thus a complex and integrated process (Arciniegas et al., 2018). Using RAS in task-oriented exercises may help stimulate rhythm perception in the vestibular system and subsequently relay activations to the cerebella and the premotor area, which eventually transmitted to the internal "beat keeper" pathway, including basal ganglia and supplementary motor area, to assist motor production in good quality (Todd and Lee, 2015). The regimen using RAS reported before showed similar benefits in FMA (Malcolm et al., 2009; Thielman, 2010). In chronic stroke (≥ 4 months), the clinically importance difference (CID) for patients with mild to moderate upper extremity hemiparesis (baseline FMA-UE ≥ 28 and ≤50) was considered to be 4.25–7.25 points (Page et al., 2012), while in the relatively acute stage (on average 1.5 months after stroke onset), with moderate to severe hemiparesis (baseline FMA-UE scores around 14), the CID could be 9–12.4 points (Hiragami et al., 2019). The minimal CID of the WMFT was 3–6 points in chronic stroke patients (≥6 months) (Lin et al., 2009). The minimal CID of the BI was 1.85 points (Hsieh et al., 2007). The patients in the control group showed functional improvements comparable with the above proposed CIDs. The patients in the RAS group had more prominent improvements than those in the control group, suggesting additional clinical benefits of using RAS. The effect size of the FMA-UE was not as high as expected, which may be related to the higher functional baseline and the ceiling effect. The functional improvements were also reflected on the increments of the tempo achieved at the end of the study, which may be an indirect manifestation of the improved efficiency, coordination, and motor priming of the hemiparetic upper extremity. Other researchers combined RAS with bilateral arm training also showed promising results on strength, range of motion and motor performance of the affected arm (Whitall et al., 2000; Cauraugh and Summers, 2005), although there were reports on its ineffectiveness (Richards et al., 2008; Mainka et al., 2018). Moderate to significant discrepancies existed among the regimens in terms of the audio type (metronome/use of music), the duration and frequency of the treatment, the aimed body structures (wrist/elbow/shoulder/fingers), the choice of the rhythm regime (participants' preference/increase by certain percentage), and the concomitant exercise paradigm (Ghai, 2018), as well as patient selection. The discrepancies make comparisons on the effects difficult. The abovementioned RAS components should be taken into account in the future studies and clinical application. Currently, the duration and frequency of RAS therapy were recommended to be at least 30 min to 1 h per session, more than 3 sessions per week, and more than 10 sessions in total (Ghai, 2018). Based on the results, our RAS regimen is considered feasible for clinical application in the selected population. The detailed RAS regimen and expected advancement of the therapy were also provided for future reference (**Table 1**).

Co-contraction Features on sEMG During Elbow Flexion and Extension After RAS Therapy

Spastic co-contraction of the agonist and the antagonist is a common pathological change after stroke (Lin et al., 2009). It is characterized by undesired involuntary muscle activity in the antagonist during voluntary recruitment of the agonist, which makes isolated movements difficult (Baude et al., 2019; Chalard et al., 2020). Our results revealed significant reduction in the co-activation interval following RAS therapy, especially during elbow extension. In a previous study, the sEMG signals of the biceps and triceps were obtained from healthy subjects during elbow bi-articular movements. The co-activation interval during elbow extension and flexion appeared to be around 30–40% and 10–15%, respectively (Thaut et al., 1991). RAS therapy may help modulate tonicity and motor planning (Schaffert et al., 2019), which appeared to bring the agonist/antagonist activation pattern close to normal. The conventional therapy did not show such benefit. The between-group difference after treatment during elbow flexion was not supported by the group–time effect, maybe because of less prominent changes over time, or insufficient sample size, or insufficient treatment duration.

Root mean square was used to reflect the muscle activation signal changes during the elbow bi-articular voluntary tasks. A previous study showed that smoother motor performance was achieved with the restoration of the time-domain reciprocal EMG activities in bi-articular arm muscles (Miyoshi et al., 2010). Based on the formula, a decrease in the co-contraction index was expected to reflect the dominating agonist activation (Kiewiet et al., 2017). In our study, although no statistical significance was found in the RMS of either biceps or triceps, or their respective co-contraction index during elbow flexion or extension, an inversed change was observed in the co-contraction indexes before and after the treatments between groups. A decrease of the co-contraction index in the RAS group was found, compared with an increase in the control group during elbow extension, while an increase in the RAS group was found, compared with a decrease in the control group during elbow flexion. It indicated higher recruitments of the triceps, either as an agonist during elbow extension or as an antagonist during elbow flexion, than that of the biceps after RAS therapy. It may be explained by a greater volitional control of the triceps achieved during elbow extension as the primary agonist and an evidence of improved eccentric contraction of the triceps during the elbow flexion, which might contribute to well-controlled movements. Further studies with larger sample size and longer treatment duration are needed to confirm these findings.

Limitations

The study was explorative to reveal the potential role of RAS in post-stroke upper extremity motor rehabilitation. The sample size of the study was relatively small but was comparable with previous studies and validated by sample size calculation. Most of the participants reached Brunnstrom IV–VI as it is required to perform the RAS therapy items, which is usually considered relatively high functional level in the recovery process. The distribution of the demographics and the baseline functions was comparable between groups, and the homogeneity of the functional outcomes was acceptable. Therefore, the statistical significance in the functional outcomes between groups may be mainly attributed to the difference in interventions. However, the study did not examine its efficacy on patients with Brunnstrom I–III, which may require a different RAS regimen to match patient's functional levels. In the study, multiple comparison correction was not performed for sEMG data as false-positive results from chance was less of a concern in the small sample size explorative study. However, it may exist; therefore, it is important to bring this up to the readers' attention for further interpretation. The relationship between the sEMG and the force generated from the muscles was not examined in the study, as well as the trajectory of the motion. Further studies are needed with a larger sample size to stratify the effects of RAS on different functional levels and to illustrate its effects on different domains of motor functions. Comparison with a group of healthy age- and gender-compatible subjects is warranted to confirm our sEMG findings.

CONCLUSION

Using RAS in task-oriented exercises in post-stroke rehabilitation was effective in moderating co-contraction, facilitating task-oriented movements of the hemiparetic upper extremity, and improving ADLs among those who had emerging isolated joint movements. The effects were evident on sEMG possibly by adjusting the balance of recruitments between the agonist and the antagonist.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Huashan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RT and YZ contributed in study design, patient recruitment, therapy supervision, and data collection. RT and BZ contributed in data analysis, data interpretation, and manuscript preparation. All authors contributed to the article and approved the submitted version.

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REFERENCES

Arciniegas, D. B., Anderson, C. A., and Filley, C. M. (2018). *Behavioral Neurology & Neuropsychiatry*, 7th Edn. Cambridge: Cambridge University Press.

Baude, M., Nielsen, J. B., and Gracies, J. M. (2019). The neurophysiology of deforming spastic paresis: a revised taxonomy. *Ann. Phys. Rehabil. Med.* 62, 426–430. doi: 10.1016/j.rehab.2018.10.004

Boffa, G., Tacchino, A., Sbragia, E., Schiavi, S., Droby, A., Piaggio, N., et al. (2019). Preserved brain functional plasticity after upper limb task-oriented rehabilitation in progressive multiple sclerosis. *Eur. J. Neurol.* 27, 77–84. doi: 10.1111/ene.14059

Cauraugh, J. H., and Summers, J. J. (2005). Neural plasticity and bilateral movements: a rehabilitation approach for chronic stroke. *Prog. Neurobiol.* 75, 309–320. doi: 10.1016/j.pneurobio.2005.04.001

Cha, Y., Kim, Y., Hwang, S., and Chung, Y. (2014). Intensive gait training with rhythmic auditory stimulation in individuals with chronic hemiparetic stroke: a pilot randomized controlled study. *Neurorehabilitation* 35, 681–688. doi: 10.3233/nre-141182

Chalard, A., Belle, M., Montané, E., Marque, P., Amarantini, D., and Gasq, D. (2020). Impact of the EMG normalization method on muscle activation and the antagonist-agonist co-contraction index during active elbow extension practical implications for post-stroke subjects. *J. Electromyogr. Kines* 51:102403. doi: 10.1016/j.jelekin.2020.102403

Ghai, S. (2018). Effects of Real-Time (Sonification) and rhythmic auditory stimuli on recovering arm function post stroke: a systematic review and meta-analysis. *Front. Neurol.* 9:488. doi: 10.3389/fneur.2018.00488

Hayden, R., Clair, A. A., Johnson, G., and Otto, D. (2009). The effect of rhythmic auditory stimulation (RAS) on physical therapy outcomes for patients in gait training following stroke: a feasibility study. *Int. J. Neurosci.* 119, 2183–2195. doi: 10.3109/00207450903152609

Hiragami, S., Inoue, Y., and Harada, K. (2019). Minimal clinically important difference for the Fugl-Meyer assessment of the upper extremity in convalescent stroke patients with moderate to severe hemiparesis. *J. Phys. Ther. Sci.* 31, 917–921. doi: 10.1589/jpts.31.917

Hsieh, Y. W., Wang, C. H., Wu, S. C., Chen, P. C., Sheu, C. F., and Hsieh, C. L. (2007). Establishing the minimal clinically important difference of the Barthel Index in stroke patients. *Neurorehabil. Neural Repair* 21, 233–238. doi: 10.1177/1545968306294729

Hsieh, Y. W., Wu, C. Y., Lin, K. C., Chang, Y. F., Chen, C. L., and Liu, J. S. (2009). Responsiveness and validity of three outcome measures of motor function after stroke rehabilitation. *Stroke* 40, 1386–1391. doi: 10.1161/strokeaha.108.530584

Hu, S., Cui, B., Mlynash, M., Zhang, X., Mehta, K. M., and Lansberg, M. G. (2019). Stroke epidemiology and stroke policies in China from 1980 to 2017: a systematic review and meta-analysis. *Int. J. Stroke* 15, 18–28. doi: 10.1177/1747493019873562

Kiewiet, H., Bulsink, V. E., Beugels, F., and Koopman, H. (2017). The co-contraction index of the upper limb for young and old adult cyclists. *Accid. Anal. Prev.* 105, 95–101. doi: 10.1016/j.aap.2016.04.036

Kim, J., Jung, M., Yoo, E., Park, J., Kim, S., and Lee, J. (2014). Effects of rhythmic auditory stimulation during hemiplegic arm reaching in individuals with stroke: an exploratory study. *Hong Kong J. Occup. Ther.* 24, 64–71. doi: 10.1016/j.hkjot.2014.11.002

Kim, S. J., Kwak, E. E., Park, E. S., Lee, D. S., Kim, K. J., Song, J. E., et al. (2011). Changes in gait patterns with rhythmic auditory stimulation in adults with cerebral palsy. *Neurorehabilitation* 29, 233–241. doi: 10.3233/nre-2011-0698

Kokotilo, K. J., Eng, J. J., and Boyd, L. A. (2009). Reorganization of brain function during force production after stroke: a systematic review of the literature. *J. Neurol. Phys. Ther.* 33, 45–54. doi: 10.1097/npt.0b013e31819824f0

Li, S. (2017). Spasticity, motor recovery, and neural plasticity after stroke. *Front. Neurol.* 8:120. doi: 10.3389/fneur.2017.00120

Lin, K. C., Hsieh, Y. W., Wu, C. Y., Chen, C. L., Jang, Y., and Liu, J. S. (2009). Minimal detectable change and clinically important difference of the Wolf Motor Function Test in stroke patients. *Neurorehabil. Neural Repair* 23, 429–434. doi: 10.1177/1545968308331144

Mackala, K., Stodolka, J., Siemienski, A., and Coh, M. (2013). Biomechanical analysis of standing long jump from varying starting positions. *J. Strength Cond. Res.* 27, 2674–2684. doi: 10.1519/jsc.0b013e31825fce65

Mainka, S., Wissel, J., Voller, H., and Evers, S. (2018). The use of rhythmic auditory stimulation to optimize treadmill training for stroke patients: a randomized controlled trial. *Front. Neurol.* 9:755. doi: 10.3389/fneur.2018.00755

Malcolm, M. P., Massie, C., and Thaut, M. (2009). Rhythmic auditory-motor entrainment improves hemiparetic arm kinematics during reaching movements: a pilot study. *Top. Stroke Rehabil.* 16, 69–79. doi: 10.1310/tsr1601-69

Miyoshi, T., Takahashi, Y., Lee, H., Suzuki, T., and Komeda, T. (2010). Upper limb neurorehabilitation in patients with stroke using haptic device system: reciprocal bi-articular muscle activities reflect as a result of improved circle-drawing smoothness. *Disabil. Rehabil. Assist. Technol.* 5, 370–375. doi: 10.3109/17483100903437633

Naghdi, S., Ansari, N. N., Mansouri, K., and Hasson, S. (2010). A neurophysiological and clinical study of Brunnstrom recovery stages in the upper limb following stroke. *Brain Inj.* 24, 1372–1378. doi: 10.3109/02699052.2010.506860

Padua, L., Imbimbo, I., Aprile, I., Loreti, C., Germanotta, M., Coraci, D., et al. (2019). Cognitive reserve as a useful variable to address robotic or conventional upper limb rehabilitation treatment after stroke. A multicenter study of the Fondazione Don Carlo Gnocchi. *Eur. J. Neurol.* 27, 392–398.

Page, S. J., Fulk, G. D., and Boyne, P. (2012). Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke. *Phys. Ther.* 92, 791–798. doi: 10.2522/ptj.20110009

Pollock, A., Farmer, S. E., Brady, M. C., Langhorne, P., Mead, G. E., Mehrholz, J., et al. (2014). Interventions for improving upper limb function after stroke. *Cochrane Database Syst. Rev.* 2014:D10820.

Richards, L. G., Senesac, C. R., Davis, S. B., Woodbury, M. L., and Nadeau, S. E. (2008). Bilateral arm training with rhythmic auditory cueing in chronic stroke: not always efficacious. *Neurorehabil. Neural Repair* 22, 180–184. doi: 10.1177/1545968307305355

Rosa, M. C., Marques, A., Demain, S., Metcalf, C. D., and Rodrigues, J. (2013). Methodologies to assess muscle co-contraction during gait in people with neurological impairment – a systematic literature review. *J. Electromyogr. Kines.* 24, 179–191. doi: 10.1016/j.jelekin.2013.11.003

Schaffert, N., Janzen, T. B., Mattes, K., and Thaut, M. H. (2019). A review on the relationship between sound and movement in sports and rehabilitation. *Front. Psychol.* 10:244. doi: 10.3389/fpsyg.2019.00244

Schreiber, C., Remacle, A., Chantraine, F., Kolanowski, E., and Moissenet, F. (2016). Influence of a rhythmic auditory stimulation on asymptomatic gait. *Gait Posture* 50, 17–22. doi: 10.1016/j.gaitpost.2016.07.319

Suh, J. H., Han, S. J., Jeon, S. Y., Kim, H. J., Lee, J. E., Yoon, T. S., et al. (2014). Effect of rhythmic auditory stimulation on gait and balance in hemiplegic stroke patients. *Neurorehabilitation* 34, 193–199. doi: 10.3233/nre-131008

Thaut, M., Schleiffers, S., and Davis, W. (1991). Analysis of EMG Activity in biceps and triceps muscle in an upper extremity gross motor task under the influence of auditory rhythm. *J. Music Ther.* 28, 64–88. doi: 10.1093/jmt/28.2.64

Thaut, M. H., Kenyon, G. P., Hurt, C. P., McIntosh, G. C., and Hoemberg, V. (2002). Kinematic optimization of spatiotemporal patterns in paretic arm training with stroke patients. *Neuropsychologia* 40, 1073–1081. doi: 10.1016/s0028-3932(01)00141-5

Thaut, M. H., Leins, A. K., Rice, R. R., Argstatter, H., Kenyon, G. P., McIntosh, G. C., et al. (2007). Rhythmic auditory stimulation improves gait more than NDT/Bobath training in near-ambulatory patients early poststroke: a single-blind, randomized trial. *Neurorehabil. Neural Repair* 21, 455–459. doi: 10.1177/1545968307300523

Thaut, M. H., Stephan, K. M., Wunderlich, G., Schicks, W., Tellmann, L., Herzog, H., et al. (2009). Distinct cortico-cerebellar activations in rhythmic auditory motor synchronization. *Cortex* 45, 44–53. doi: 10.1016/j.cortex.2007.09.009

Thielman, G. (2010). Rehabilitation of reaching poststroke: a randomized pilot investigation of tactile versus auditory feedback for trunk control. *J. Neurol. Phys. Ther.* 34, 138–144. doi: 10.1097/npt.0b013e3181efa1e8

Todd, N. P., and Lee, C. S. (2015). The sensory-motor theory of rhythm and beat induction 20 years on: a new synthesis and future perspectives. *Front. Hum. Neurosci.* 9:444. doi: 10.3389/fnhum.2015.00444

van Delden, A. L., Peper, C. L., Nienhuys, K. N., Zijp, N. I., Beek, P. J., and Kwakkel, G. (2013). Unilateral versus bilateral upper limb training after stroke:

the upper limb training after stroke clinical trial. *Stroke* 44, 2613–2616. doi: 10.1161/strokeaha.113.001969

Whitall, J., McCombe, W. S., Silver, K. H., and Macko, R. F. (2000). Repetitive bilateral arm training with rhythmic auditory cueing improves motor function in chronic hemiparetic stroke. *Stroke* 31, 2390–2395. doi: 10.1161/01.str.31.10.2390

WHO (2014). *Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012*. Geneva: WHO.

Yoo, G. E., and Kim, S. J. (2016). Rhythmic auditory cueing in motor rehabilitation for stroke patients: systematic review and meta-analysis. *J. Music Ther.* 53, 149–177. doi: 10.1093/jmt/thw003

Zerna, C., Burley, T., Green, T. L., Dukelow, S. P., Demchuk, A. M., and Hill, M. D. (2019). Comprehensive assessment of disability post-stroke using the newly developed miFUNCTION scale. *Int. J. Stroke* 15, 167–174. doi: 10.1177/1747493019840933

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The Effect of Music Intervention on Attention in Children: Experimental Evidence

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Although music has been utilized as a therapeutic tool for children with cognitive impairments, how it improves children's cognitive function remains poorly understood. As a first step toward understanding music's effectiveness and as a means of assessing cognitive function improvement, we focused on attention, which plays an important role in cognitive development, and examined the effect of a music intervention on children's attention. Thirty-five children, aged 6 to 9 years, participated in this study, with data from 29 of the children being included in the analysis. A single 30-minute interactive music intervention was compared with a single 30-minute interactive video game intervention accompanied by computer-generated background music using a within-subjects repeated-measures design. Each intervention was implemented individually. Participants completed a standardized attention assessment, the Test of Everyday Attention for Children, before and after both interventions to assess changes in their attentional skills. The results indicated significant improvement in attention control/switching following the music intervention after controlling for the children's intellectual abilities, while no such changes were observed following the video game intervention. This study provides the first evidence that music interventions may be more effective than video game interventions to improve attention control in children, and furthers our understanding of the importance of music interventions for children with attention control problems.

Keywords: music intervention, attention, children, cognitive function, cognitive development

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INTRODUCTION

Music is a powerful sensory stimulus that produces physiological, psychological, and social effects (Hodges, 1996; Davis et al., 2008; Thaut and Hoemberg, 2014; Wheeler, 2015). The clinical application of music, when utilized in a purposeful and systematic way, reportedly enhances development in special needs children (Robb, 2003a). Although the effectiveness of music interventions on communication, social skills, and emotional development in children has been well documented, and therapeutic effects of music on cognition in adults have also been shown – for example, on episodic memory in patients with dementia (Irish et al., 2006) and traumatic brain injuries (Särkämö et al., 2008) focused attention in stroke patients (Särkämö et al., 2008) and sustained attention in adults with cognitive deficits (Gregory, 2002) evidence pertaining to music's effects on attention and other cognitive functions in children is limited, and the mechanisms by which music improves cognitive functions in children remain poorly understood.

Several studies have reported that music interventions may have a positive impact on attention. It has been proposed that music itself contains therapeutic factors that enhance attention skills; for example, rhythmic patterns drive attention focus, and musical elements such as rhythm, melody, and harmony provide multidimensional stimuli that facilitate switching attention (Gardiner, 2005; Thaut and Gardiner, 2014). The perception of rhythmic, melodic, harmonic, and dynamic patterns in music may influence the focus and organization of the flow of our attention (Thaut et al., 2008). Attention is a fundamental skill for good cognitive functioning and thus plays an important role in cognitive, social, and communication development (Muris, 2006; van de Weijer-Bergsma et al., 2008; Cornish and Wilding, 2010; Matson et al., 2010; Rueda et al., 2010; Janzen and Thaut, 2018). Several studies examining preterm infants have found that individual differences in attentional problems early in development can predict later cognitive and behavioral functioning (van de Weijer-Bergsma et al., 2008). Furthermore, attention control in school-age children is positively correlated with academic achievement (Muris, 2006; Rueda et al., 2010). Attention skills develop in a stepwise fashion from infancy through engagement with one's environment (Ruff and Rothbart, 2001; Atkinson and Braddick, 2012) exploring the external world, and orienting to, shifting between, and maintaining focus on events, objects, and tasks (van de Weijer-Bergsma et al., 2008). When the development of these basic skills is hindered, there may be adverse effects on cognitive, social, and communication skills; thus, it is important to learn more about the potential therapeutic effects of music intervention on children's attention.

Only a few mixed studies have reported on the effects of music intervention on children's attention. For instance, Wolfe and Noguchi (2009) examined the effects of music on sustained attention in 5-year-old children using vigilance tasks that required verbal and motor responses. The children listened to a musical or spoken story with or without distraction, and results indicated that the children listening to a musical story in the distraction condition performed significantly better than the children listening to a spoken story with distraction. Morton et al. (1990) investigated 10-to-12-year-old children using a verbal dichotomous listening task that was preceded by exposure to music and exposure to silence. The authors observed reduced distractibility in the children in the directed-report task and increased memory capacity in the children in the free-report task, after being exposed to music.

Other studies have investigated music therapy in children with special needs, where music is used as a therapeutic tool. For example, Lee (2006) reported a case study of a 5-year-old child with autism spectrum disorder (ASD) who showed better attention span in behavioral observations after 20 sessions. Kasuya (2011) reported a case study of an 8-year-old boy with attention deficit/hyperactive disorder (ADHD) whose attentive behaviors improved during music therapy sessions (measured with behavioral observations), and sustained attention and impulsive behaviors also improved on a continuous performance task after 24 sessions. Robb (2003b) investigated attentive behavior among six preschool children with visual impairments and found that the children's attentive behaviors were significantly more frequent during music-based sessions than during play-based sessions. Knox et al. (2003) reported that a brain injured adolescent showed improvements in alternating attention following intervention from a Musical Attention Training Program, which required participants to switch concentration between a melodic line and a drum track. Pasiali et al. (2014) examined the effectiveness of a standardized music therapy technique, Musical Attention Control Training (MACT; Thaut and Gardiner, 2014) in nine 13-to-20-year-old adolescents with varying severity of neurodevelopmental delays. The authors found positive improvements in selective attention and attention control on an attention test battery after eight group sessions. Abrahams and van Dooren (2018) also found positive trends in attention tests for children with attention deficits after six weekly MACT sessions. They pointed out, however, that the sample size was small, with only two participants in each of the experimental and control groups, and that attention outcomes varied with individual participants. Although these studies have yielded limited and mixed results regarding the effects of music interventions on children's attention, they suggest that music may have a positive impact. However, none of the previous studies evaluated the influence of music interventions on different types of attention (i.e. sustained attention, selective attention, and attention control) in multiple participants.

More recent longitudinal studies conducted in children have focused on the impact of music training on non-musical cognitive functions (Miendlarzewska and Trost, 2014; Benz et al., 2016; Dumont et al., 2017; Sala and Gobet, 2017). For example, Schellenberg (2004) found greater increases in full-scale IQ after one year of keyboard or voice lessons. Barbaroux et al. (2019) evaluated the impact of an 18-month classic music training program on the cognitive functions of children from low socio-economic backgrounds and found significant improvements in general intelligence, processing speed, concentration abilities, and reading precision. On the other hand, while Linnavalli et al. (2018) found that music playschool over the course of two school years significantly improved phoneme processing and vocabulary skills, they did not see improvements in non-verbal reasoning or inhibitory control. Yang et al. (2014) found that long-term music training significantly improved musical achievement and second language development, but there was no improvement in first language or mathematics. Nan et al. (2018) found that 6 months of piano training significantly improved auditory word discrimination compared to a reading training or a control group, however, no differences were found in general cognitive measures, including attention, which improved equally among the three groups. Although these studies have reported mixed evidence, their findings suggest that long-term music engagement intended to improve musical skills has beneficial effects on non-musical functions, including intellectual abilities.

Currently it is unknown whether music interventions designed to improve children's attention are effective. Thus, in this study we examined the effect of a short-term music intervention (i.e., a single 30-minute trial) on attention in children using a therapeutic technique, Musical Attention Control Training (Thaut and Gardiner, 2014) as a first step toward broadly investigating the effectiveness of music therapy for improving cognitive functions. To investigate the pure effect of the music intervention, we used an active control intervention with similar features as the music intervention, except with no live music. The specific aims were: (1) to investigate the effects of a music intervention on children's attention and (2) to assess whether specific subtypes of attention (i.e., sustained attention, selective attention, attention control/switching, and divided attention) are responsive to this music intervention. Although certain factors, such as intelligence and ADHD traits, may affect attentional performance (Manly et al., 2001; Imada et al., 2003; Cornish and Wilding, 2010; Hurford et al., 2017; Mous et al., 2017) no previous investigations have controlled for these influences. Thus, we investigated changes in children's attention skills (behavior measured before and after a music intervention as an experimental task and a video game intervention as a control task) using a standardized attention test, alongside the ADHD Rating Scale (ADHD-RS; Ichikawa and Tanaka, 2008) and Raven's Colored Progressive Matrices (Raven, 1998) which were administered at the start of the experiment. Our goal was to offer initial information regarding the effects of a music intervention on children's cognitive functions and to provide evidence on the feasibility of music interventions for future clinical research with children who have cognitive impairment.

MATERIALS AND METHODS

Participants

Participants were recruited through advertisements for healthy children, aged 6 to 9 years, without a history of serious neurological illness (e.g., brain injuries), as confirmed via a parental report (n = 35). The above-mentioned age range was chosen because the Test of Everyday Attention for Children (Manly et al., 1999) used in this study has been standardized and normed for children between the ages of 6 and 16. In addition, to ensure that the developmental stage of the participants' working memory and self-awareness were as similar as possible, children under 10 years of age were targeted. The sample size was determined with reference to previous studies (Schlaug et al., 2005; Tamm et al., 2010; Scott, 1992) which examined the positive impact of interventions on children's cognitive functioning. Parents contacted the first author by phone or e-mail to schedule 2 days for participation in this study. On the first day of the experiment, with their parents present, participants were interviewed by an expert child psychiatrist to identify any signs of developmental disorders. All 35 participants completed the experimental procedure, however, six participants were excluded from statistical analysis: three were excluded for possibly having developmental disabilities, as assessed by the child psychiatrist and their scores on the ADHD-RS as completed by their parents; the other three were excluded because their TEA-Ch scores were extreme outliers (more than two standard deviations). Therefore, data from 29 participants were analyzed, including five pairs of siblings. **Table 1** shows the demographic characteristics of the participants who were included in our statistical analyses.

TABLE 1 | Demographic Characteristics of the Participants (n = 29).

Male:Female	15:14	
	Mean (SD)	**Range**
Age	7.4 (1.3)	6.0 to 9.11
ADHD-RS	8 (7.7)	0 to 36
RCPM	28.3 (4.9)	19 to 35

Procedure

An experimental within-subjects repeated-measures design was used. The experimenter administered the TEA-Ch to the children prior to and after participating in an experimental task (i.e., music intervention) and a control task (i.e., video game intervention), which were conducted individually on separate days at least one week apart in a quiet office at the university.

On the first day of each experimental procedure, the participant and the participant's parent entered the office, and the experimenter verbally explained the study and provided individual written informed consent forms; all participants assented to participate and all parents consented to having their child(ren) participate by signing the consent document. Next, the parent completed the ADHD-RS while the participant was administered the RCPM by the experimenter. Then, the participant and the parent were interviewed by the child psychiatrist. After the interview, the parent left the office and the participant was administered the TEA-Ch by the experimenter and an assistant. The TEA-Ch has two parallel versions, version A (pre-test) and version B (post-test), that allow for assessing test-taker improvement; thus, version A was administered prior to a 30-minute music intervention or video game intervention and version B was administered after the intervention and a brief break (about 10 min). If the participant completed the music intervention on the first day, they completed the video game intervention on the second day, or vice versa. Intervention order was counterbalanced by alternate assignment, where half of the participants completed the music intervention first, and the other half completed the video game intervention first. On the second day, the participant was administered the TEA-Ch version A, prior to the 30-minute music or video game intervention, and version B after the intervention and a brief break. Total time required for the experiments was approximately two-and-a-half to 3 h on the first day and two to two-and-a-half hours on the second day. During test and intervention implementation, participants were videotaped with their parents' permission.

Measures

ADHD Rating Scale-IV (ADHD-RS)

The ADHD-RS, originally created by DuPaul et al. (1998) and translated into Japanese by Ichikawa and Tanaka (2008) is an 18-item scale that takes approximately 5 min to complete.

It measures ADHD symptoms according to the DSM-IV diagnostic criteria (American Psychiatric Association, 1994). Each of the 18 items is scored from 0 to 3: 0 = none (never or rarely); 1 = mild (sometimes); 2 = moderate (often); 3 = severe (very often). We used the home version, where a parent reports the frequency of symptoms over the past 6 months, and obtained the total score by summing all scores. The maximum score possible is 54 and the minimum is 0, with higher scores indicating greater severity of ADHD. We referred to this score when interviewing the participants and their parents and used it as a covariate to control for participants' ADHD traits.

Raven's Colored Progressive Matrices (RCPM)

The RCPM (Raven, 1998) is a fast and easy-to-administer test of non-verbal reasoning used to verify that participants had no intellectual disabilities. It contains 36 items in three sets to assess general intellectual development for children aged 5 to 11 years and adults. Each item presents participants with an incomplete design and six alternatives; they must choose the one that best completes the design. We obtained a total score by summing the items that were correctly answered. The maximum score is 36 and the minimum is 0, with higher scores indicating better performance. We used this score as a covariate to control for participants' intellectual abilities.

Test of Everyday Attention for Children (TEA-Ch)

The TEA-Ch was created by Manly et al. (1999) and includes nine subtests of different types of skills (e.g., sustained attention, selective attention, attention control, and ability to inhibit verbal and motor responses). This assessment, which is conducted on a one-to-one basis, has been standardized and normed for children and adolescents between the ages of 6 and 16. The assessment takes about one hour to complete; thus, we used only the first four subtests to briefly measure each attentional factor and dual task performance (Manly et al., 1999) within the allotted time to avoid fatiguing the children. The four subtests were completed in 20 to 30 min and yielded seven raw scores, which were then converted to age-scaled scores by using the appropriate normative table provided in the test manual (Manly et al., 1999). The age-scaled scores for each subtest range from 1 to 20, with 20 representing the best performance. The age-scaled scores had a mean of 10 and standard deviation of 3. The tool has two parallel versions (version A and B) to allow for test-retest. Test-retest reliability coefficients for the subtests ranged from 0.57 to 0.87.

The four subtests were (1) "Sky Search" for selective/focused attention, (2) "Score!" for sustained attention, (3) "Creature Counting" for attention control/switching, and (4) "Sky Search Dual Task" ("Sky Search DT") for sustained-divided attention.

(1) *Sky Search.* In this task, the participant is given a large sheet filled with spaceship pairs and distractor dissimilar spaceships and is asked to find and circle pairs of spaceships that are the same as quickly as possible. The second part of the task, which has no distractor items, is used as a control for motor speed differences. Scoring involves counting the number of correct pairs circled and the time taken; a test administrator records time per target by dividing the latter by the former, after which a motor control score is subtracted from the time per target score. Three scores ("accuracy," "time per target," and "attention score") are obtained to measure the child's selective/focused attention skill.
(2) *Score!* This task involves silently counting the number of shooting sounds a participant hears (ranging from 9 to 15) on a 6-minute audio track, without using fingers and with long gaps between sounds. The raw score is obtained by giving one point for each of the 10 trials counted correctly. The "accuracy" score is obtained to measure the child's sustained attention skill.
(3) *Creature Counting.* The participant counts the number of creatures in a burrow in the cue book, following a visual pathway—counting up when the arrow points up and down when it points down. Time taken and accuracy for each of the seven trials are recorded and two scores ("accuracy" and "speed") are obtained to measure the child's attention control/switching skill.
(4) *Sky Search DT.* The participant performs the subtests "Score!" and "Sky Search" at the same time, meaning they visually find spaceship pairs as quickly as possible while auditorily keeping count of shooting sounds on the audio track. Time taken is recorded, correct responses for both tasks are counted, and a dual score is calculated. The "decrement" score is obtained to measure the child's sustained-divided attention skill.

Tasks

The video game intervention was adopted as a control task administered under similar conditions as the experimental task except with no live music. Both tasks (1) involved upper extremity movement, (2) were interactive with the experimenter, and (3) were easy to play and child friendly. Furthermore, most children find both video games and musical instruments enjoyable, and both activities tend to grab children's attention. For the video game intervention, participants played a bowling video game from Nintendo Wii Sports with the experimenter, which was a straight-up, 10-pin, 10-frame game with standard rules for two players. The players took turns holding and swinging the Wii remote in one hand to roll the ball with sufficient force and aim to get a good score. Three or four sets of the game were played in 30 min.

Musical Attention Control Training (MACT; Thaut and Gardiner, 2014) was used as the experimental music intervention. The MACT involves 'structured active or receptive musical exercises involving precomposed performance or improvisation in which musical elements cue different musical responses to practice attention functions' (Thaut and Gardiner, 2014 p. 257). In this study, the participant played percussion instruments with the experimenter who sang, played a keyboard, or played percussion. During the first 10 min, the experimenter held a hand drum in each hand, facing the participant, who held a mallet in each hand, and asked the participant to hit the drums held up alternately by the experimenter with the left and right hand, as the experimenter sang a simple, original "Let's play the drum" song. In the next 10 min, the participant played three kinds of percussion instruments (congas, cymbal, and

Remo Tubano) as follows: (1) played them freely while the experimenter played the keyboard; (2) played an appropriate one as the experimenter played high, middle, or low range on the keyboard, following instructions (e.g., asked to play the cymbal when hearing high notes); and (3) played by matching how the experimenter played on the keyboard (e.g., played loudly when the experimenter played loudly and stopped playing when the experimenter stopped). In the last 10 min, the experimenter and participant faced each other and imitated each other's rhythmic patterns while taking turns on the same percussion instruments set between them. These activities implemented in the music intervention were designed according to our participants' ages to easily produce rhythmic responses against a clear, steady beat (Thaut and Gardiner, 2014).

Data Analysis

After excluding 6 of 35 participants (as described previously), data from the remaining 29 participants were analyzed using IBM SPSS Statistics, version 24.0. Mean TEA-Ch scores under each condition were calculated for each participant. First, seven raw scores were converted to age-scaled scores by using the appropriate normative table from the test manual (Manly et al., 1999). Thus, raw data were transformed to a normal distribution, effectively removing the influence of age (Manly et al., 2001) this was done to examine whether attentional performance, including selective/focused attention, sustained attention, attention control/switching, and sustained-divided attention were influenced by the music or video game interventions. Since the four attentional performance subtests do not equally contribute to the scoring, we investigated whether attentional performance was modulated by the music or video game interventions under selective/focused attention, sustained attention, attention control/switching, and sustained-divided attention, separately. Thus:

(1) In "Sky Search," we examined "accuracy" (subscore 1; s1) "time per target" (subscore 2; s2) and "attention score" (subscore 3; s3) during selective/focused attention to assess whether attentional performance was modulated by the music or video game interventions. Score differences were analyzed using a repeated-measures analysis of variance (ANOVA) with Task (music, game), Time (pre, post), and TEA-Ch Score (s1, s2, s3) as within-participant factors.
(2) In "Score!," we examined "accuracy" (subscore 4; s4) during sustained attention to assess whether attentional performance was modulated by the music or video game interventions. Score differences were analyzed using a repeated-measures ANOVA with Task (music, game), Time (pre, post), and TEA-Ch Score (s4) as within-participant factors.
(3) In "Creature Counting," we examined "accuracy" (subscore 5; s5) and "speed" (subscore 6; s6) during attention control/switching to assess whether attentional performance was modulated by the music or video game interventions. Score differences were analyzed using a repeated-measures ANOVA with Task (music, game), Time (pre, post), and TEA-Ch Score (s5, s6) as within-participant factors.
(4) In "Sky Search DT," we examined "decrement" (subscore 7; s7) during sustained-divided attention to assess whether attentional performance was modulated by the music or video game interventions. Score differences were analyzed using a repeated-measures ANOVA with Task (music, game), Time (pre, post), and TEA-Ch Score (s7) as within-participant factors.

If an interaction was significant, a follow-up simple main effect analysis (i.e., assessing the effect of each independent variable at each level of the other independent variable) was conducted to interpret the result ($p < 0.05$, uncorrected for multiple tests).

Finally, to avoid the influence of individual characteristics, including participants' intellectual abilities and ADHD traits during selective/focused attention, sustained attention, attention control/switching, and sustained-divided attention, score differences were analyzed using repeated-measures analysis of covariance (ANCOVA) with Task (music, game), Time (pre, post), and TEA-Ch Score (e.g., s1, s2, s3) as within-participant factors, and participant RCPM scores, ADHD-RS scores, and RCPM scores × ADHD-RS scores as covariates.

Additionally, we examined whether attentional performance differences were influenced by task order. The results indicated that attentional performance was not modulated by task order during selective/focused attention, sustained attention, attention control/switching, or sustained-divided attention (see **Supplementary Material**).

RESULTS

Table 2 shows the averaged pre and post age-scaled scores for each of the seven subscores (s1–s7) from the four TEA-Ch subtests. **Table 3** shows the difference in Time condition between pre and post during music and video game intervention.

Sky Search Accuracy, Time per Target, and Attention Score

ANOVAs

We conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s1, s2, s3) repeated-measures ANOVA (**Figure 1** and **Table 3**). Significant main effects were detected for TEA-Ch Score [$F(1,28) = 10.906$, $p < 0.001$, partial $\eta^2 = 0.447$] among 11.56, 12.741, and 12.026, and Time [$F(1,28) = 15.321$, $p = 0.001$, partial $\eta^2 = 0.354$] with scores from pre (11.609) and post (12.609), but not for Task [$F(1,28) = 0.001$, $p = 0.979$, partial $\eta^2 < 0.001$] with scores from pre (12.115) and post (12.103). The results thus indicated that selective/focused attention was facilitated by the music and video game interventions.

ANCOVAs

We used participants' RCPM score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s1, s2, s3) repeated-measures ANCOVA (**Table 3**). Significant main effect was detected for TEA-Ch Score [$F(1,27) = 0.23$,

TABLE 2 | Mean Scores for Each Subtest of TEA-Ch at Pre/Post Using Age-Scaled Scores.

TEA-Ch subscores		Music intervention (*n* = 29)		Video game intervention (*n* = 29)	
		Mean (SD)			
		Pre	Post	Pre	Post
Selective/focused attention					
s1	Sky Search Accuracy	11.4 (2.4)	12.1 (2.6)	11.3 (2.5)	11.4 (3.1)
s2	Sky Search Time per Target	12.0 (3.1)	13.3 (2.6)	12.1 (3.1)	13.6 (2.6)
s3	Sky Search Attention Score	11.3 (3.1)	12.6 (2.7)	11.6 (3.5)	12.7 (3.1)
Sustained attention					
s4	Score! Accuracy	10.6 (3.8)	10.6 (3.0)	10.1 (3.2)	9.4 (3.9)
Attention control/switching					
s5	Creature Counting Accuracy	12.0 (2.9)	12.9 (2.7)	11.2 (3.3)	12.2 (3.1)
s6	Creature Counting Speed	10.4 (3.7)	11.8 (2.6)	11.0 (3.5)	11.7 (3.3)
Sustained-divided attention					
s7	Sky Search DT Decrement	8.0 (3.7)	9.3 (3.7)	8.5 (4.2)	8.8 (3.7)

TABLE 3 | Difference in Time condition between pre- and post-test during the music and video game interventions.

TEA-Ch subscores		Music intervention (*n* = 29)				Video game intervention (*n* = 29)			
		p-value of ANOVA	*p*-value of ANCOVA			*p*-value of ANOVA	*p*-value of ANCOVA		
			RCPM	ADHD-RS	RCPM + ADHD-RS		RCPM	ADHD-RS	RCPM + ADHD-RS
Selective/focused attention									
s1	Sky Search Accuracy	0.001**	0.131	0.008**	0.01*	0.001**	0.131	0.007**	0.006**
s2	Sky Search Time per Target	0.001**	0.131	0.008**	0.01*	0.001**	0.131	0.007**	0.006**
s3	Sky Search Attention Score	0.001**	0.131	0.008**	0.01*	0.001**	0.131	0.007**	0.006**
Sustained attention									
s4	Score! Accuracy	0.514	0.646	0.956	0.892	0.514	0.646	0.956	0.892
Attention control/switching									
s5	Creature Counting Accuracy	< 0.001***	0.128	0.011*	0.011*	< 0.001***	0.797	0.011*	0.011*
s6	Creature Counting Speed	< 0.001***	0.003**	0.011*	0.011*	< 0.001***	0.797	0.011*	0.011*
Sustained-divided attention									
s7	Sky Search DT Decrement	0.194	0.086	0.379	0.35	0.194	0.086	0.379	0.35

*In this study, we applied ANOVA and ANCOVA using participants' RCPM score, ADHD-RS score, and RCPM × ADHD-RS scores as covariates. Significant differences between pre- and post-test were found in both the music and video game interventions. Notably, the intervention effects were modulated by participants' IQ traits; specifically, when controlling for RCPM score, "Creature Counting Speed" was facilitated by the music intervention but not by the video game intervention during attention control/switching. ***p < 0.001; **p < 0.01; *p < 0.05.*

$p = 0.796$, partial $\eta^2 = 0.017$]. No significant main effects were detected for Task [$F(1,27) = 0.236$, $p = 0.631$, partial $\eta^2 = 0.009$] or Time [$F(1,27) = 2.422$, $p = 0.131$, partial $\eta^2 = 0.082$], and no significant interaction effects were detected for Task × RCPM [$F(1,27) = 0.247$, $p = 0.624$, partial $\eta^2 = 0.009$], Time × RCPM [$F(1,27) = 0.846$, $p = 0.366$, partial $\eta^2 = 0.03$], TEA-Ch × RCPM [$F(1,27) = 0.388$, $p = 0.682$, partial $\eta^2 = 0.029$], Task × Time × RCPM [$F(1,27) = 0.092$, $p = 0.764$, partial $\eta^2 = 0.003$], Task × TEA-Ch × RCPM [$F(1,27) = 0.158$, $p = 0.855$, partial $\eta^2 = 0.012$], Time × TEA-Ch × RCPM [$F(1,27) = 0.297$, $p = 0.746$, partial $\eta^2 = 0.022$], or Task × Time × TEA-Ch × RCPM [$F(1,27) = 1.327$, $p = 0.283$, partial $\eta^2 = 0.093$]. The results thus indicated that, when controlling for IQ traits, selective/focused attention was not modulated by the music or video game interventions.

Moreover, we used participants' ADHD-RS score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s1, s2, s3) repeated-measures ANCOVA (**Table 3**). Although no significant main effect was detected for Task [$F(1,27) = 2.082$, $p = 0.161$, partial $\eta^2 = 0.072$] and no significant interaction effects were detected for Task × ADHD-RS [$F(1,27) = 3.727$, $p = 0.064$, partial $\eta^2 = 0.121$], Time × ADHD-RS [$F(1,27) = 0.616$, $p = 0.439$, partial $\eta^2 = 0.022$], TEA-Ch × ADHD-RS [$F(1,27) = 0.178$, $p = 0.838834$, partial $\eta^2 = 0.013$], Task × TEA-Ch × ADHD-RS [$F(1,27) = 1.288$, $p = 0.293$, partial $\eta^2 = 0.09$], Time × TEA-Ch × ADHD-RS [$F(1,27) = 0.025$, $p = 0.976$, partial $\eta^2 = 0.002$], or Task × Time × TEA-Ch × ADHD-RS [$F(1,27) = 0.565$, $p = 0.575$, partial $\eta^2 = 0.042$], a significant interaction effect was detected for Task × Time × ADHD-RS [$F(1,27) = 7.229$, $p = 0.012$, partial $\eta^2 = 0.211$].

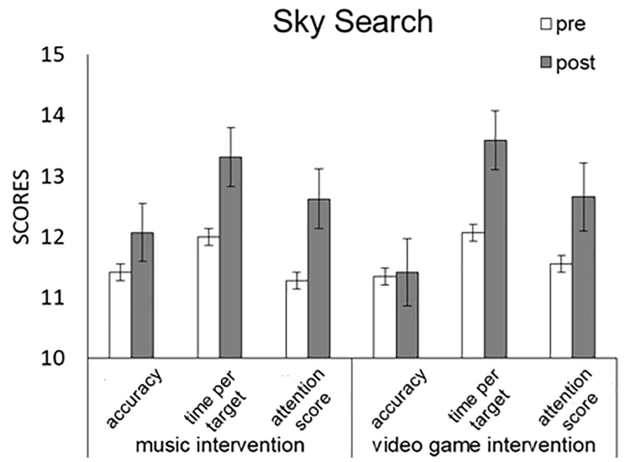

FIGURE 1 | Comparison of mean (with SE) attention score of TEA-Ch between pre and post music and video game interventions in "Sky Search." Error bars represent standard errors.

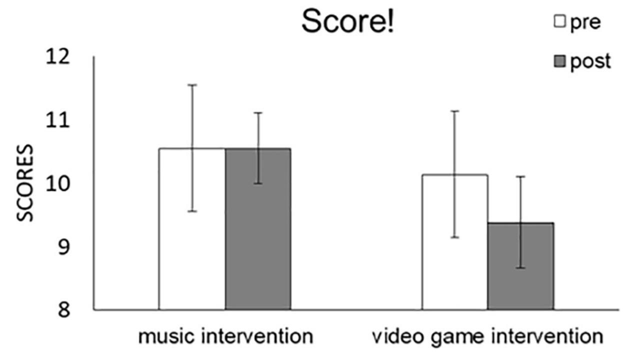

FIGURE 2 | Comparison of mean (with SE) attention score of TEA-Ch between pre and post music and video game interventions in 'Score!'. Error bars represent standard errors.

A *post hoc* test showed that, when controlling for the ADHD-RS score, selective/focused attention was facilitated by the music intervention (p = 0.008) with scores from pre (11.563) and post (12.667) and by the video game intervention (p = 0.007) with scores from pre (11.655) and post (12.552). The results showed that, when controlling for ADHD traits, "accuracy," "time per target," and "attention score" were facilitated by the music and video game interventions during selective/focused attention.

Finally, we used participants' RCPM score × ADHD-RS score as covariates, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s1, s2, s3) repeated-measures ANCOVA (**Table 3**). Although no significant main effect was detected for Task [F(1,27) = 2.016, p = 0.167, partial η^2 = 0.069] and no significant interaction effects were detected for Task × RCPM × ADHD-RS [F(1,27) = 3.689, p = 0.065, partial η^2 = 0.12], Time × RCPM × ADHD-RS [F(1,27) = 0.36, p = 0.553, partial η^2 = 0.013], TEA-Ch × RCPM × ADHD-RS [F(1,27) = 0.077, p = 0.926, partial η^2 = 0.006], Task × TEA-Ch × RCPM × ADHD-RS [F(1,27) = 0.112, p = 0.341, partial η^2 = 0.079], Time × TEA-Ch × RCPM × ADHD-RS [F(1,27) = 0.032, p = 0.969, partial η^2 = 0.002], or Task × Time × TEA-Ch × RCPM × ADHD-RS [F(1,27) = 1.036, p = 0.369, partial η^2 = 0.074], significant main effects were detected for TEA-Ch Score [F(1,27) = 4.968, p = 0.015, partial η^2 = 0.277] and Time [F(1,27) = 4.876, p = 0.036, partial η^2 = 0.153] and a significant interaction effect was detected for Task × Time × RCPM × ADHD-RS [F(1,27) = 6.371, p = 0.018, partial η^2 = 0.191].

A *post hoc* test showed that, when controlling for IQ and ADHD traits (RCPM and ADHD scores), selective/focused attention was facilitated by the music intervention (p = 0.01) with scores from pre (11.567) and post (12.655) and the video game intervention (p = 0.006) with scores from pre (11.631) and post (12.536). The results showed that, when simultaneously controlling for IQ and ADHD traits, "accuracy," "time per target," and "attention score" were facilitated by the music and video game interventions during selective/focused attention.

Score! Accuracy

ANOVAs

We conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s4) repeated-measures ANOVA (**Figure 2** and **Table 3**). No significant main effects were detected for Task [F(1,28) = 3.119, p = 0.088, partial η^2 = 0.1] with scores from pre (10.552) and post (9.759) or Time [F(1,28) = 0.438, p = 0.514, partial η^2 = 0.015] with scores from pre (10.345) and post (9.966). Moreover, no significant interaction effect was detected for Task × Time [F(1,28) = 0.921, p = 0.345, partial η^2 = 0.032]. The results thus indicated that sustained attention was not modulated by the music or video game interventions.

ANCOVAs

We used participants' RCPM score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s4) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [F(1,27) = 0.163, p = 0.689, partial η^2 = 0.006] or Time [F(1,27) = 0.215, p = 0.646, partial η^2 = 0.008], and no significant interaction effects were detected for Task × RCPM [F(1,27) = 0.014, p = 0.908, partial η^2 = 0.001], Time × RCPM [F(1,27) = 0.337, p = 0.566, partial η^2 = 0.012], or Task × Time × RCPM [F(1,27) = 0.96, p = 0.336, partial η^2 = 0.034]. The results thus indicated that, when controlling for IQ traits, sustained attention was not modulated by the music or video game interventions.

Moreover, we used participants' ADHD-RS score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s4) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [F(1,27) = 0.1582, p = 0.219, partial η^2 = 0.055] or Time [F(1,27) = 0.003, p = 0.956, partial η^2 < 0.001], and no significant interaction effects were detected for Task × ADHD-RS [F(1,27) = 0.014, p = 0.907, partial η^2 = 0.001], Time × ADHD-RS [F(1,27) = 0.272, p = 0.606, partial η^2 = 0.01], or Task × Time × ADHD-RS [F(1,27) = 0.153, p = 0.699, partial

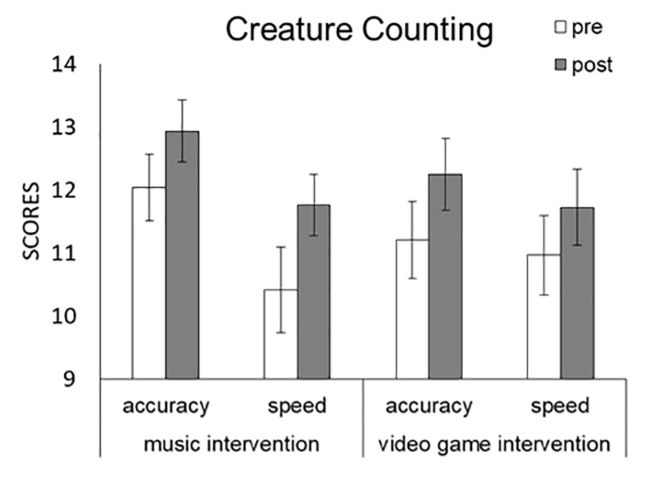

FIGURE 3 | Comparison of mean (with SE) attention score of TEA-Ch between pre and post music and video game interventions in "Creature Counting." Error bars represent standard errors.

$\eta^2 = 0.006$]. The results indicated that, when controlling for ADHD traits, sustained attention was not modulated by the music or video game interventions.

Finally, we used participants' RCPM score × ADHD-RS score as covariates, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s4) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [$F(1,27) = 1.861$, $p = 0.184$, partial $\eta^2 = 0.064$] or Time [$F(1,27) = 0.019$, $p = 0.892$, partial $\eta^2 = 0.001$], and no significant interaction effects were detected for Task × RCPM × ADHD-RS [$F(1,27) = 0.059$, $p = 0.811$, partial $\eta^2 = 0.002$], Time × RCPM × ADHD-RS [$F(1,27) = 0.179$, $p = 0.676$, partial $\eta^2 = 0.007$], or Task × Time × RCPM × ADHD-RS [$F(1,27) = 0.151$, $p = 0.701$, partial $\eta^2 = 0.006$]. The results indicated that, when simultaneously controlling for IQ and ADHD traits, sustained attention was not modulated by the music or video game interventions.

Creature Counting Accuracy and Speed

ANOVAs

We conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANOVA (**Figure 3** and **Table 3**). A significant main effect was detected for Time [$F(1,28) = 20.429$, $p < 0.001$, partial $\eta^2 = 0.422$] with pre (11.155) and post (12.164) scores, but no significant main effects were detected for Task [$F(1,28) = 0.308$, $p = 0.583$, partial $\eta^2 = 0.011$] with pre (11.784) and post (11.534) scores or TEA-Ch [$F(1,28) = 2.071$, $p = 0.161$, partial $\eta^2 = 0.069$] with pre (12.103) and post (11.216) scores. The results indicated that attention control/switching was facilitated by the music and video game interventions.

However, no significant interaction effects were detected for Task × Time [$F(1,28) = 0.169$, $p = 0.684$, partial $\eta^2 = 0.006$], Task × TEA-Ch [$F(1,28) = 2.355$, $p = 0.136$, partial $\eta^2 = 0.078$], Time × TEA-Ch [$F(1,28) = 0.029$, $p = 0.867$, partial $\eta^2 = 0.001$], or Task × Time × TEA-Ch [$F(1,28) = 0.789$, $p = 0.382$, partial $\eta^2 = 0.027$].

ANCOVAs

We used participants' RCPM score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANCOVA (**Table 3**). Although no significant main effects were detected for Task [$F(1,27) = 0.248$, $p = 0.623$, partial $\eta^2 = 0.009$] or Time [$F(1,27) = 0.429$, $p = 0.518$, partial $\eta^2 = 0.016$], and no significant interaction effects were detected for Task × RCPM [$F(1,27) = 0.357$, $p = 0.555$, partial $\eta^2 = 0.013$], Time × RCPM [$F(1,27) = 0.007$, $p = 0.933$, partial $\eta^2 < 0.001$], Task × Time × RCPM [$F(1,27) = 0.727$, $p = 0.401$, partial $\eta^2 = 0.026$], Task × TEA-Ch × RCPM [$F(1,27) = 0.486$, $p = 0.492$, partial $\eta^2 = 0.018$], or Time × TEA-Ch × RCPM [$F(1,27) = 0.518$, $p = 0.478$, partial $\eta^2 = 0.019$], a significant main effect was detected for TEA-Ch Score [$F(1,27) = 5.241$, $p = 0.03$, partial $\eta^2 = 0.163$] and significant interaction effects were detected for TEA-Ch × RCPM [$F(1,27) = 4.265$, $p = 0.049$, partial $\eta^2 = 0.136$] and Task × Time × TEA-Ch × RCPM [$F(1,27) = 8.47$, $p = 0.007$, partial $\eta^2 = 0.239$].

In the music intervention condition, we used participants' RCPM score as a covariate, and conducted a Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANCOVA. A significant main effect was detected for TEA-Ch Score [$F(1,27) = 7.184$, $p = 0.012$, partial $\eta^2 = 0.21$] and significant interaction effects were detected for TEA-Ch × RCPM [$F(1,28) = 5.457$, $p = 0.027$, partial $\eta^2 = 0.168$] and Task × TEA-Ch × RCPM [$F(1,28) = 4.812$, $p = 0.037$, partial $\eta^2 = 0.151$]. No significant main effect was detected for Time [$F(1,27) = 5.457$, $p = 0.23$, partial $\eta^2 = 0.053$], and no significant interaction effects were detected for TEA-Ch × RCPM [$F(1,28) = 5.457$, $p = 0.027$, partial $\eta^2 = 0.168$] or Time × RCPM [$F(1,28) = 0.439$, $p = 0.513$, partial $\eta^2 = 0.016$]. A *post hoc* test showed that, when controlling for IQ traits (RCPM score), "speed" ($p = 0.003$), with scores from pre (12.034) and post (12.931) ($p = 0.128$), but not "accuracy" ($p = 0.081$), with scores from pre (10.414) and post (11.759) ($p = 0.128$), was facilitated by the music intervention during attention control/switching. The results indicated that, when controlling for IQ traits, "speed" was facilitated by the music intervention during attention control/switching.

In the video game intervention condition, we used participants' RCPM score as a covariate, and conducted a Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANCOVA. No significant main effects were detected for Time [$F(1,27) = 0.068$, $p = 0.797$, partial $\eta^2 = 0.002$] or TEA-Ch Score [$F(1,27) = 1.985$, $p = 0.17$, partial $\eta^2 = 0.068$], and no significant interaction effects were detected for Time × RCPM [$F(1,28) = 0.43$, $p = 0.518$, partial $\eta^2 = 0.016$], TEA-Ch × RCPM [$F(1,28) = 1.798$, $p = 0.191$, partial $\eta^2 = 0.062$], or Time × TEA-Ch × RCPM [$F(1,28) = 1.261$, $p = 0.271$, partial $\eta^2 = 0.045$]. The results indicated that "accuracy" and "speed" were not facilitated by the video game intervention during attention control/switching.

We used participants' ADHD-RS score as a covariate and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANCOVA (**Table 3**).

A significant main effect was detected for Time [$F(1,27) = 7.53$, $p = 0.011$, partial $\eta^2 = 0.218$). No significant main effects were detected for Task (F (1, 27) = 1.693, $p = 0.204$, partial $\eta^2 = 0.059$] or TEA-Ch Score [$F(1,27) = 1.858$, $p = 0.184$, partial $\eta^2 = 0.064$], and no significant interaction effects were detected for Task × ADHD-RS [$F(1,27) = 1.564$, $p = 0.222$, partial $\eta^2 = 0.055$], Time × ADHD-RS [$F(1,27) = 0.123$, $p = 0.729$, partial $\eta^2 = 0.005$], TEA-Ch × ADHD-RS [$F(1,27) = 0.3$, $p = 0.589$, partial $\eta^2 = 0.011$], Task × Time × ADHD-RS [$F(1,27) = 0.407$, $p = 0.529$, partial $\eta^2 = 0.015$], Task × TEA-Ch × ADHD-RS [$F(1,27) = 0.816$, $p = 0.374$, partial $\eta^2 = 0.029$], Time × TEA-Ch × ADHD-RS [$F(1,27) < 0.001$, $p = 0.991$, partial $\eta^2 < 0.001$], or Task × Time × TEA-Ch × ADHD-RS [$F(1,27) = 1.135$, $p = 0.296$, partial $\eta^2 = 0.04$]. The results indicated that, when controlling for ADHD traits, "accuracy" and "speed" were not modulated by the music and video game interventions during attention control/switching.

We used participants' RCPM score × ADHD-RS score as covariates, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s5, s6) repeated-measures ANCOVA (**Table 3**). A significant main effect was detected for Time [$F(1,27) = 7.364$, $p = 0.011$, partial $\eta^2 = 0.214$]. No significant main effects were detected for Task [$F(1,27) = 1.573$, $p = 0.221$, partial $\eta^2 = 0.055$] or TEA-Ch Score [$F(1,27) = 2.252$, $p = 0.145$, partial $\eta^2 = 0.077$], and no significant interaction effects were detected for Task × RCPM × ADHD-RS [$F(1,27) = 1.428$, $p = 0.242$, partial $\eta^2 = 0.05$], Time × RCPM × ADHD-RS [$F(1,27) = 0.209$, $p = 0.651$, partial $\eta^2 = 0.008$], TEA-Ch × RCPM × ADHD-RS [$F(1,27) = 0.517$, $p = 0.478$, partial $\eta^2 = 0.019$], Task × Time × RCPM × ADHD-RS [$F(1,27) = 0.28$, $p = 0.601$, partial $\eta^2 = 0.01$], Task × TEA-Ch × RCPM × ADHD-RS [$F(1,27) = 0.556$, $p = 0.462$, partial $\eta^2 = 0.02$], Time × TEA-Ch × RCPM × ADHD-RS [$F(1,27) = 0.013$, $p = 0.911$, partial $\eta^2 < 0.001$], or Task × Time × TEA-Ch × RCPM × ADHD-RS [$F(1,27) = 0.279$, $p = 0.601$, partial $\eta^2 = 0.01$]. The results indicated that, when simultaneously controlling for IQ and ADHD traits, "accuracy" and "speed" were not modulated by the music and video game interventions during attention control/switching.

Sky Search DT Decrement

ANOVAs

We conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s7) repeated-measures ANOVA (**Figure 4** and **Table 3**). No significant main effects were detected for Task [$F(1,28) = 0.001$, $p = 0.977$, partial $\eta^2 < 0.001$] with pre (8.655) and post (8.638) scores or Time [$F(1,28) = 1.772$, $p = 0.194$, partial $\eta^2 = 0.06$] with pre (8.276) and post (9.017) scores. Moreover, no significant interaction effect was detected for Task × Time [$F(1,28) = 1.331$, $p = 0.258$, partial $\eta^2 = 0.045$]. The results indicated that sustained-divided attention was not modulated by the music or video game interventions.

ANCOVAs

We used participants' RCPM score as a covariate and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s7) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [$F(1,27) = 0.062$, $p = 0.805$, partial $\eta^2 = 0.002$] or Time [$F(1,27) = 3.166$, $p = 0.086$, partial $\eta^2 = 0.105$], and no significant interaction effects were detected for Task × RCPM [$F(1,27) = 0.066$, $p = 0.799$, partial $\eta^2 = 0.002$], Time × RCPM [$F(1,27) = 2.477$, $p = 0.127$, partial $\eta^2 = 0.084$], or Task × Time × RCPM [$F(1,27) = 0.527$, $p = 0.474$, partial $\eta^2 = 0.019$]. The results indicated that, when controlling for IQ traits, sustained-divided attention was not modulated by the music or video game interventions.

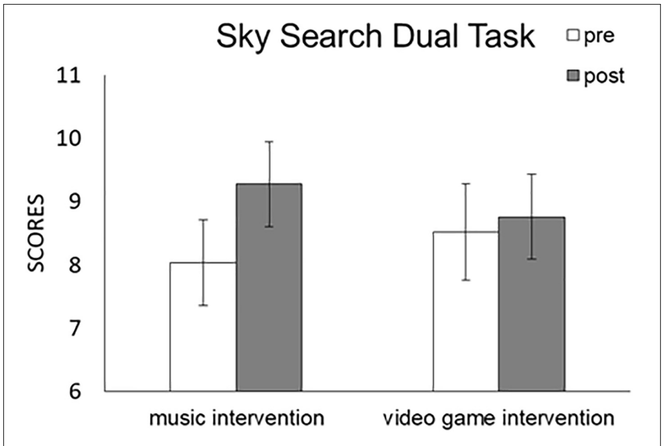

FIGURE 4 | Comparison of mean (with SE) attention score of TEA-Ch between pre and post music and video game interventions in "Sky Search DT." Error bars represent standard errors.

Moreover, we used participants' ADHD-RS score as a covariate, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s7) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [$F(1,27) = 0.093$, $p = 0.763$, partial $\eta^2 = 0.003$] or Time [$F(1,27) = 0.799$, $p = 0.379$, partial $\eta^2 = 0.029$], and no significant interaction effects were detected for Task × ADHD-RS [$F(1,27) = 0.192$, $p = 0.664$, partial $\eta^2 = 0.007$], Time × ADHD-RS [$F(1,27) < 0.001$, $p = 0.988$, partial $\eta^2 < 0.001$], or Task × Time × ADHD-RS [$F(1,27) = 0.005$, $p = 0.943$, partial $\eta^2 < 0.001$]. The results indicated that, when controlling for ADHD traits, sustained-divided attention was not modulated by the music or video game interventions.

Finally, we used participants' RCPM score × ADHD-RS score as covariates, and conducted a Task (music, game) × Time (pre, post) × TEA-Ch Score (s7) repeated-measures ANCOVA (**Table 3**). No significant main effects were detected for Task [$F(1,27) = 0.165$, $p = 0.688$, partial $\eta^2 = 0.006$] or Time [$F(1,27) = 0.903$, $p = 0.35$, partial $\eta^2 = 0.032$], and no significant interaction effects were detected for Task × RCPM × ADHD-RS [$F(1,27) = 0.339$, $p = 0.565$, partial $\eta^2 = 0.012$], Time × RCPM × ADHD-RS [$F(1,27) = 0.006$, $p = 0.939$, partial $\eta^2 < 0.001$], or Task × Time × RCPM × ADHD-RS [$F(1,27) = 0.028$, $p = 0.869$, partial $\eta^2 = 0.001$]. These results indicated that, when simultaneously controlling for IQ and ADHD traits, sustained-divided attention was not modulated by the music or video game interventions.

DISCUSSION

The present study examined the effect of a music intervention on healthy children's attention, using a standardized attention test battery. In the music intervention, we found an enhanced effect on the response speed of attention control/switching when participants' IQ traits were controlled, compared to the video game intervention. On selective/focused attention, results showed that both music and video game interventions yielded significant improvement, however, the effects disappeared when controlling for participants' IQ traits. These findings indicate that IQ traits influence attentional performance (Manly et al., 2001; Hurford et al., 2017) and extend our knowledge by demonstrating that IQ traits also influence intervention effects. Notably, there were no effects found for sustained attention and sustained-divided attention under either the music or video game interventions. This is the first study to investigate different types of attention with multiple participants.

Our results show that the music intervention significantly improved children's attention control/switching compared to the video game intervention, even when controlling for IQ traits. However, when controlling for ADHD traits, the effects disappeared. This may be because ADHD-RS and this subtest of the TEA-Ch reflect common elements of attention. Our finding that the music intervention improved children's attention control substantiates the previous findings of Pasiali et al. (2014) and Knox et al. (2003) who found positive changes in adolescents with neurodevelopmental delays and brain injury using small sample sizes.

In the present study's music intervention, participants were asked to play percussion instruments following and/or matching the experimenter's singing or keyboard playing. During the music intervention, participants found it necessary to switch their attention auditorily and visually between the experimenter's singing or playing and their own playing while following the tempo, rhythm, and listening to the melody provided by the experimenter (Thaut and Gardiner, 2014; Gfeller, 2008). Attention control is defined as 'the ability to exert effortful control in order to inhibit a dominant response, to hold in working memory newly relevant rules that require the suppression or activation of previously learned responses, and to shift attention between tasks' (Cornish and Wilding, 2010, p. 372). When participants played three kinds of percussion instruments to music, they needed to shift their attention to play the instruments while following musical cues from the experimenter. The musical cues were multi-layered and changed randomly; thus, throughout the activity, participants needed to rapidly shift their attention back and forth to the rhythm to play along to the beats, to the pitch to change their instrument, and to the volume to change their loudness. That is, it was not adequate to just pay attention to what they were playing on their own instruments; they also needed to change how they played, depending on the pitch, volume, and tempo of the music that was produced by the experimenter and to determine when to start/stop–all of which changed over time.

Active music listening to play along could have required attention control, as participants frequently switched back and forth from each musical element (Lipscomb, 1996). It also required the participants to hold these instructions in working memory; specifically, how to play along while following the musical cues and when to pause playing when the music stopped, which were possibly new rules for them. In sum, referring to the concept of attention control, active participation in the music intervention, while interacting with the experimenter, required participants to: (1) exert effortful control to inhibit steady continuous performance and follow and respond to musical cues that were changing over time; (2) hold in working memory new instructions on how to respond that were possibly different from their previous music experience, which allowed them to simply play along; and (3) shift their attention rapidly between the experimenter/keyboard and their instruments (Thaut and Gardiner, 2014; Lipscomb, 1996; Gfeller, 2008). The music used in this study was structured with multiple elements that included both verticality (simultaneity) and horizontality (sequentiality) at the same time (Thaut, 2005) which may have enhanced participants' attention control. In conjunction with these possible factors, the unpredictability of the music intervention may be another factor to consider in our results. That is, in the music intervention, participants had to adapt to music stimuli that were provided by the experimenter to respond appropriately over time in the temporal structure. Thus, compared to the video game intervention, in which participants responded to relatively constant requirements and took turns doing so, the music intervention was more unpredictable. The constantly changing nature of the music, including the varied elements, could have impacted attention control. Thus, these components of music may positively influence participants' attention control; hence, music appears to be a suitable tool for attention control training.

When controlling for IQ traits, the significant intervention effects on the selective attention subtest scores disappeared. The general view is that children with higher IQs score better, and in this case, the children with higher IQs found the targets faster and more accurately. In fact, different searching strategies were observed in participants during test taking. For example, some children darted impulsively from one part of the test sheet to another and others looked systematically through the sheet columns one at a time to find the targets. This may indicate that these differing strategies are influenced by IQ and may affect this subtest score. In other words, this attention subtype may involve IQ factors that the RCPM measures, with some factors influencing attentional performance, depending on the attention subtypes.

With the subtests that measured sustained and divided attention, no significant improvements were found across the music and video game interventions. Regarding sustained attention, our finding is contrary to those of previous studies (Robb, 2003b; Lee, 2006; Wolfe and Noguchi, 2009; Kasuya, 2011). Two possible factors should be considered. First, some studies (Robb, 2003b; Lee, 2006; Wolfe and Noguchi, 2009) investigated participants' sustained attention during one or more music interventions or conditions, meaning that it is unclear whether the effects can be generalized to other tasks, like attention tests, although children exert higher sustained attention in musical environments. Another possibility is the frequency and period of intervention administration. More specifically Kasuya (2011) observed improvements on a computer-based attention test after 24 sessions across 11 months. In contrast, our finding is based on a single, short intervention. Pasiali et al. (2014) also did not observe changes in sustained attention after eight interventions across 6 weeks. This suggests that longer and more frequent interventions may be necessary to improve children's sustained attention. It is likely that the interventions we employed did not activate the divided attention subtype.

Data obtained from the various attentional tasks suggest the possibility of cross-modal effects of music intervention on attention. That is, the attention control/switching subtest ("Creature Counting"), which required visual attention, improved participants' performance after the music intervention. The performance on selective attention subtest ("Sky Search") improved significantly after both interventions and also required visual attention. However, no significant improvement was found in the auditory sustained attention subtest ('Score!') nor in the auditory and visual sustained-divided attention subtest ("Sky Search DT"), following the music intervention, which is inconsistent with previous findings (Degé et al., 2011; Strait and Kraus, 2011). Music interventions likely require more auditory attention, although both interventions required visual attention as well; therefore, our findings did not support our hypothesis that a music intervention would improve auditory attention more than a video game intervention. Nevertheless, our results suggest that attention is not a modality-specific function. Furthermore, because of the multimodality of instrumental music activity (Pantev et al., 2009) even with the low complexity of playing instruments in our study, music interventions with instruments have yielded cross-modal effects (Janzen and Thaut, 2018). However, some previous studies have reported no significant effects of music instrument lessons on visual attention (Strait et al., 2010; Roden et al., 2014) thus, further studies are needed to examine potential cross-modal effects of a simple music activity, especially since previous studies that reviewed the influence of long-term musical training reported that benefits may be restricted to the auditory domain (Roden et al., 2014; Martens et al., 2015).

The emotional and motivational factors associated with music are often addressed when considering the influence of music on children's cognitive function (Thaut and Gardiner, 2014; Gfeller, 2008). Research findings indicate that these factors help children focus and facilitate learning (Abikoff et al., 1996; Geist and Geist, 2008, 2012; Xu et al., 2010). However, our results suggest that this outcome may be related to both motivational and engaging factors of music and the music components, since the control intervention employed in this study was also motivational for children and contained engaging factors. This result suggests that the music itself, with its components described above, contains factors that enhance attention control in children, since the video game intervention was also fun and child friendly, with an adequate attentional requirement. Observations revealed that the competing scores obtained on each bowling turn with the experimenter were motivational for participants and elicited positive emotions. During the 30-minute intervention, participants seemed to concentrate on the video game intervention as well as they did in the music intervention. Previous studies that have found effects of music on attention in typical children (Morton et al., 1990; Wolfe and Noguchi, 2009) compared music conditions to speech or quiet conditions, which are control conditions that may be less motivational and engaging for children than the video game used here. Thus, the results of the present study may reflect the intrinsic features of the music intervention more than the impact of emotional and motivational factors on attention control.

Previous studies show that longitudinal music training influences at least some non-musical functioning in children (Yang et al., 2014; Linnavalli et al., 2018; Nan et al., 2018; Barbaroux et al., 2019; Fasano et al., 2019; Schellenberg, 2004) however, findings on the enhancing effects on cognitive functions in children have been inconsistent. One factor that has contributed to this inconsistency may be differences in musical content (Dumont et al., 2017) which varies greatly between the studies, from general music programs for young children (Linnavalli et al., 2018) to intense instrumental music lessons (Nan et al., 2018). If the participants' musical content differs, both musical and non-musical skills and the brain regions and networks used during music engagement likely differ, leading to different results in measured cognitive functions. The present study examined the effects of a short-term music intervention designed for attention training and set a similar non-music intervention as an active control task, with results that contradicted those of some previous studies on music training (Scott, 1992; Rickard et al., 2010; Degé et al., 2011; Roden et al., 2014). For instance, our music intervention resulted in significant improvement in attention control compared to the non-musical intervention. It is possible that differences in musical content may underlie the inconsistencies between the present study results and those of previous studies that focused on music training to learn music and/or instrumental performance skills.

Computerized programs developed specifically for attention training (Tucha et al., 2011; Rueda et al., 2012; Kirk et al., 2016; Spaniol et al., 2018) and Attention Process Training programs adapted for children (Kerns et al., 1999; Tamm et al., 2013) have been extensively studied. In computerized programs, children play games to train various attention skills. However, while studies on computerized programs have shown promising effects on children's attention, they have yielded mixed findings by attention subtypes, targeted populations, and participants' ages (Tucha et al., 2011; Rueda et al., 2012; Kirk et al., 2016). Our study shows that interactive music intervention improves attention control/switching when controlling for participants' IQ traits compared to the active control intervention, but no previous studies on computerized programs have reported similar effects. The intrinsic features of music interventions, such as their highly social aspects (Davis et al., 2008; Wheeler, 2015) may have influenced our results. Behaviors resulting from poor attention skills can cause problems, mostly in social situations such as in the classroom or in educational conversations (DuPaul et al., 1998) thus, interactive music interventions may be beneficial for some children with attentional difficulties. Some researchers have recommended that attention rehabilitation should involve an intervenient to monitor progress, give feedback, and teach strategies (Gardiner, 2005) arguing that stand-alone use of computers may not be appropriate for some children who need attention rehabilitation (Cicerone et al., 2000; Weber, 1990). Given that previous findings are inconsistent regarding attention subtypes, targeted populations and ages, and the intervention's frequency and duration, future research should investigate which programs benefit specific attention subtypes and children's functional attention skills to develop evidence-based practices.

This study has a few limitations. First, we targeted 6-to-9-year-old children, whose neuroplasticity would have been relatively high in relation to the overall age range of the TEA-Ch (i.e., 6 to 16 years). Thus, the children's age may have influenced the results. Second, we caution the reader against generalizing our results, because this study investigated immediate and short-term effects of an individual music intervention on attention skills using a neuropsychological test. It is possible that our results were affected by changes in arousal state, since we administered the retest immediately after the intervention. Since our results represent a first step toward uncovering the short-term effects of a music intervention on typically developing children, further longitudinal studies of attention-targeted music interventions are needed to verify that music positively impacts non-musical attentive behaviors. Future studies should follow the child's progress on attentional performance and examine whether intervention effects are generalizable to attentional performance in the real world for both typically developing children and children with attentional deficits.

It is also necessary to examine the transfer effects of music interventions beyond the scope of this study to discover whether attention-targeted music interventions influence other functions beyond attention, compared to non-music interventions. Since attention skills underlie higher cognitive functions and could possibly affect overall child development, future studies should examine whether attention control improvements driven by music intervention, as found in the present study, have a long-term influence on other cognitive functions, such as general intelligence and executive function. For those with attentional deficits, especially individuals with ADHD and ASD, who are often observed to have attention control difficulties (Fan, 2013; Townsend et al., 1996; Allen and Courchesne, 2001; Goldstein et al., 2001; Rinehart et al., 2001; Landry and Bryson, 2004; Zwaigenbaum et al., 2005; Cornish and Wilding, 2010) we need to investigate whether the effects of music interventions influence their core symptoms. Given that children with ASD have shown improvements in social communication following interventions to improve attention (Matson et al., 2010; Kerns et al., 2017) transfer effects of music intervention to other domains (i.e., social and communication domains) should also be investigated. Children with ADHD, who potentially have core deficits with tracking the beat of music (Puyjarinet et al., 2017) may benefit from music interventions with rhythm-based activities, such as employed in the present study, over background music intervention (Maloy and Perterson, 2014) because children who can synchronize to rhythm display better attentive behaviors (Khalil et al., 2013). An intervention with simple and easy-to-follow musical activities, like those used in this study, should be feasible to implement for children with cognitive impairments and/or developmental disorders (Pasiali et al., 2014; Abrahams and van Dooren, 2018). These possibilities will be the focus of future studies in music interventions.

Although the study by Rueda et al. (2005) showed that attention network development is subject to interventions during childhood, results from widely implemented attention training programs (e.g., computerized training) have been inconsistent. Our results, coupled with a limited number of previous studies with small sample sizes, show that music interventions may have positive impacts on children's and adolescents' attention. Currently, there is no gold standard for attention training and the best and most effective approaches may differ, depending on the child's age, diagnosis, and severity of the attention deficit. Additionally, in future studies of attention, we recommend that researchers uncover details of participants' past experiences with the research tasks, since familiarity may influence the outcomes. It is possible that the level of attention and cognitive load may be different for a first-time activity than for an experienced activity.

Finally, another limitation should be noted: implementing music interventions with children requires many competencies, such as musical and teaching skills, and the ability to interact, be motivating, and build good relationships. Given that we only implemented a one-time music intervention, it is likely that there were no effects from the intervener-child relationship, however, the intervener's competence may also have influenced our study results (Standley, 2000). Thus, in future studies, it will be necessary to investigate whether intervener factors (e.g., years of experience and education history) influence intervention effects.

CONCLUSION

Our findings indicate that a music intervention has short-term effects on children's attention control. This is the first evidence showing that an interactive intervention with live music in which a child plays accessible instruments may benefit attention control. Our results suggest that music intervention may be a promising tool to train attention control in children by eliciting underlying induced oscillatory activity associated with attentional ability and neuroplasticity (Trainor et al., 2009; Thaut and Gardiner, 2014). Given that previous studies have reported similar neurological observations following long-term musical engagement (Schlaug et al., 2005, 2009; Hyde et al., 2009) neuroimaging studies are needed to examine the effects of music on brain activity and to deepen our understanding of how music improves children's cognitive function. Our findings not only provide evidence for the effectiveness of music intervention, they also provide clues toward understanding its neural mechanisms.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Kyoto University Graduate School of Medicine in accordance with the Declaration of Helsinki (approval number: E1856), and all methods were implemented in accordance with relevant guidelines and regulations. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YK-U and MT developed the study methods and design. YK-U collected the data, conducted the experiment, and wrote the manuscript. MT interviewed the participants and their parents. SZ performed the statistical analyses. All authors contributed to the manuscript preparation.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2020.00757/full#supplementary-material

REFERENCES

Abikoff, H., Courtney, M. E., Szeibel, P. J., and Koplewicz, H. S. (1996). The effects of auditory stimulation on the arithmetic performance of children with ADHD and nondisabled children. *J. Learn. Disabil.* 29, 238–246. doi: 10.1177/002221949602900302

Abrahams, T. P., and van Dooren, J. C. (2018). Music attention control training (MACT) in secure residential youth care: a randomised controlled pilot study. *Arts Psychother.* 57, 80–87. doi: 10.1016/j.aip.2017.10.008

Allen, G., and Courchesne, E. (2001). Attention function and dysfunction in autism. *Front. Biosci.* 6, d105–d119. doi: 10.2741/allen

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Publishing.

Atkinson, J., and Braddick, O. (2012). Visual attention in the first years: typical development and developmental disorders. *Dev. Med. Child Neurol.* 54, 589–595. doi: 10.1111/j.1469-8749.2012.04294.x

Barbaroux, M., Kittinger, E., and Besson, M. (2019). Music training with Démos program positively influences cognitive functions in children from low socio-economic backgrounds. *PLoS One* 14:e0216874. doi: 10.1371/journal.pone.0216874

Benz, S., Sellaro, R., Hommel, B., and Colzato, L. S. (2016). Music makes the world go round: the impact of musical training on non-musical cognitive functions – A review. *Front. Psychol.* 6:2023. doi: 10.3389/fpsyg.2015.02023

Cicerone, K. D., Dahlberg, C., Kalmar, K., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., et al. (2000). Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Arch. Phys. Med. Rehabil.* 81, 1596–1615. doi: 10.1053/apmr.2000.19240

Cornish, K., and Wilding, J. M. (2010). *Attention, Genes, and Developmental Disorders*. Oxford: Oxford University Press.

Davis, W. B., Gfeller, K. E., and Thaut, M. H. (2008). *An Introduction to Music Therapy: Theory and Practice*. Silver Spring, MD: American Music Therapy Association.

Degé, F., Wehrum, S., Stark, R., and Schwarzer, G. (2011). The influence of two years of school music training in secondary school on visual and auditory memory. *Eur. J. Dev. Psychol.* 8, 608–623. doi: 10.1080/17405629.2011.590668

Dumont, E., Syurina, E. V., Feron, F. J. M., and van Hooren, S. (2017). Music interventions and child development: a critical review and further directions. *Front. Psychol.* 8:1694. doi: 10.3389/fpsyg.2017.01694

DuPaul, G. J., Power, T. J., Anastopoulos, A. D., and Reid, R. (1998). *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. London: Guilford Press.

Fan, J. (2013). "Attentional network deficits in autism spectrum disorders," in *Neuroscience of Autism Spectrum Disorders*, eds J. D. Buxbaum and P. R. Hof (Amsterdam: The Elsevier), 281–288. doi: 10.1016/b978-0-12-391924-3.00019-3

Fasano, M. C., Semeraro, C., Cassibba, R., Kringelbach, M. L., Monacis, L., de Palo, V., et al. (2019). Short-term orchestral music training modulates hyperactivity and inhibitory control in school-age children: a longitudinal behavioural study. *Front. Psychol.* 10:750. doi: 10.3389/fpsyg.2019.00750

Gardiner, J. C. (2005). "Neurologic music therapy in cognitive rehabilitation," in *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications*, ed. M. H. Thaut (London: Routledge), 179–201.

Geist, K., and Geist, E. A. (2008). Do re mi, 1-2-3: that's how easy math can be-using music to support emergent mathematics. *Young Child.* 63, 20–25.

Geist, K., and Geist, E. A. (2012). Bridging music neuroscience evidence to music therapy best practice in the early childhood classroom: implications for using rhythm to increase attention and learning. *Music Ther. Perspect.* 30, 141–144. doi: 10.1093/mtp/30.2.141

Gfeller, K. E. (2008). "Music: a human phenomenon and therapeutic tool," in *An Introduction to Music Therapy: Theory and Practice*, 3rd Edn, eds W. B. Davis, K. E. Gfeller, and M. H. Thaut (Silver Spring, MD: American Music Therapy Association), 41–75.

Goldstein, G., Johnson, C. R., and Minshew, N. J. (2001). Attentional processes in autism. *J. Autism Dev. Disord.* 31, 433–440. doi: 10.1023/A:1010620820786

Gregory, D. (2002). Music listening for maintaining attention of older adults with cognitive impairments. *J. Music Ther.* 39, 244–264. doi: 10.1093/jmt/39.4.244

Hodges, D. A. (1996). *Handbook of Music Psychology*, 2nd Edn. San Antonio, TX: IMR Press.

Hurford, D. P., Fender, A. C., Boux, J. L., Swigart, C. C., Boydston, P. S., Butts, S. R., et al. (2017). Examination of the effects of intelligence on the test of variables of attention for elementary students. *J. Attent. Disord.* 21, 929–937. doi: 10.1177/1087054714550480

Hyde, K., Lerch, J., Norton, A., Forgeard, M., Winner, E., Evans, A. C., et al. (2009). The effects of musical training on structural brain development: a longitudinal study. *Ann. N. Y. Acad. Sci.* 1169, 182–186. doi: 10.1111/j.1749-6632.2009.04852.x

Ichikawa, H., and Tanaka, Y. (2008). *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. Tokyo: Akashi Shoten.

Imada, R., Komatsu, S., and Takahashi, T. (2003). Attentional functions: development of a group-administered test battery for children. *Jpn. J. Educ. Psychol.* 51, 22–32. doi: 10.5926/jjep1953.51.1_22

Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., et al. (2006). Investigating the enhancing effect of music on autobiographical memory in mild Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 22, 108–120. doi: 10.1159/000093487

Janzen, T. B., and Thaut, M. H. (2018). Rethinking the role of music in the neurodevelopment of autism spectrum disorder. *Music Sci.* 1, 1–18. doi: 10.1177/2059204318769639

Kasuya, Y. (2011). Musical attention control training influences on sustained attention of a child with ADHD in a continuous performance test. *Paper Presented at the 18th Shinshu Hoiku Gakkai Annual Conference*, Okayama.

Kerns, K. A., Eso, K., and Thomson, J. (1999). Investigation of a direct intervention for improving attention in young children with ADHD. *Dev. Neuropsychol.* 16, 273–295. doi: 10.1207/S15326942DN1602_9

Kerns, K. A., Macoun, S., MacSween, J., Pei, J., and Hutchison, M. (2017). Attention and working memory training: a feasibility study in children with neurodevelopmental disorders. *Appl. Neuropsychol. Child* 6, 120–137. doi: 10.1080/21622965.2015.1109513

Khalil, A. K., Minces, V., McLoughlin, G., and Chiba, A. (2013). Group rhythmic synchrony and attention in children. *Front. Psychol.* 4:564. doi: 10.3389/fpsyg.2013.00564

Kirk, H. E., Gray, K. M., Ellis, K., Taffe, J., and Cornish, K. M. (2016). Computerised attention training for children with intellectual and developmental disabilities: a randomised controlled trial. *J. Child Psychol. Psychiatry* 57, 1380–1389. doi: 10.1111/jcpp.12615

Knox, R., Yokota-Adachi, H., Kershner, J., and Jutai, J. (2003). Musical attention training program and alternating attention in brain injury: an initial report. *Music Ther. Perspect.* 21, 99–104. doi: 10.1093/mtp/21.2.99

Landry, R., and Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *J. Child Psychol. Psychiatry* 45, 1115–1122. doi: 10.1111/j.1469-7610.2004.00304.x

Lee, L. (2006). Music therapy enhances attention span and promotes language ability in young special needs children. *Paper Presented at the Commission Seminar in Kuala Lumpur, Malaysia, and the Special Session at the 27th ISME World Conference*, Kuala Lumpur.

Linnavalli, T., Putkinen, V., Lipsanen, J., Huotilainen, M., and Tervaniemi, M. (2018). Music playschool enhances children's linguistic skills. *Sci. Rep.* 8:8767. doi: 10.1038/s41598-018-27126-5

Lipscomb, S. D. (1996). "The cognitive organization of musical sound," in *Handbook of Music Psychology*, 2nd Edn, ed. D. A. Hodges (San Antonio, TX: IMR Press), 150–151.

Maloy, M., and Perterson, R. (2014). A meta-analysis of the effectiveness of music interventions for children and adolescents with attention-deficit/hyperactivity disorder. *Psychomusicol. Music Mind Brain* 24, 328–339. doi: 10.1037/pmu0000083

Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P., and Robertson, I. H. (2001). The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *J. Child Psychol. Psychiatry* 42, 1065–1081. doi: 10.1111/1469-7610.00806

Manly, T., Robertson, I. H., Anderson, V., and Mimmo-Smith, I. (1999). *Test of Everyday Attention for Children*. London: Pearson Assessment.

Martens, S., Wierda, S. M., Dun, M., de Vries, M., and Smid, H. (2015). Musical minds: attentional blink reveals modality-specific restrictions. *J. Vis.* 15:1233. doi: 10.1167/15.12.1233

Matson, J. L., Worley, J. A., Neal, D., Mahan, S., and Fodstad, J. C. (2010). The effects of inattention/impulsivity and ASD symptom severity on social skills in toddlers. *Dev. Neurorehab.* 13, 408–412. doi: 10.3109/17518423.2010.510819

Miendlarzewska, E., and Trost, W. (2014). How musical training affects cognitive development: rhythm, reward and other modulating variables. *Front. Neurosci.* 7:279. doi: 10.3389/fnins.2013.00279

Morton, L. L., Kershner, J. R., and Siegel, L. S. (1990). The potential for therapeutic applications of music on problems related to memory and attention. *J. Music Ther.* 27, 195–208. doi: 10.1093/jmt/27.4.195

Mous, S. E., Schoemaker, N. K., Blanken, L. M. E., Thijssen, S., van der Ende, J., Polderman, T. J. C., et al. (2017). The association of gender, age, and intelligence with neuropsychological functioning in young typically developing children: the generation R study. *Appl. Neuropsychol. Child* 6, 22–40. doi: 10.1080/21622965.2015.1067214

Muris, P. (2006). Relation of attention control and school performance in normal children. *Percept. Mot. Skills* 102, 78–80. doi: 10.2466/pms.102.1.78-80

Nan, Y., Liu, L., Geiser, E., Shu, H., Gong, C. C., Dong, Q., et al. (2018). Piano training enhances the neural processing of pitch and improves speech perception in Mandarin-speaking children. *Proc. Natl. Acad. Sci. U.S.A.* 115, E6630–E6639. doi: 10.1073/pnas.1808412115

Pantev, C., Lappe, C., Herholz, S. C., and Trainor, L. (2009). Auditory-somatosensory integration and cortical plasticity in musical training. *Ann. N. Y. Acad. Sci.* 1169, 143–150. doi: 10.1111/j.1749-6632.2009.04588.x

Pasiali, V., LaGasse, A. B., and Penn, S. L. (2014). The effect of musical attention control training (MACT) on attention skills of adolescents with neurodevelopmental delays: a pilot study. *J. Music Ther.* 51, 333–354. doi: 10.1093/jmt/thu030

Puyjarinet, F., Bégel, V., Lopez, R., Dellacherie, D., and Dalla Bella, S. (2017). Children and adults with Attention-Deficit/Hyperactivity Disorder cannot move to the beat. *Sci. Rep.* 7:11550. doi: 10.1038/s41598-017-11295-w

Raven, J. C. (1998). *Progressive Matrices Couleur/Colored Progressive Matrices*. Paris: Centre de Psychologie Appliquée.

Rickard, N. S., Vasquez, J. T., Murphy, F., Gill, A., and Toukhsati, S. R. (2010). Benefits of a classroom based instrumental music program on verbal memory of primary school children: a longitudinal study. *Aust. J. Music Educ.* 1, 36–47.

Rinehart, N. J., Bradshaw, J. L., Moss, S. A., Brereton, A. V., and Tonge, B. J. (2001). A deficit in shifting attention present in high-functioning autism but not Asperger's disorder. *Autism* 5, 67–80. doi: 10.1177/1362361301005001007

Robb, S. L. (2003a). *Music Therapy in Pediatric Healthcare*. Silver Spring, MD: American Music Therapy Association.

Robb, S. L. (2003b). Music interventions and group participation skills of preschoolers with visual impairments: raising questions about music, arousal, and attention. *J. Music Ther.* 40, 266–282. doi: 10.1093/jmt/40.4.266

Roden, I., Könen, T., Bongard, S., Frankenberg, E., Friedrich, E. K., and Kreutz, G. (2014). Effects of music training on attention, processing speed and cognitive music abilities: findings from a longitudinal study. *Appl. Cogn. Psychol.* 28, 545–557. doi: 10.1002/acp.3034

Rueda, M. R., Checa, P., and Combita, L. M. (2012). Enhanced efficiency of the executive attention network after training in preschool children: immediate changes and effects after two months. *Dev. Cogn. Neurosci.* 2, S192–S204. doi: 10.1016/j.dcn.2011.09.004

Rueda, M. R., Checa, P., and Rothbart, M. K. (2010). Contributions of attentional control to socioemotional and academic development. *Early Educ. Dev.* 21, 744–764. doi: 10.1080/10409289.2010.510055

Rueda, M. R., Rothbart, M. K., McCandliss, B. D., Saccomanno, L., and Posner, M. I. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proc. Natl. Acad. Sci. U.S.A.* 102, 14931–14936. doi: 10.1073/pnas.0506897102

Ruff, H. A., and Rothbart, M. K. (2001). *Attention in Early Development: Themes and Variations*. Oxford: Oxford University Press.

Sala, G., and Gobet, F. (2017). When the music's over. Does music skill transfer to children's and young adolescents' cognitive and academic skills? A meta-analysis. *Educ. Res. Rev.* 20, 55–67. doi: 10.1016/j.edurev.2016.11.005

Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., et al. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain* 131, 866–876. doi: 10.1093/brain/awn013

Schellenberg, E. G. (2004). Music lessons enhance IQ. *Psychol. Sci.* 15, 511–514. doi: 10.1111/j.0956-7976.2004.00711.x

Schlaug, G., Forgeard, M., Zhu, L., Norton, A., and Winner, E. (2009). Training-induced neuroplasticity in young children. *Ann. N. Y. Acad. Sci.* 1169, 205–208. doi: 10.1111/j.1749-6632.2009.04842.x

Schlaug, G., Norton, A., Overy, K., and Winner, E. (2005). Effects of music training on the child's brain and cognitive development. *Ann. N. Y. Acad. Sci.* 1060, 219–230. doi: 10.1196/annals.1360.015

Scott, L. (1992). Attention and perseverance behaviours of preschool children enrolled in Suzuki violin lessons and other activities. *J. Res. Music Educ.* 40, 225–235. doi: 10.2307/3345684

Spaniol, M. M., Shalev, L., Kossyvaki, L., and Mevorach, C. (2018). Attention training in autism as a potential approach to improving academic performance: a school-based pilot study. *J. Autism Dev. Disord.* 48, 592–610. doi: 10.1007/s10803-017-3371-2

Standley, J. (2000). "Music research in medical/dental treatment: an update of a prior meta-analysis," in *Effectiveness of Music Therapy Procedures: Documentation of Research and Clinical Practice*, 3rd Edn, ed. D. Smith (Silver Spring, MD: American Music Therapy Association), 1–64.

Strait, D., and Kraus, N. (2011). Playing music for a smarter ear: cognitive, perceptual and neurobiological evidence. *Music Percept.* 29, 133–146. doi: 10.1525/mp.2011.29.2.133

Strait, D. L., Kraus, N., Parbery-Clark, A., and Ashley, R. (2010). Musical experience shapes top-down auditory mechanisms: evidence from masking and auditory attention performance. *Hear. Res.* 261, 22–29. doi: 10.1016/j.heares.2009.12.021

Tamm, L., Epstein, J. N., Peugh, J. L., Nakonezny, P. A., and Hughes, C. W. (2013). Preliminary data suggesting the efficacy of attention training for school-aged children with ADHD. *Dev. Cogn. Neurosci.* 4, 16–28. doi: 10.1016/j.dcn.2012.11.004

Tamm, L., Hughes, C., Ames, L., Pickering, J., Silver, C. H., Castillo, C. L., et al. (2010). Attention training for school-aged children with ADHD: results of an open trial. *J. Atten. Disord.* 14, 86–94. doi: 10.1177/1087054709347446

Thaut, M. (2005). *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications*. London: Routledge.

Thaut, M. H., and Gardiner, J. C. (2014). "Musical attention control training," in *Handbook of Neurologic Music Therapy*, eds M. H. Thaut and V. Hoemberg (Oxford: Oxford University Press), 257–269.

Thaut, M. H., and Hoemberg, V. (2014). *Handbook of Neurologic Music Therapy*. Oxford: Oxford University Press.

Thaut, M. H., Thaut, C., and LaGasse, B. (2008). "Music therapy in neurologic rehabilitation," in *An Introduction to Music Therapy: Theory and Practice*, 3rd Edn, eds W. B. Davis, K. E. Gfeller, and M. H. Thaut (Silver Spring, MD: American Music Therapy Association), 261–304.

Townsend, J., Courchesen, E., and Egaas, B. (1996). Slowed orienting of covert visual-spatial attention in autism: specific deficits associated with cerebellar and parietal abnormality. *Dev. Psychopathol.* 8, 563–584. doi: 10.1017/S0954579400007276

Trainor, L. J., Shahin, A. J., and Roberts, L. E. (2009). Understanding the benefits of musical training: effects on oscillatory brain activity. *Ann. N. Y. Acad. Sci.* 1169, 133–142. doi: 10.1111/j.1749-6632.2009.04589.x

Tucha, O., Tucha, L., Kaumann, G., König, S., Lange, K. M., Stasik, D., et al. (2011). Training of attention functions in children with attention deficit hyperactivity disorder. *Atten. Defic. Hyperact. Disord.* 3, 271–283.

van de Weijer-Bergsma, E., Wijnroks, L., and Jongmans, M. J. (2008). Attention development in infants and preschool children born preterm: a review. *Infant Behav. Dev.* 31, 333–351. doi: 10.1016/j.infbeh.2007.12.003

Weber, A. M. (1990). A practical clinical approach to understanding and treating attentional problems. *J. Head Trauma Rehabil.* 5, 73–85. doi: 10.1097/00001199-199003000-00012

Wheeler, B. L. (2015). *Music Therapy Handbook*. New York, NY: Guilford Publications.

Wolfe, D. E., and Noguchi, L. K. (2009). The use of music with young children to improve sustained attention during a vigilance task in the presence of auditory distractions. *J. Music Ther.* 46, 69–82. doi: 10.1093/jmt/46.1.69

Xu, M., Huang, X., Lu, Y., Ku, X., Tang, Y., and Lu, P. (2010). Explorative analysis on the effects of pictures and music on the attention and emotion in autistic children. *Chin. Ment. Health J.* 24, 696–699.

Yang, H., Ma, W., Gong, D., Hu, J., and Yao, D. (2014). A longitudinal study on children's music training experience and academic development. *Sci. Rep.* 4:5854. doi: 10.1038/srep05854

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., and Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *Int. J. Dev. Neurosci.* 23, 143–152. doi: 10.1016/j.ijdevneu.2004.05.001

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An Initial Investigation of the Responsiveness of Temporal Gait Asymmetry to Rhythmic Auditory Stimulation and the Relationship to Rhythm Ability Following Stroke

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Temporal gait asymmetry (TGA) is a persistent post-stroke gait deficit. Compared to conventional gait training techniques, rhythmic auditory stimulation (RAS; i.e., walking to a metronome) has demonstrated positive effects on post-stroke TGA. Responsiveness of TGA to RAS may be related to several factors including motor impairment, time post-stroke, and individual rhythm abilities. The purpose of this study was to investigate the relationship between rhythm abilities and responsiveness of TGA when walking to RAS. Assessed using behavioral tests of beat perception and production, participants with post-stroke TGA (measured as single limb support time ratio) were categorized according to rhythm ability (as strong or weak beat perceivers/producers). We assessed change in TGA between walking without cues (baseline) and walking while synchronizing footsteps with metronome cues. Most individuals with stroke were able to maintain or improve TGA with a single session of RAS. Within-group analyses revealed a difference between strong and weak rhythm ability groups. Strong beat perceivers and producers showed significant reduction (improvement) in TGA with the metronome. Those with weak ability did not and exhibited high variability in the TGA response to metronome. Moreover, individuals who worsened in TGA when walking to metronome had poorer beat production scores than those who did not change in TGA. However, no interaction between TGA improvement when walking to metronome and rhythm perception or production ability was found. While responsiveness of TGA to RAS did not significantly differ based on strength of rhythm abilities, these preliminary findings highlight rhythm ability as a potential consideration when treating post-stroke individuals with rhythm-based treatments.

Keywords: stroke, gait, asymmetry, rhythm, auditory stimulation

INTRODUCTION

Temporal gait asymmetry (TGA; a phase inequality between the legs during gait) is a persistent issue following stroke. Exhibited by more than half of individuals with stroke (1, 2), TGA appears resistant to improvement during inpatient rehabilitation (3). This resistance to improvement is more likely a lack of training specificity for symmetry than an incapability of change (4). Improving symmetry of gait is important because persistent TGA is associated with balance control deficiencies (5), bone density loss (6), joint pain and degeneration (7), and inefficient locomotion (8). Moreover, there is evidence that TGA may worsen over time (9, 10). Therefore, development of new interventions that target TGA are needed and will depend on a clear understanding of the underlying mechanisms (11). However, the stroke-related factors contributing to TGA are not yet fully understood. TGA is associated with motor impairment (1), but degree of motor recovery does not fully explain TGA. Some individuals with good motor recovery and an ability to walk quickly still walk asymmetrically (1), therefore the unilateral expression of motor deficits following stroke is not necessarily the sole cause of an asymmetric walking pattern. Thus, it is important to investigate other potential contributing factors.

TGA can be characterized as having impaired locomotor rhythm, opposed to healthy gait, which features regular, reciprocal movements with an inherent rhythm. Interestingly, injury to the posterolateral putamen, a structure of the basal ganglia, was 60–80% more common in individuals with stroke who have TGA than those who walk symmetrically (12). Activity in the basal ganglia is also associated with perception of a regular beat (13), thus providing a potential neuroanatomical link between rhythm processing in the brain and temporal gait dysfunction. In other words, impairment of rhythm processing after a stroke involving the basal ganglia or structures sending/receiving information to the basal ganglia may inhibit individuals from producing movements that follow a regular and steady pattern.

Work by Patterson et al. (14) investigated this potential mechanism of post-stroke TGA by characterizing and describing the relationship of rhythm abilities to post-stroke clinical presentation. Rhythm abilities include the ability to perceive a beat in an auditory stimulus, such as music, and the ability to produce regular rhythmic movements such as tapping to the beat in music. The researchers found worse rhythm perception ability in those with stroke compared to healthy adults, and demonstrated that rhythm production ability was associated with TGA independently from motor impairment and time since stroke onset (14). This was an important first step in describing the association between rhythm ability and TGA post-stroke. However, it is unknown if rhythm ability is related to how well an individual responds to rhythmic auditory stimulation (RAS) gait training.

RAS, which involves walking to a rhythmic cue delivered by a metronome or music, elicits improvements to gait parameters such as velocity, step length, and symmetry (15). Landmark studies of RAS treatment in the stroke population demonstrated that after 3–6 weeks of training, significantly better outcomes were achieved with RAS compared to gait training following NDT and Bobath principles (16, 17). Moreover, a recent systematic review and meta-analysis of 10 randomized controlled trials found large effect sizes (Hedge's g range 0.456–0.984) for gait velocity, cadence, stride length, and Fugl-Meyer scores in favor of RAS treatments (18). The effect of RAS on gait symmetry was not assessed in the meta-analysis due to the lack of reporting of symmetry parameters in all but two studies. It is important to note that reported improvements to symmetry are modest compared to the improvements observed in other gait parameters (16, 17). Interestingly, participants with stroke were able to improve temporal symmetry when instructed to match their paretic leg footfall in time with a metronome (19). However, no improvement was found when participants were instructed to match their non-paretic footfall in time with the metronome (19).

Given the promise of RAS for improved outcomes for certain gait parameters (i.e., speed, stride length), it is worthwhile to investigate the apparent weaker response of TGA to RAS and the factors that may influence how gait responds to RAS. Rhythm ability is likely an important consideration when using gait interventions such as RAS. There is widespread connectivity between auditory and motor systems permitting a link between rhythmic auditory cues and motor responses known as entrainment (20, 21). This process is a key feature of RAS; thus, we may expect differential gait responses from individuals related to their ability to process rhythmic auditory cues. In fact, young healthy adults with weak beat perception walk slower and decrease their step length when walking to RAS, compared to individuals who have strong beat perception (22). Moreover, individuals with weak ability had significantly larger step-to-beat deviation times than individuals with strong ability (22). The authors postulated that the attentional demands associated with synchronizing steps to the cue are greater for those with weak beat perception causing the shorter strides and slower gait, thus negatively affecting responsiveness to RAS (22).

Given the identified relationships between rhythm ability and gait performance in both stroke and healthy populations, the following study investigated the relationship between rhythm ability and the responsiveness of TGA to RAS in people with stroke. Primarily, this study determined how post-stroke TGA changed between uncued walking to walking with auditory cues in a single session of RAS and compared change in TGA across groups of individuals with either strong or weak rhythm abilities. Secondarily, the study compared how well strong and weak rhythm ability groups synchronized their steps to the beat of RAS. It was hypothesized that the individuals with strong rhythm ability would improve TGA with auditory cueing to a greater degree than those with weak rhythm ability. Moreover, we expected to observe better synchronization of steps to the beat (smaller step-to-beat deviation times) in those with strong rhythm ability compared to those with weak ability.

METHODS

This study was a sub-study of a larger study approved by the Research Ethics Board of the University Health Network, Toronto, Ontario (REB# 15-9523).

Participants

Participants were recruited from the local community. Inclusion criteria included: first occurrence of stroke, the ability to walk 10 m without assistance from a device or therapist and exhibits TGA during self-paced over-ground walking measured with a pressure sensitive mat and calculated as single limb support time symmetry ratio (SR) (using left and right single limb support times with the larger value in the numerator). The threshold for temporally symmetric gait is SR = 1.06 (9). Thus, participants exhibiting a baseline self-selected pace SR > 1.06 were included in this study. Exclusion criteria were moderate or severe hearing loss as measured by audiometry, and other health conditions or injuries that affect gait (e.g., Parkinson's disease).

Procedure

The study was completed in one visit to the Toronto Rehabilitation Institute. Once informed consent was provided, and hearing was successfully screened through audiometry, study procedures commenced. All study procedures, including clinical outcome testing, took ∼3 h to complete.

Behavioral Rhythm Testing

Beat perception and production ability was assessed using separate test components of the Beat Alignment Test [BAT; (23)] delivered by computer using E-prime software[a]. Musical clips used in both components were contemporary Western music, and each clip lasted approximately 15 s. Participants were provided practice trials of each test. After the practice trials, the study investigator asked the participant if they understood the test, and if necessary, clarified any uncertainties before proceeding to the test trials.

Beat perception

For each trial, the musical clip was overlaid with a series of tones. The participant responded yes or no to the question "are the tones on the beat of the music?" Seventeen experimental trials were completed. Beat perception was quantified as accuracy and was calculated as the percentage of correct responses for 17 trials.

Beat production

For each trial, the participant was instructed to find the beat of the musical clip and, once found, tap the computer keyboard spacebar (with the unaffected hand) to the beat until the clip ends. Participants completed 13 experimental trials. Beat production was quantified offline, as degree of asynchrony, using a custom E-prime program[a]. The custom program matches the participant's tap times to the nearest beat time in the music and calculates the absolute value of the difference between the times in milliseconds. Asynchrony is calculated as the mean of the absolute differences across the 13 trials. Thus, more accurate beat production is represented by lower asynchrony times.

Classification by Rhythm Abilities and Study Groups

Participants' perceptual and production abilities were classified separately. First, each participant was classified as a strong or weak beat perceiver based on their accuracy score (strong = 9 of 17 correct responses or more; weak = 8 of 17 correct responses or fewer). Second, strong vs. weak beat producers were determined by classifying them with respect to the median asynchrony score for the current study group. Participants were classified as a strong producer if their asynchrony score was below the median (less asynchrony) or weak producers if it was above the median.

Therefore, all participants were separated into strong and weak perception and production groups separately. This means, for example, that an individual participant could be allocated to the strong beat perceiver group and the weak beat producer group based on the scores of the individual rhythm tests.

Gait Analysis

Baseline spatiotemporal parameters of gait were assessed using Zeno Walkway pressure-sensitive mat (490 × 90 × 0.4 cm) and Protokinetics analysis software[b]. The mat has a sensor resolution of 1.27 cm collecting at a sample rate of 120 Hz. Participants walked across the mat at their comfortable walking speed until a minimum of 18 footfalls were captured to ensure reliable measurement (24). This means a trial was 2–4 passes of the walkway, depending on each participant's stride length. Participants began and ended each pass 2 m off the mat in order to collect steady state gait. Once 18 footfalls were achieved the individual would finish the pass and the trial would end.

RAS Experimental Procedure

After the baseline gait analysis was performed, participants were exposed to the songs to be used for some of the synchronized walking trials. Then participants completed 12 experimental walk trials consisting of nine synchronization trials [three metronome trials and six music trials (three trials each of two different songs)] and three dual task trials, which involved backward spelling during the walk. The music was Western contemporary songs created for research purposes (different from the BAT test songs). The 12 trials were presented in random order to each participant. For the synchronization trials, tempi of the metronome and music were set to the participant's baseline comfortable self-pace cadence. Before each synchronization trial, participants were instructed to take their time to find the beat of the music or metronome. Participants could use any strategy necessary to help find the beat such as marching in the spot or tapping their leg with their hand. Once they found the beat, participants were to begin walking across the walkway matching their footsteps to beat as best as possible. Participants were instructed that if they lost track of the beat, they should pause between passes to reacquire the beat before continuing the next pass.

As a first step in this line of investigation, the aim of this study was to understand the relationship between rhythm abilities and immediate response of TGA to a single session of metronome RAS. We only analyze metronome RAS (hereafter referred to as "metronome") for two reasons: (1) the clear beat of the auditory cue, compared to the more complex structure of music, facilitated the assessment of RAS effects without the potential dual task effects inherent in extracting a beat percept from a complex stimulus while also synchronizing footsteps, and (2) the Protokinetics software outputs the metronome beat onset times, but this data is not available for the music trials. A future study will analyze the relationship of rhythm abilities and the response of TGA to music RAS and compare the potential dual task effects.

Clinical Descriptors and Musical Background

Clinical presentation of participants was characterized using several measures. Stroke severity was characterized using the National Institutes of Health Stroke Scale [NIHSS; (25)]. Level of motor recovery of the leg and foot was assessed using the Chedoke McMaster Stroke Assessment [CMSA; (26)]. Cognitive ability was accessed using the Montreal Cognitive Assessment [MoCA; (27)]. The MoCA is valid and reliable in the stroke population (28). Rhythm abilities may be influenced by musical training (29, 30) and thus could have an impact on BAT performance. Therefore, participants' previous musical training (instrumental or voice) was collected by self-report and recorded as years of training outside of typical school-based music classes.

Measures of Interest

SR was measured during baseline and metronome conditions and was used as a marker of TGA. The, primary outcome measure was change in TGA between the two conditions. In addition to SR, gait velocity and cadence were parameters chosen to characterize gait performance. The ability to match footfalls to auditory cues was quantified with the interbeat interval deviation (IBD). IBD was calculated during the metronome condition and is the difference between the metronome mean interbeat interval and mean interstep interval divided by the interbeat interval (Equation 1). Lower IBD indicates greater step-to-beat synchronization.

$$\text{IBD} = \frac{|\text{ mean interstep interval} - \text{interbeat interval}|}{\text{interbeat interval}} \quad (1)$$

Data and Statistical Analysis

Spatiotemporal processing of footfalls for all walking trials was performed by one investigator (LC) using the manufacturer software (PKMAS). Data processing and analysis to calculate the IBD during metronome trials was performed in a custom MATLAB program[c] that compared metronome beat onset times to recorded footfall events. Statistical analysis was performed using SAS version 9.2[d] and plots created using estimation statistics[e] (31).

To investigate how TGA changed during a single session of RAS, TGA change between baseline and metronome conditions was analyzed using a paired t-test. The significance of TGA change from baseline was assessed independently for strong and weak groups with separate paired t-tests for each group (within-group comparisons). Change in TGA was calculated by subtracting baseline TGA from TGA in the metronome condition; a negative change value indicates reduced (improved) TGA. To compare the change from baseline between strong and weak groups (between-group comparison) two-sample t-tests were used. Finally, to determine between-group differences in IBDs non-parametric Mann-Whitney tests of significance were used. Data is visualized using Cumming and Gardner-Altman estimation plot statistics with effect sizes presented as bootstrapped 95% confidence intervals (CI) (31). All tests were two-sided and $p < 0.05$ was considered statistically significant.

TABLE 1 | Study participant demographics.

Characteristic	Count or mean (*SD*)
N	22
Sex (male/female)	15/7
Age (years)	61.5 (10.4)
Time post-stroke (years)	6.4 (6.8)
Musical training (years)	2.7 (3.9)
Affected side (right/left)	6/16
CMSA leg	5.2 (1.0)
CMSA foot	3.7 (1.5)
MoCA	25.7 (2.6)
Self-pace velocity (cm/s)	72.5 (21.5)
Self-pace TGA (ratio)	1.38 (0.27)

RESULTS

Participant Demographics and Rhythm Ability Scoring

Twenty-two individuals with TGA after stroke were included in this study. **Table 1** describes the demographic and clinical characteristics of the study sample.

Median score on the beat perception test was 53% (9 out of 17 correct responses) with 7 individuals scoring <50%. Median score on the beat production test was 111 ms of asynchrony. **Table 2** reports the clinical descriptors, rhythm ability scores, ands selected baseline gait parameters of participants within the beat perception and production groups. Gardner-Altman two-group estimation tests revealed strong and weak perception and production groups did not significantly differ in age, time post-stroke, years of musical training, clinical descriptors, nor self-pace gait velocity or SR.

Change in TGA With Metronome

Overall, TGA improved during a single session of metronome cued gait: paired mean difference between metronome and baseline SR for the entire study sample is −0.08 [95%CI −0.144, −0.006], $p = 0.032$ (**Figure 1**).

Effect of Rhythm Ability on TGA With Metronome

Beat Perception

Within-group change in TGA from baseline to metronome across strong and weak perceivers is displayed in **Figure 2A**. Both strong and weak perception groups improved TGA when walking to metronome on average, with the strong group reaching a significant reduction in TGA (mean, [95% CI]): −0.1 [−0.184, −0.051], $p = 0.002$; whereas the weak group reduction in TGA

TABLE 2 | Rhythm ability group demographics.

	Strong perceivers	Weak perceivers	Strong producers	Weak producers
N	15	7	11	11
Sex (male/female)	11/4	4/3	7/4	8 / 3
Age (years)	60.5 (9.7)	63.9 (12.3)	62.2 (10.2)	60.9 (11.0)
Time post-stroke (years)	4.3 (4.3)	11.2 (8.5)	5.1 (5.8)	7.9 (7.9)
Musical training (years)	3.4 (4.5)	1.1 (1.4)	2.7 (4.0)	2.6 (4.0)
Mean Beat Perception score* (%)	64.7 (9.9)	39.5 (6.5)	54.5 (14.9)	58.8 (15.3)
Mean Beat Asynchrony* (ms)	116 (10.6)	114 (10.4)	107 (4.2)	124 (6.8)
CMSA leg	5.2 (1.2)	5.3 (0.5)	5.1 (0.8)	5.4 (1.1)
CMSA foot	4.1 (1.4)	2.9 (1.6)	3.7 (1.4)	3.7 (1.7)
MoCA	25.8 (2.6)	25.6 (2.9)	25.7 (3.0)	25.8 (2.3)
Self-pace velocity (cm/s)	77.6 (21.4)	61.5 (18.5)	67.4 (26.2)	77.6 (14.9)
Self-pace TGA (ratio)	1.37 (0.28)	1.42 (0.27)	1.35 (0.26)	1.42 (0.29)

*Mean (SD). *Mean beat perception score and beat asynchrony significantly differed between the respective groups ($p < 0.001$). Differences between groups non-significant for all other variables ($p > 0.05$).*

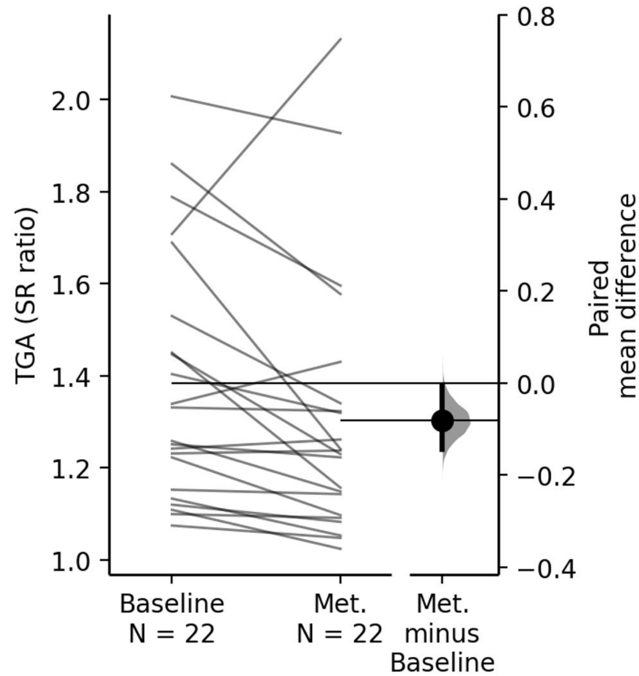

FIGURE 1 | The paired mean difference of TGA between baseline and metronome (Met.) for the study group is shown in the above paired mean difference plot. The raw data is plotted on the left axes, where each paired set of subject observations is connected by a line. On the right axes, the paired mean difference is plotted as a bootstrap sampling distribution. Mean difference is depicted as the dot; 95% CI are indicated by the ends of the vertical error bars. The paired mean difference of TGA between baseline and metronome condition is −0.08 [95.0%CI −0.144, −0.006], $p = 0.032$.

did not reach significance (−0.037 [−0.172, 0.17], $p = 0.822$). Paired t-tests revealed the variability of mean change within respective groups (standard error, strong: 0.033; weak: 0.091). Beat perception ability did not affect magnitude of change in TGA as the between-group comparison revealed no effect on change in TGA: the two sample mean difference on change is 0.063 [95%CI −0.076, 0.278], $p = 0.361$.

Beat Production

Within-group change in TGA from baseline to metronome across strong and weak producers is displayed in **Figure 2B**. Like the beat perception analysis, on average both strong and weak production groups improved TGA when walking to metronome. Again, the strong group achieved a significant reduction in TGA (mean, [95% CI]): −0.09 [95%CI −0.154, −0.039], $p = 0.007$; whereas the weak group reduction in TGA did not reach significance (−0.07 [95%CI −0.178, 0.072], $p = 0.298$). Paired t-tests revealed the variability of mean change within respective groups (standard error, strong: 0.031; weak: 0.066). Like beat perception, beat production ability had no effect on the magnitude of change in TGA, as no effect was revealed in the between-group comparison: the two sample mean difference on change is 0.015 [95%CI −0.106, 0.17], $p = 0.853$.

Step-to-Beat Synchronization

During the metronome condition, strong perceivers had a mean (SD) IBD of 0.11 (0.06) sec, and weak perceivers had a mean IBD of 0.14 (0.08) s. Strong producers had a mean IBD of 0.09 (0.04) s and weak producers had a mean IBD of 0.14 (0.08) s. While those with strong rhythm perception and production had less deviation in foot strike from the metronome beat, these differences were not significant ($p > 0.05$). **Figure 3** displays the Gardner-Altman estimation plots for metronome condition IBD.

Post hoc Analysis: Responders, Maintainers, and Non-responders to Metronome

The estimation plots from the primary analyses revealed variability in individual responses to metronome. Four individuals exhibited worse TGA during the metronome condition compared to baseline (worse; >5% worsening in SR). The remaining 18 participants were divided into those that maintained TGA during the metronome condition (maintain; 0–5% improvement in SR) and those that improved TGA during the metronome condition (improved; >5% improvement in SR). A threshold of 5% improvement was chosen based on a meta-analysis of treatment effects for self-selected gait symmetry (32). Hollands et al. (32) reported that gait treatments overall have a moderate positive effect on gait symmetry (effect size of 0.38). Two of the studies in the review demonstrated improvements in symmetry of 32–39% using 3–6-weeks RAS treatment regimens (16, 17). Since the current study observed only the immediate effects of one session of RAS, we would not expect as large an improvement as that observed in an

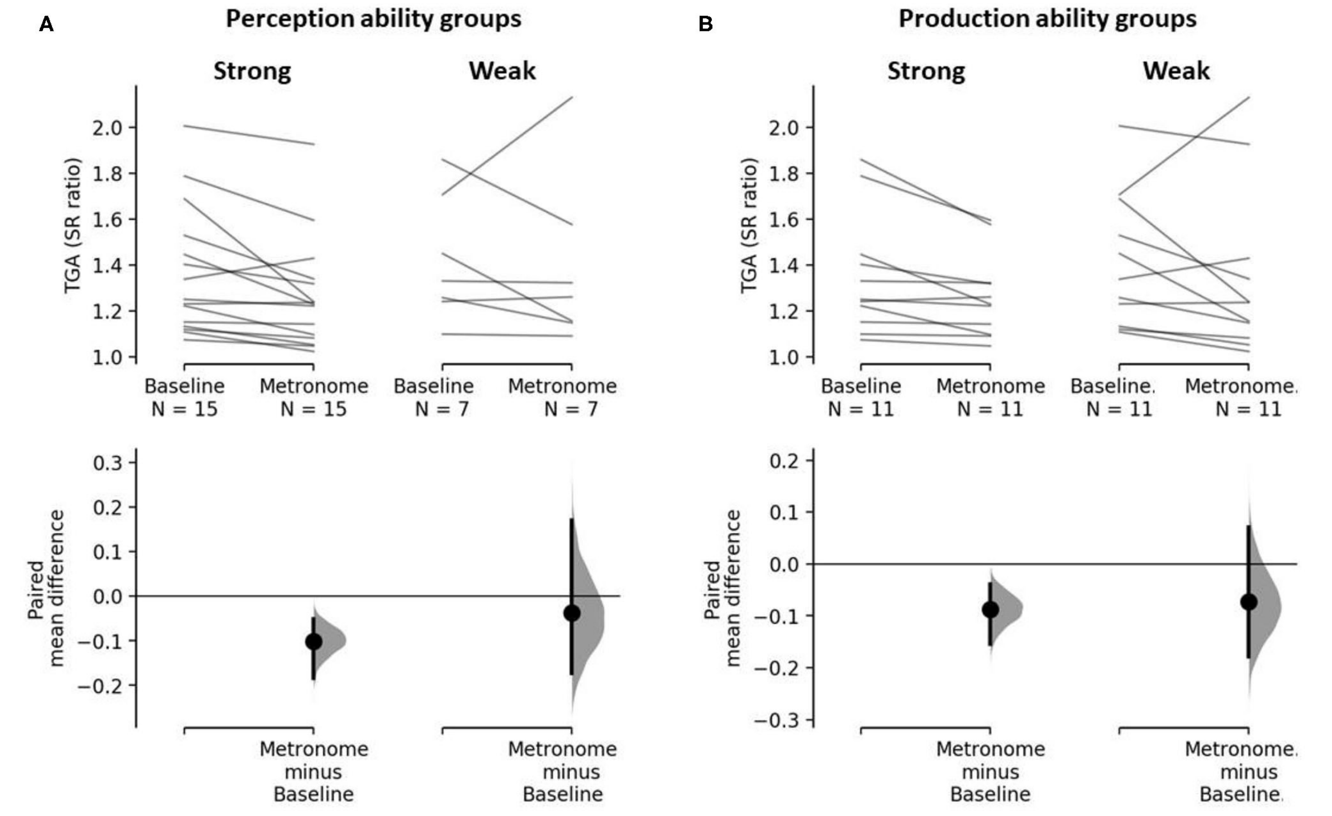

FIGURE 2 | The paired mean differences of TGA between baseline and metronome gait for **(A)** strong and weak beat perceivers and **(B)** strong and weak beat producers are shown in the above Cumming estimation plots. The raw data is plotted on the upper axes; each paired set of subject observations is connected by a line. On the lower axes, each paired mean difference is plotted as a bootstrap sampling distribution. Mean differences are depicted as dots; 95% CI are indicated by the ends of the vertical error bars. **(A)** The paired mean difference of TGA between baseline and metronome for strong perceivers is −0.1 [95%CI −0.184, −0.051], $p = 0.002$. The paired mean difference of TGA between baseline and metronome for weak perceivers is −0.037 [95%CI −0.172, 0.17], $p = 0.499$. **(B)** The paired mean difference of TGA between baseline and metronome for strong producers is −0.09 [95%CI −0.154, −0.039], $p = 0.007$. The paired mean difference of TGA between baseline and metronome for weak producers is −0.07 [95%CI −0.178, 0.072], $p = 0.298$.

intervention study, thus we chose a more modest threshold for improvement.

To study the varied response to metronome, we conducted a subsequent analysis to determine what factors (if any) differ in the worse group. Chosen factors included baseline TGA, degree of beat production asynchrony, IBD, time post-stroke, and CMSA scores of the leg and foot. Separate one-way analyses of variance were conducted for each factor to determine differences between the three response groups. The only significant factor was beat production. *Post hoc* Tukey's significant difference test revealed the worse group had significantly greater mean asynchrony [124.9 (11.8) ms] than the maintain group (109.4 (8.5) ms; $p = 0.047$), and greater mean asynchrony than the improved group [115 (8.8) ms], but not significantly different ($p > 0.05$). The mean difference between maintain and worse groups is 15.5 ms [95%CI −0.246, 24.5] ($p = 0.047$). To display this effect, **Figure 4** shows the shared control Cumming estimation plot for beat production asynchrony between the three response groups using the maintain group as the control.

DISCUSSION

The aim of this study was to investigate the relationship between rhythm ability and the immediate responsiveness of TGA to a single session of walking with metronome. Our primary analyses refuted our hypothesis that people with strong rhythm abilities would exhibit greater change in TGA with RAS than those with weak abilities. In fact, both strong and weak perceiver/producer groups improved TGA with metronome. Furthermore, the ability to synchronize to the beat may not be dependent rhythm abilities, since IBDs also did not differ between strong and weak perceiver/producer groups. However, within-group analyses of change in TGA provided some support for our hypothesis since only the strong perceivers and producers exhibited significant change with metronome. Moreover, our *post hoc* analysis revealed that participants who exhibited worse TGA change with metronome also had weaker beat production ability. Thus, this initial investigation provides some preliminary (albeit conflicting) evidence for a potentially complex relationship between beat perception/production abilities and responsiveness

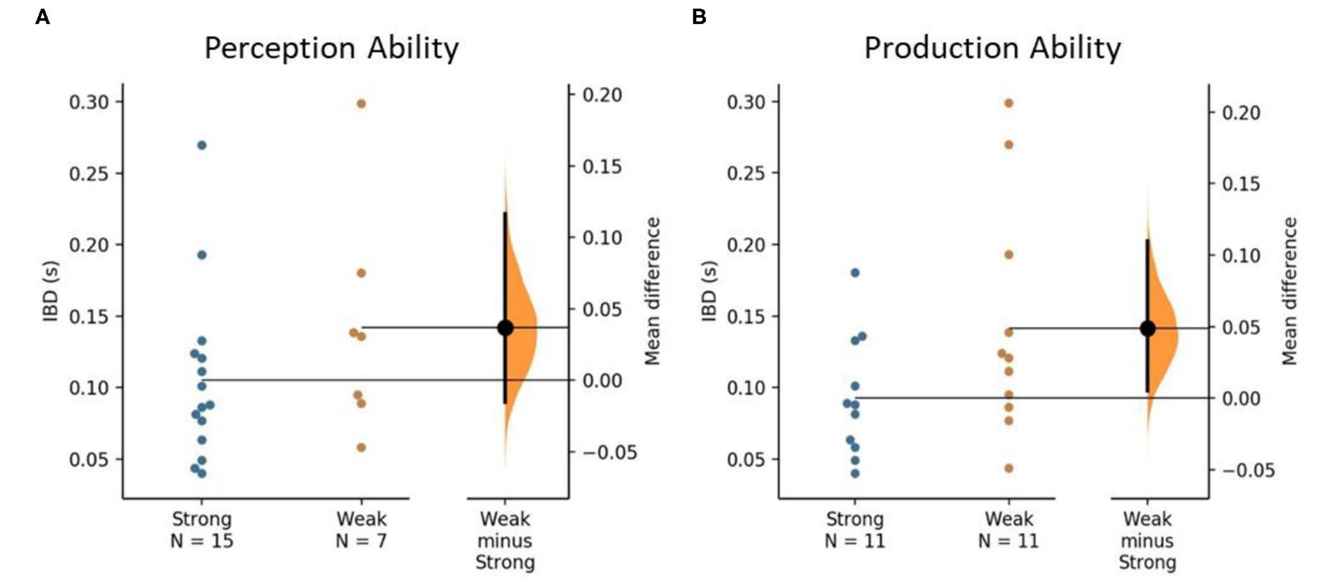

FIGURE 3 | The mean difference in interbeat interval deviation (IBD) between strong and weak rhythm ability groups is shown in the above Gardner-Altman estimation plots. Groups are plotted on the left axes; the mean difference is plotted on a floating axis on the right of each figure as a bootstrap sampling distribution. The mean differences are depicted as a dot; the 95% CI are indicated by the ends of the vertical error bars. **(A)** The unpaired mean difference between strong and weak perceivers is 0.037 [95%CI −0.015, 0.116], $p = 0.159$. **(B)** The unpaired mean difference between strong and weak producers is 0.049 [95%CI 0.005, 0.11], $p = 0.131$.

of TGA to RAS which may not be mediated by the ability to match footsteps to the RAS cue.

The present study extends the findings of previous work which hypothesized that TGA is attributable to impaired rhythm ability following stroke. Patterson and colleagues (14) revealed that beat production ability was associated with TGA independent from motor impairment and time post-stroke. It should be noted that Patterson and colleagues (14) also reported that motor impairment of the leg and foot was correlated with beat perception ability. It is possible that stroke-related damage to motor areas linked to rhythm abilities (e.g., basal ganglia and the supplementary motor area) underlie both deficits (14). Based on these previous results, it could be proposed that in the present study, participants in the weak beat perception group also had greater motor impairment and this may have contributed to reduced responsiveness to RAS. However, motor impairment was not significantly different between the strong and weak groups. Future work with a larger sample and a longer RAS intervention may be able to disentangle the relationships between motor impairment, rhythm abilities, and responsiveness to RAS.

Compared to individuals with strong rhythm abilities, individuals with weak production and weak perception were approximately two and three times as variable in their TGA response to metronome, respectively. Previous work in neurotypical young adults observed similar findings in spatial gait parameters. Weak beat perceivers had more variable change in step length from baseline when walking to a metronome than strong perceivers (22). Moreover, in another study of metronome-cued walking, individuals with weak beat perception demonstrated a narrowing of strides with higher variability of change from uncued walking than strong perceivers (33). The variability of motor response has also been documented with tapping tasks. Greater variability in tapping to the beat (i.e., poor rhythm production ability) is associated with poorer sustained auditory attention (34) and decreased neural response to sound (35). It is possible it is more difficult for individuals with weak rhythm abilities to attend to the timing of auditory cues and make the appropriate motor reaction, thus increasing the variability in temporal gait response to RAS. Previous work with gait interventions other than RAS has also shown variability in single session responses to training across individuals with stroke (36). Moreover, reviews of treadmill gait training studies reported large variability for the mean differences in gait velocity following training (37, 38). The variability in the training response suggests the need for a more individualized approach to therapy that is based on specific indicators that would affect individual positive change (39).

The ability to benefit from RAS and improve TGA after stroke likely involves more dimensions than motor impairment, inherently strong rhythmic perception of auditory cues, and/or strong rhythmic production of movement. Integration of perception and action is also important. It is possible that people with stroke are impaired in this domain as well, although it is investigated to a lesser extent than motor impairments (40). According to Gibson (41), the perception-action integration process is cyclical: individuals use their perceptual systems (audition, vision) to gain information and interact with their environment to generate action. To generate action, individuals initiate movements that change their position in their environment. This then affects how the environment

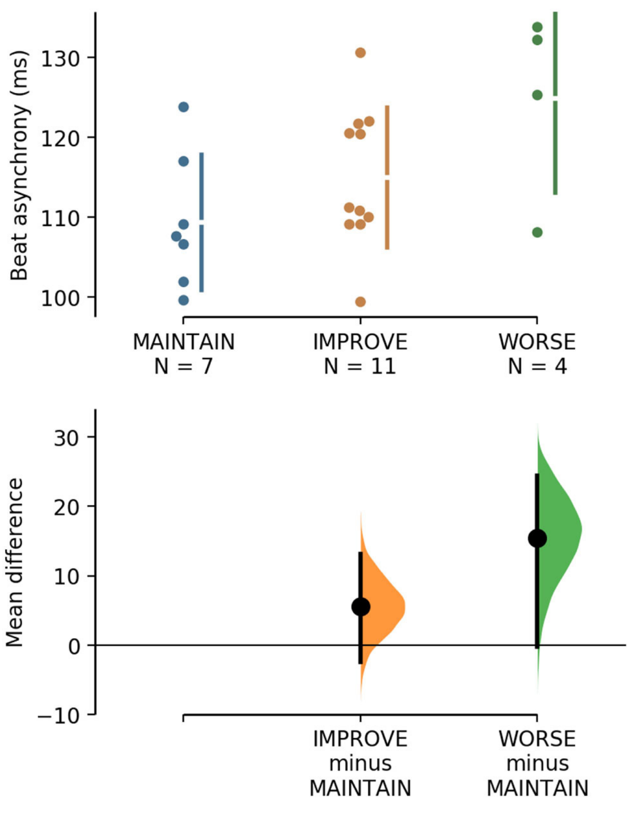

FIGURE 4 | The mean difference for groups IMPROVE and WORSE against the shared control MAINTAIN are shown in the above Cumming estimation plot. The raw data is plotted on the upper axes. On the lower axes, mean differences are plotted as bootstrap sampling distributions. Each mean difference is depicted as a dot. Each 95% CI is indicated by the ends of the vertical error bars. The unpaired mean difference between MAINTAIN and WORSE is 15.5 [95%CI −0.246, 24.5], $p = 0.047$. The unpaired mean difference between MAINTAIN and IMPROVE is 5.61 [95%CI −2.42, 13.1], $p = 0.15$.

is perceived completing the cycle. How well an individual integrates the processing of perceptual information (such as rhythmic auditory cues) and generates action in response to that information (such as matching footsteps to the cue) will affect their ability to respond to treatments like RAS. This is further compounded by sensorimotor impairment associated with stroke; therefore, the resulting constraints will affect perception-action integration as well. How individuals perceive and act in their environment needs to be considered when investigating recovery of function in rehabilitation (42).

An individual's cultural background can have an impact their ability to perceive and produce the beat in music. This is most recognizable when an individual is asked to perceive the beat in music that is foreign to them (43). The present study used Western contemporary music in the rhythm perception and production testing. Characteristics of the participant's cultural upbringing or song preferences were not collected in this study. It is possible that performance in the rhythm ability testing (perceiving the beat in Western contemporary music) was affected by cultural differences in musical preference and experience. Comparisons of rhythm perception ability between English and Ugandan schoolchildren revealed that the Ugandan group showed a greater affinity for learning long and short sounds, whereas the English group favored strong and weak sounds (44). Moreover, African music culture places emphasis on rhythmic performance (44), therefore is not surprising Ugandan schoolchildren showed better rhythm synchronization, rhythm repetition, and steady beating time than their English counterparts (45). Future studies that explore individual rhythm abilities may consider the individual's cultural background and how that may influence their ability to perceive/produce the beat in the music selected for their research.

In addition to factors intrinsic to the individual such as rhythm ability, cultural background, and stroke-related motor impairment, it is possible that external factors also contribute to the effectiveness of RAS. This study employed the commonly used metronome cue for RAS delivery, though recent work has demonstrated the benefit of RAS that uses footstep sounds instead (46, 47). The use of footstep sounds is equally effective in improving motor recovery scores and more effective than metronome cueing for improving spatiotemporal gait parameters such as speed, cadence, and step length for individuals with Parkinson's disease (48). Given its relation to the motor task being performed, it is possible the use of footstep sounds as RAS may facilitate the rhythmic perception of individuals with weak ability who attempt to match their gait to the cue. Music, metronome, and biological sounds like footsteps are all effective types of RAS delivery, but which type may elicit the most benefit to those with differing rhythm ability is left to future investigation.

This research has limitations. We do not have stroke lesion location confirmed by imaging for our participants. Thus, we cannot comment on the impact of damage to areas known to contribute to rhythm processing (e.g., basal ganglia, supplemental motor areas) on our results. The small sample size of this study may have impacted the overall strength of the results. Given the nature of defining rhythm perception ability with percentage of correct responses, only 7 of 22 participants in our study scored less than chance on the beat perception test. A larger sample size may have shown a greater effect of rhythm ability on the responsiveness of TGA to RAS. Finally, this study was an initial step to explore the immediate response of TGA to RAS, as a first, proof-of-concept. Typical RAS interventions involve treatments over multiple days (18). Therefore, it is possible that response of TGA to RAS may change over repeated assessments, and rhythm abilities may affect the rate and magnitude of that change. Future work should investigate these longitudinal responses.

When aiming to treat rhythmical movements like the temporal symmetry of gait, assessing rhythm ability prior to using treatments like RAS may be of clinical relevance. Since individuals who worsen TGA when walking to metronome have, on average, poorer rhythm production scores, assessing rhythm ability prior to intervention may help identify those who are unlikely to benefit as much from, or enjoy, rhythm-based treatments. The threshold of weak vs. strong rhythm production ability was calculated as the median for this sample. Therefore, currently it is not possible to identify a clear, universal threshold of weak rhythm ability to apply in clinical settings to identify individuals unlikely to benefit from RAS. Future work may seek to identify such a threshold with a larger sample size with a wider range of scores, or measure test-retest reliability. Given the variability in TGA response, individuals with weak rhythm ability may benefit from other methods to improve gait and specifically TGA. Furthermore, future work should investigate the value of first training rhythm ability in people with post-stroke TGA and weak rhythm ability, to improve responsiveness to subsequent RAS gait training.

Suppliers

(a) E-prime version 2.0; Psychology Software Tools
(b) Zeno Walkway; Protokinetics, Havertown, PA
(c) MATLAB; The MathWorks, Inc.
(d) SAS 9.2; SAS Institute, Inc.
(e) Estimationstats.com, web application © 2017-2020.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Board of the University Health Network, Toronto, Ontario. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC contributed to this study by performing data collection and analysis, table and figure preparation, and manuscript writing. JW contributed to this research by performing participant recruitment and data collection and manuscript editing. JC, JG, and KP contributed to the writing and editing of the manuscript, in addition to procedural and analysis mentorship. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Patterson KK, Parafianowicz I, Danells CJ, Closson V, Verrier MC, Staines WR, et al. Gait asymmetry in community-ambulating stroke survivors. *Arch Phys Med Rehabil*. (2008) 89:304–10. doi: 10.1016/j.apmr.2007.08.142
2. Patterson KK, Gage WH, Brooks D, Black SE, McIlroy WE. Changes in gait symmetry and velocity after stroke: a cross-sectional study from weeks to years after stroke. *Neurorehabil Neural Repair*. (2010) 24:783–90. doi: 10.1177/1545968310372091
3. Patterson KK, Mansfield A, Biasin L, Brunton K, Inness EL, McIlroy WE. Longitudinal changes in poststroke spatiotemporal gait asymmetry over inpatient rehabilitation. *Neurorehabil Neural Repair*. (2015) 29:153–62. doi: 10.1177/1545968314533614
4. Mauritz KH. Gait training in hemiplegia. *Eur J Neurol*. (2002) 9(Suppl. 1):23–9. doi: 10.1046/j.1468-1331.2002.0090s1023.x
5. Teasell RW, Bhogal SK, Foley NC, Speechley MR. Gait retraining post stroke. *Top Stroke Rehabil*. (2003) 10:34–65. doi: 10.1310/UDXE-MJFF-53V2-EAP0
6. Jorgensen L, Crabtree NJ, Reeve J, Jacobsen BK. Ambulatory level and asymmetrical weight bearing after stroke affects bone loss in the upper and lower part of the femoral neck differently: Bone adaptation after decreased mechanical loading. *Bone*. (2000) 27:701–7. doi: 10.1016/S8756-3282(00)00374-4
7. Norvell DC, Czerniecki JM, Reiber GE, Maynard C, Pecoraro JA, Weiss NS. The prevalence of knee pain and symptomatic knee osteoarthritis among veteran traumatic amputees and nonamputees. *Arch Phys Med Rehabil*. (2005) 86:487–93. doi: 10.1016/j.apmr.2004.04.034
8. Ellis RG, Howard KC, Kram R. The metabolic and mechanical costs of step time asymmetry in walking. *Proc R Soc Biol Sci*. (2013) 280:20122784. doi: 10.1098/rspb.2012.2784
9. Patterson KK, Gage WH, Brooks D, Black SE, McIlroy WE. Evaluation of gait symmetry after stroke: a comparison of current methods and recommendations for standardization. *Gait Posture*. (2010) 31:241–6. doi: 10.1016/j.gaitpost.2009.10.014
10. Turnbull G, Wall J. Long-term changes in hemiplegic gait. *Gait Posture*. (1995) 3:258–61. doi: 10.1016/0966-6362(96)82856-6
11. Redfern J, McKevitt C, Wolfe CDA. Development of complex interventions in stroke care: a systematic review. *Stroke*. (2006) 37:2410–9. doi: 10.1161/01.STR.0000237097.00342.a9
12. Alexander LD, Black SE, Patterson KK, Gao F, Danells CJ, McIlroy WE. Association between gait asymmetry and brain lesion location in stroke patients. *Stroke*. (2009) 40:537–44. doi: 10.1161/STROKEAHA.108.527374
13. Grahn JA, Brett M. Rhythm and beat perception in motor areas of the brain. *J Cogn Neurosci*. (2007) 19:893–906. doi: 10.1162/jocn.2007.19.5.893
14. Patterson KK, Wong JS, Knorr S, Grahn JA. Rhythm perception and production abilities and their relationship to gait after stroke. *Arch Phys Med Rehabil [Internet]*. (2018) 99:945–51. doi: 10.1016/j.apmr.2018.01.009
15. Thaut MH, McIntosh GC, Prassas SG, Rice RR. Effect of rhythmic auditory cuing on temporal stride parameters and EMG patterns in hemiparetic gait of stroke patients. *Neurorehabil Neural Repair*. (1993) 7:9–16. doi: 10.1177/136140969300700103
16. Thaut MH, Leins AK, Rice RR, Argstatter H, Kenyon GP, McIntosh GC, et al. Rhythmic auditory stimulation improves gait more than NDT/Bobath training in near-ambulatory patients early poststroke: a single-blind, randomized trial. *Neurorehabil Neural Repair*. (2007) 21:455–9. doi: 10.1177/1545968307300523
17. Thaut MH, McIntosh GC, Rice RR. Rhythmic facilitation of gait training in hemiparetic stroke rehabilitation. *J Neurol Sci*. (1997) 151:207–12. doi: 10.1016/S0022-510X(97)00146-9
18. Yoo G, Kim S. Rhythmic auditory cueing in motor rehabilitation for stroke patients: systematic review and meta-analysis. *J Music Ther*. (2016) 53:149–77. doi: 10.1093/jmt/thw003

19. Lee SH, Lee KJ, Song CH. Effects of rhythmic auditory stimulation (RAS) on gait ability and symmetry after stroke. *J Phys Ther Sci*. (2012) 24:311–4. doi: 10.1589/jpts.24.311
20. Chen JL, Penhune VB, Zatorre RJ. Moving on time: brain network for auditory-motor synchronization is modulated by rhythm complexity and musical training. *J Cogn Neurosci*. (2008) 20:226–39. doi: 10.1162/jocn.2008.20018
21. Thaut MH. Chapter 13 - The discovery of human auditory-motor entrainment and its role in the development of neurologic music therapy. In: Altenmüller E, Finger S, Boller F, editors. *Progress in Brain Research: Music, Neurology, and Neuroscience: Evolution, the Musical Brain, Medical Conditions, and Therapies*. 1st ed. Vol. 217, Elsevier B.V. (2015). p, 253–66.
22. Leow LA, Parrott T, Grahn JA. Individual differences in beat perception affect gait responses to low- and high-groove music. *Front Hum Neurosci*. (2014) 8:811. doi: 10.3389/fnhum.2014.00811
23. Iversen JR, Patel AD. The beat alignment test (BAT): surveying beat processing abilities in the general population. In: Miyazaki K, Hiraga Y, Adachi M, Nakajima Y, Tsuzaki M, editors. *Proceedings of the 10th International Conference on Music Perception and Cognition*. Sapporo (2008). p. 465–8.
24. Wong JS, Jasani H, Poon V, Inness EL, McIlroy WE, Mansfield A. Inter- and intra-rater reliability of the GAITRite system among individuals with sub-acute stroke. *Gait Posture*. (2014) 40:259–61. doi: 10.1016/j.gaitpost.2014.02.007
25. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. (1989) 20:864–70. doi: 10.1161/01.STR.20.7.864
26. Gowland C, Stratford P, Ward M, Moreland J, Torresin W, Van Hullenaar S, et al. Measuring physical impairment and disability with the Chedoke-McMaster Stroke Assessment. *Stroke*. (1993) 24:58–63. doi: 10.1161/01.STR.24.1.58
27. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
28. Wu CY, Hung SJ, Lin KC, Chen KH, Chen P, Tsay PK. Responsiveness, minimal clinically important difference, and validity of the MoCA in stroke rehabilitation. *Occup Ther Int*. (2019) 2019:2517658. doi: 10.1155/2019/2517658
29. Drake C, Penel A, Bigand E. Tapping in time with mechanically and expressively performed music. *Music Percept*. (2000) 18:1–23. doi: 10.2307/40285899
30. Yee W, Holleran S, Riess Jones M. Sensitivity to event timing in regular and irregular sequences: Influences of musical skill. *Percept Psychophys*. (1994) 56:461–71. doi: 10.3758/BF03206737
31. Ho J, Tumkaya T, Aryal S, Choi H, Claridge-Chang A. Moving beyond P values: data analysis with estimation graphics. *Nat Methods*. (2019) 16:565–6. doi: 10.1038/s41592-019-0470-3
32. Hollands KL, Pelton TA, Tyson SF, Hollands MA, van Vliet PM. Interventions for coordination of walking following stroke: systematic review. *Gait Posture*. (2012) 35:349–59. doi: 10.1016/j.gaitpost.2011.10.355
33. Ready EA, McGarry LM, Rinchon C, Holmes JD, Grahn JA. Beat perception ability and instructions to synchronize influence gait when walking to music-based auditory cues. *Gait Posture*. (2019) 68:555–61. doi: 10.1016/j.gaitpost.2018.12.038
34. Tierney AT, Kraus N. The ability to tap to a beat relates to cognitive, linguistic, and perceptual skills. *Brain Lang*. (2013) 124:225–31. doi: 10.1016/j.bandl.2012.12.014
35. Tierney A, Kraus N. The ability to move to a beat is linked to the consistency of neural responses to sound. *J Neurosci*. (2013) 33:14981–8. doi: 10.1523/JNEUROSCI.0612-13.2013
36. Kesar TM, Binder-Macleod SA, Hicks GE, Reisman DS. Minimal detectable change for gait variables collected during treadmill walking in individuals post-stroke. *Gait Posture*. (2011) 23:314–7. doi: 10.1016/j.gaitpost.2010.11.024
37. Moseley A, Stark A, Cameron I, Pollock A. Treadmill training and body weight support for walking after stroke. *Cochrane Database Syst Rev*. (2005) 4:CD002840. doi: 10.1002/14651858.CD002840.pub2
38. Mehrholz J, Thomas S, Elsner B. Treadmill training and body weight support for walking after stroke. *Cochrane Database Syst Rev*. (2017) 8:CD002840. doi: 10.1002/14651858.CD002840.pub4
39. Nadeau S, Duclos C, Bouyer L, Richards CL. Guiding task-oriented gait training after stroke or spinal cord injury by means of a biomechanical gait analysis. *Prog Brain Res*. (2011) 192:161–80. doi: 10.1016/B978-0-444-53355-5.00011-7
40. Brown KE, Neva JL, Feldman SJ, Staines WR, Boyd LA. Sensorimotor integration in chronic stroke: Baseline differences and response to sensory training. *Restor Neurol Neurosci*. (2018) 36:245–59. doi: 10.3233/RNN-170790
41. Gibson J. *The Ecological Approach to Visual Perception*. Boston, MA: Houghton Mifflin (1979).
42. Newell KM, Verhoeven FM. Movement rehabilitation: are the principles of re-learning in the recovery of function the same as those of original learning? *Disabil Rehabil*. (2017) 39:121–6. doi: 10.3109/09638288.2016.1170895
43. Hannon EE, Soley G, Ullal S. Familiarity overrides complexity in rhythm perception: a cross-cultural comparison of American and Turkish listeners. *J Exp Psychol Hum Percept Perform*. (2012) 38:543–8. doi: 10.1037/a0027225
44. Igaga JM, Versey J. Cultural differences in rhythmic perception. *Psychol Music*. (1977) 5:23–7. doi: 10.1177/030573567751003
45. Igaga JM, Versey J. Cultural differences in rhythmic performance. *Psychol Music*. (1978) 6:61–4. doi: 10.1177/030573567861006
46. Young WR, Rodger MWM, Craig CM. Auditory observation of stepping actions can cue both spatial and temporal components of gait in Parkinson's disease patients. *Neuropsychologia*. (2014) 57:140–53. doi: 10.1016/j.neuropsychologia.2014.03.009
47. Rodger MWM, Craig CM. Beyond the metronome: auditory events and music may afford more than just interval durations as gait cues in Parkinson's disease. *Front Neurosci*. (2016) 10:272. doi: 10.3389/fnins.2016.00272
48. Murgia M, Pili R, Corona F, Sors F, Agostini TA, Bernardis P, et al. The use of footstep sounds as rhythmic auditory stimulation for gait rehabilitation in Parkinson's disease: a randomized controlled trial. *Front Neurol*. (2018) 9:348. doi: 10.3389/fneur.2018.00348

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neurophysiological Synchrony Between Children With Severe Physical Disabilities and Their Parents During Music Therapy

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Although physiological synchronization has been associated with the level of empathy in emotionally meaningful relationships, little is known about the interbrain synchrony between non-speaking children with severe disabilities and their familial caregivers. In a repeated measures observational study, we ascertained the degree of interbrain synchrony during music therapy in 10 child-parent dyads, where the children were non-speaking and living with severe motor impairments. Interbrain synchrony was quantified via measurements of spectral coherence and Granger causality between child and parent electroencephalographic (EEG) signals collected during ten 15-min music therapy sessions per dyad, where parents were present as non-participating, covert observers. Using cluster-based permutation tests, we found significant child-parent interbrain synchrony, manifesting most prominently across dyads in frontal brain regions within β and low γ frequencies. Specifically, significant dyadic coherence was observed contra-laterally, between child frontal right and parental frontal left regions at β and lower γ bands in empathy-related brain areas. Furthermore, significant Granger influences were detected bidirectionally (from child to parent and vice versa) in the same frequency bands. In all dyads, significant increases in session-specific coherence and Granger influences were observed over the time course of a music therapy session. The observed interbrain synchrony suggests a cognitive-emotional coupling during music therapy between child and parent that is responsive to change. These findings encourage further study of the socio-empathic capacity and interpersonal relationships formed between caregivers and non-speaking children with severe physical impairments.

Keywords: neural synchrony, spectral coherence, granger influence, child-parent dyad, interbrain synchrony, EEG, children with severe physical disabilities, music therapy

1. INTRODUCTION

1.1. Interpersonal Physiological Synchrony

Interpersonal synchronization broadly describes the spontaneous, contemporaneous alignment of physiological indicators or the automatic mirroring of behaviors between people during social interactions (Feldman, 2007). Behavioral synchronization has been observed in many interpersonal activities, including co-ambulation (Bernieri and Rosenthal, 1991) and rhythmic movements of child and therapist during music therapy (Dvir et al., 2020). Physiological synchrony may involve the autonomic nervous system, as in the respiratory alignment in psychotherapist-client dyads (Tschacher and Meier, 2020), or the central nervous system, as in hemodynamic synchronization in the prefrontal cortex of the brain during cooperative game play (Liu et al., 2016). In fact, behavioral and physiological synchrony can co-occur, as recently clarified by Gordon et al. (2020) in their study of the covariation of behavioral and autonomic nervous system synchrony during group drumming tasks.

In the mutually calibrated physiological state, people are said to be in "sync"Ĭ with each other. The strength of such synchrony can be quantified through a plethora of measures, including for example, cardiac rhythms between mothers and infants (Feldman et al., 2011), cortisol readings between mothers and adolescents (Papp et al., 2009), electrodermal activity between patients and therapists (Marci et al., 2007), and hemodynamic brain responses (i.e., higher-order information and emotion processing) between speakers and listeners (Stephens et al., 2010).

1.2. A Putative Link Between Synchrony and Socio-Emotional Connection

When an individual observes or interacts with another human being, there is a tendency to adopt the physiology and behaviors corresponding to the partner's affective state (Stephens et al., 2010; Ebisch et al., 2012). This unconscious calibration of one's own body and brain to another's emotional experience has been associated with motor, cognitive, and emotional empathy. For example, Pauly et al. (2020) observed that stronger cortisol synchrony occurred in the presence of a partner and subsequent to positive socio-emotional interactions in older couples. Likewise, Coutinho et al. (2019) found greater electrodermal synchrony during positive interactions between romantic couples when the males had higher dyadic empathy. This connection between synchrony and socio-emotional experience is not limited to the peripheral nervous system and extends to the brain. For example, Dikker et al. (2017) reported that empathy predicted the amount of electroencephalographic brain synchrony among high school students in a naturalistic classroom setting. More recently, Azhari et al. (2020) showed that the unique presence of a spouse elevated a couple's hemodynamic brain-to-brain synchrony while attending to salient stimuli.

While the above evidence points to an association between synchrony and socio-emotional bonding, the putative role of mirror neurons in this association remains contested (Hickok, 2009; Lamm and Majdandžić, 2015). Nonetheless, it has been suggested that empathy has neurobiological underpinnings in the mirror neuron system (Gallese, 2001; Tononi, 2020) or more broadly the action-observation network (Jospe et al., 2020), the constellation of neurons that allows one to anticipate the goals of others through observation of their associated actions.

1.3. Music and Interpersonal Synchrony

There is growing evidence that music affords a facilitative environment for the development of both behavioral and physiological synchrony. When an experimenter tapped synchronously to music with a participant, the latter behaved in a more helpful manner toward the former (Stupacher et al., 2017). The same was not observed when tapping asynchronously or to a metronome. In a joint-music making task requiring no previous musical training, Novembre et al. (2019) found that participants with high levels of empathy were more accurate at synchronizing their musical output with that of another person. Indeed, literature has suggested that synchronized rhythmic behavior in collective settings such as dance and music promotes group cohesion and cooperative behavior (Freeman, 1998; Bispham, 2009).

On the physiological front, Gordon et al. (2020) reported increased synchrony of cardiac interbeat intervals of participants during a synchronous group drumming task, while Ardizzi et al. (2020) noted elevated levels of cardiac synchrony in an audience watching a live performance together, contending that a collective aesthetic experience may enhance group cohesion. Of particular relevance to the present study, (Fachner et al., 2019) reported that peaks in frontal and parietal alpha asymmetries in electroencephalographic recordings of therapist and patient aligned at various points during music therapy. Recently, using an EEG hyperscanning method, (Fachner et al., 2019) reported that classical music induced meaningful interbrain synchronization between a music therapist and a client during sessions of Guided Imagery and Music.

Music can evoke emotions or modulate ongoing emotions expressed through physiological arousal (automatic and endocrine changes) and motoric expression (e.g., smiling, clapping, dancing, and singing) (Koelsch, 2014). Musical communication also facilitates social, emotional, and cognitive development for infants and young children (Trehub, 2003; Fitch, 2006).

1.4. The Importance of Parent-Child Brain-to-Brain Synchrony

Brain-to-brain synchrony between parent and child is an emerging neurobiological marker of socio-emotional development. For example, Reindl et al. (2018) recently observed interbrain synchrony only in a parent-child cooperative play condition, whereas child-stranger play, whether cooperative or competitive, yielded no such synchrony. This finding suggests that synchrony reflected the unique emotional bond between parent and child, which the authors note is related to the child's development of emotion regulation. Others have associated parent-child synchrony with positive social interactions (Cui et al., 2012), development of empathy during childhood and adolescence (Feldman, 2007), cognitive processing in infancy and school adjustment (Leclère et al., 2014), and the development of self-regulation such as recovery from periods of irritability (Quiñones-Camacho et al., 2020). By extension, the emerging importance of synchrony as a neurophysiological predictor of a broad range of developmental outcomes suggests the eventual need to study the risks to parent-child synchrony and the interventions which may strengthen such interbrain coupling.

1.5. Propensity for Interbrain Synchrony in Non-speaking Children With Severe Physical Disabilities

Few studies have quantified the development of interbrain synchrony in children with severe disabilities and limited or delayed expressive communication. For example, Kasari et al. (2003) reported that children with Down syndrome exhibited more prosocial behaviors than typically developing peers in response to distress in others, but no corresponding study of interbrain synchrony involving this population has yet been published. In terms of the functional brain, atypical mirror neuron system activation has been observed in children with cerebral palsy, compared to their typically developing counterparts (Errante et al., 2019). Anatomically, reductions in gray matter volume of the salience and mirror neuron networks have been reported in pediatric brain injury and have been associated with lower Theory of Mind scores, suggesting social-cognitive impairment (Ryan et al., 2017). Further, it is well-documented that children with the most severe forms of cerebral palsy have the most restrictions in social function and communication (Voorman et al., 2010). Taken collectively, these studies and others point to likely impacts on the propensity for interbrain synchrony among non-speaking children with severe physical disabilities but the degree and nature of such impacts remain largely unexplored.

The above literature supports the notion that synchrony plays an important role in interpersonal interactions, that music has potential to serve as a facilitator of synchrony, and that little is known at present about interbrain synchrony in non-speaking children with severe disabilities. In the local health system, music therapy is a service afforded to children and youth with severe physical disabilities. However, to date, very little is known about the capacity for synchronization between a non-speaking child with severe physical disabilities and cognate caregivers given the limited opportunities for conventional interpersonal interaction through conversational speech and transactional gestures. The measurement of neurophysiological synchrony in a music therapy context may thus shed light on the social connections between children with severe disabilities and parental caregivers. In turn, this information may inform the provision of optimal and personalized opportunities for development.

The present study sought to answer the following questions.

1. Does parent-child brain synchrony (as measured by coherence and Granger influence) during music therapy exceed levels observed during corresponding pre-session baselines?
2. Does parent-child brain synchrony (as measured above) increase over successive time intervals within a music therapy session?

Based on the reviewed literature, we expected the presence of neural synchrony between parent and child during music therapy at levels significantly above baseline. We further hypothesized that the level of synchrony would increase throughout the music therapy session.

TABLE 1 | Child/youth participant characteristics.

Child/youth participant	Age	Sex	Residential status
1	26	F	Inpatient
2	20	M	Outpatient
3	19	M	Outpatient
4	15	M	Inpatient
5	9	M	Inpatient
6	3.5	M	Outpatient
7	18	F	Inpatient
8	7	F	Inpatient
9	15	M	Outpatient
10	15	M	Outpatient

2. MATERIALS AND METHODS

2.1. Participants

We recruited a convenience sample of 10 participants with disabilities (14.7 ± 6.7 years, 7 males, 3 females), one of their parents (7 mothers; 3 fathers), and one music therapist (female) from a local pediatric rehabilitation hospital. Participants were not actively taking seizure medications or other medications that affect heart rate, cortisol levels or skin conductance. The child/youth participants were all non-speaking and had one or more severe forms of disability, including cerebral palsy, seizure, epilepsy, and anoxic brain disorder. All child/youth participants had profound physical limitations (e.g., children with cerebral palsy were all level V on the Gross Motor Classification System). **Table 1** lists the age, sex and residential status of the child/youth participants. Parents or therapists with a history of neurological, cardiopulmonary, or metabolic illness or with current medication affecting the peripheral nervous system were excluded. All participants were asked to refrain from eating (2 h prior), drinking caffeine (4 h prior), and smoking (4 h prior). All participants were compensated for their time. The therapist and the parents, both as participants and proxy decision makers for their children, gave written informed consent. The Research Ethics Boards of the Holland Bloorview Kids Rehabilitation Hospital and University of Toronto approved the study protocol.

2.2. Experimental Design

Each child-parent dyad attended ten 18−min experimental sessions that were no more than two weeks apart. Each session consisted of a 3-min baseline followed by a 15−min music therapy session. All participants sat quietly without any interactions or music during the 3-min baseline period. The parents watched and listened to the therapy sessions via a live audio-video feed in either a separate room or in a partitioned area so that there were no interactions with their children or the therapist. The camera was positioned such that the parents had exclusively a frontal view of the faces of their children. This design was adopted to emulate current clinical practice. Both rooms were maintained at 20–23 °C and 35% relative humidity. EEG signals were simultaneously recorded from participants (except therapist) with the wireless Emotiv EPOC[1] headsets throughout the baseline and therapy session at 128 Hz. The EEG headset consisted of 14 channels permanently situated at AF3, AF4, F7, F8, F3, F4, FC5, FC6, T7, T8, P7, P8, O1, and O2 according to the International $10-20$ system. The headset deployed saline-based electrodes. The child and parental EEG signals were recorded on separate computers. Experimental recordings were synchronized temporally via a button press that annotated all data streams (including video and audio) with a common sync pulse. Custom software and hardware were developed for this purpose. Additionally, electrodermal activity and heart rate were collected continuously throughout baseline and the therapy session. Saliva was collected four times from parent and child after the session in 5-min intervals. **Figure 1** summarizes the experimental setup while **Figure 2** depicts the sessional protocol. Only the EEG data are presented in this paper.

2.3. Music Therapy

Music and instrument selection were customized to the preference of each child and documented according to standardized guidelines for reporting music-based interventions (Robb et al., 2011) in **Tables 2–4**, which summarize the intervention theory, sample content and example implementation, respectively. The list of each participant's favorite songs was assembled through conversations with the attending parent prior to the commencement of the study sessions. Familiar music tends to recruit activity in neural structures involved socio-emotional responses (Freitas et al., 2018; Wallmark et al., 2018).

Only the music therapist played an instrument although an instrument might be placed in the hand, on the lap, or in proximity of a child to encourage participation. Each child or youth participant sat in their wheelchair while the music therapist faced them, either in a seated or standing posture, such that eye contact could be encouraged. The music therapist communicated with each pediatric participant through improvised lyrics, sung to the melody of familiar songs selected by the participant. For example, the music therapist might have sung, "Lisa plays the drum, drum, drum" when the participant may have gestured to a drum positioned near them. The music therapist also sang about the participant's actions or responses and how she wanted the child to participate. Particularly noteworthy are the intervention strategies deployed by the attending music therapist to promote engagement and alertness (**Table 4**), such as strategic incorporation of the child's name in the music, on-the-fly modulations of rhythm, tempo, pitch, and dynamics to match the child's level of alertness and mirroring of the child's behavior.

The iso principle (Altshuler, 1948) broadly prescribes the matching of musical components (e.g., rhythm, tempo, pitch, and dynamics) to the patient's mood or physiological states (Davis et al., 2008) and has been widely applied in music therapy to build therapeutic relationship, connect patients with music, and gradually shift the patient's mood or physiological state (Heiderscheit and Madson, 2015; Kim et al., 2018). This principle can guide musical improvisation to maximize the effectiveness of music therapy for children with disabilities (Salomon-Gimmon and Elefant, 2019; Stegemann et al., 2019).

In this study, the music therapist improvised using written music by changing the words and extending the original songs. The therapist also improvised using ostinato patterns as well as altered melodies and chords. However, the improvisation was constrained within the personalized music list of each participant. Overall, the music therapist deployed a combination of free improvisation and written music. The music intervention was adapted to meet the specific participation level, physical condition, and cognitive skills of each individual participant. The music therapist was trained in neurologic music therapy (Thaut and Hoemberg, 2014) and thus deployed techniques thereof, as appropriate.

2.4. Data Analysis

Prior to signal analyses, all data streams were aligned at the synchronization pulse. Raw EEG signals during a 15−min music therapy session were divided into three sub-intervals of 5-min each, denoted as MT1, MT2, and MT3. These sub-intervals along with the preceding 3-min baseline EEG recordings were segmented into overlapping windows of 1-s duration (referred to as a trial, hereafter) with a 90% overlap. Spectral densities of the EEG trials from child and parent were then computed using fast Fourier transform with 4 Hz spectral smoothing through multi-tapering (McCoy et al., 1998) using 3 Slepian (discrete prolate spheroidal) sequences to suppress temporal jitters. The resulting spectral densities were in turn used to compute spectral coherence and Granger influences between child-parent dyads. Spectral densities, coherence, and Granger influences were computed using FieldTrip (Oostenveld et al., 2011). Coherence quantifies the frequency-specific covariation between two signals and is given by the magnitude squared of their cross-spectral density over the product of their individual spectral densities (Bendat and Piersol, 2011). Granger influence captures the directional influence of one time series on another, i.e., the degree to which future values of one time series are predicted by the combination of lagged values of itself plus those of a second time series (Granger, 1969). Child-parent spectral coherence and directional Granger influences between EEG channel-pairs were computed for baseline and music therapy subintervals (MT1, MT2, and MT3). Connectivity measures (coherence and Granger influence) were computed for every 20-s recording (188 overlapping trials) with a 2−s shift between subsequent 20-s windows. This resulted in 144 and 251 connectivity measures for the baseline and each one of the music therapy subintervals, respectively. To determine whether the connectivity measures during the music therapy subintervals were significantly higher than that of the corresponding baseline, the Wilcoxon rank sum test was performed. Furthermore, connectivity measures between successive music therapy subintervals (i.e., baseline vs. MT1; MT1 vs. MT2 and MT2 vs. MT3) were compared using the Wilcoxon rank sum test to identify significant changes in connectivity over the course of the music therapy session.

A cluster-based permutation test (Groppe et al., 2011a) was implemented to evaluate the above hypotheses about

[1]www.emotiv.com

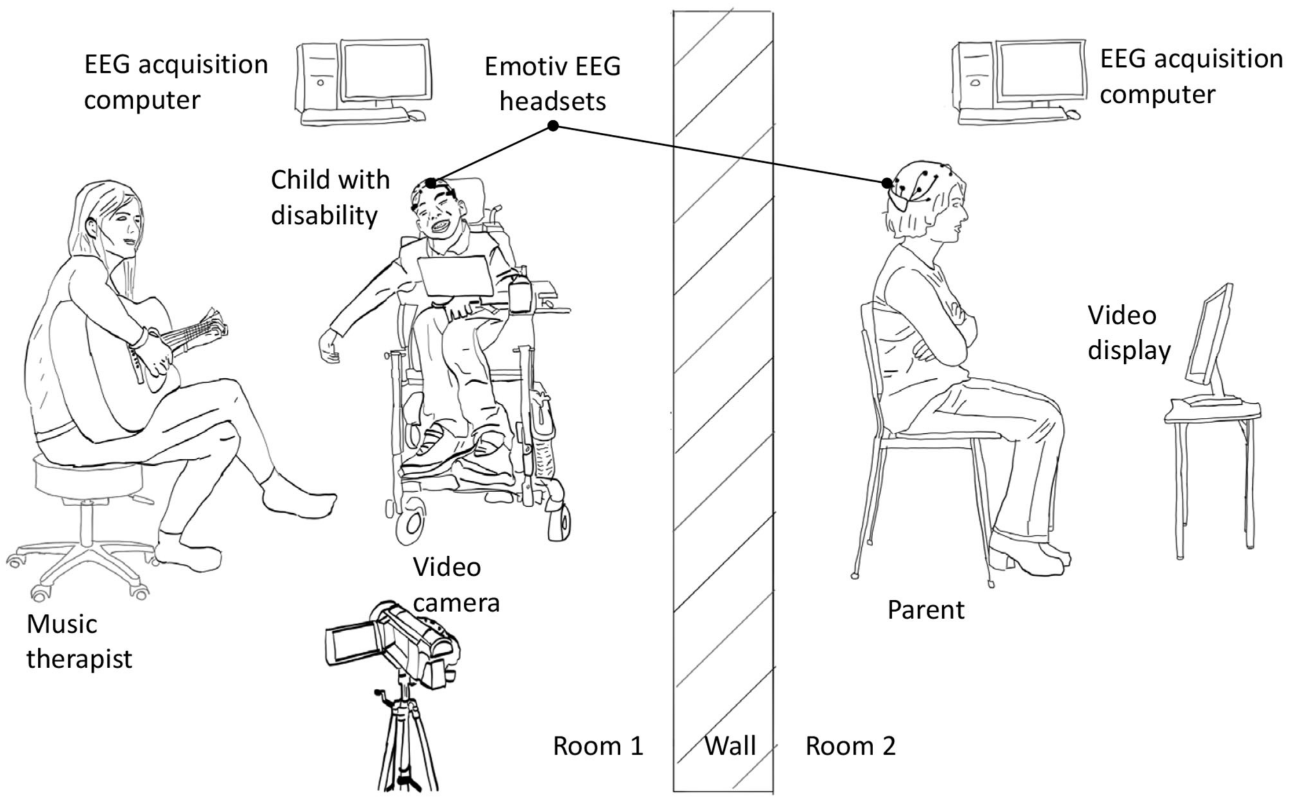

FIGURE 1 | Experimental setup for simultaneous EEG recording from children and their parents. For clarity, wired connections between data acquisition computer and sensors are not shown.

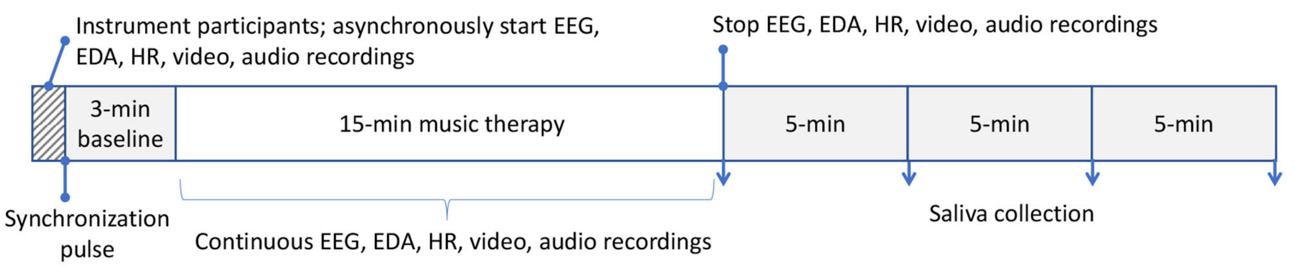

FIGURE 2 | Sessional protocol. All data streams were synchronized with an external sync pulse. Saliva was collected post-session. Only EEG data are reported here. Each of the 10 sessions per participant followed the same protocol. EEG, electroencephalography; EDA, electrodermal activity; HR, heart rate.

connectivity changes. Cluster-based approaches are touted as the most sensitive univariate mass test for broadly distributed effects (Groppe et al., 2011b). **Figure 3** shows the implemented dyadic connectivity analysis. A rank sum test was performed for connectivity measures computed for every frequency bin (1 to 64 Hz) and parent-child × channel-pairs. Only cases with $p < 0.05$ and at least a medium Cohen's d effect size ($d > 0.5$) were retained. For the cluster-based permutation test, clusters were formed based on 5 frequency bands and 4 brain regions (**Figure 4**). The frequency bands were in the δ band (0–4 Hz), θ band (4–8 Hz), α (8–14 Hz), β band (14–32 Hz), and lower γ band (32–64 Hz). Among these bands, the suppression of α band power and increased lower γ band activity are associated with shared brain activations between people, attention, perceptual awareness, and cognitive control (Fries, 2005; Wyart and Tallon-Baudry, 2008; Frenkel-Toledo et al., 2014) which may subserve empathy. The cluster-based analysis resulted in 16 child-parent region-pairs for each frequency band. Clusters where the number of active members ($p < 0.05$ and medium to large Cohen's d) constituted less than 10% of the cluster size were ignored. The z-statistics of a cluster were summed up to produce cluster-level z-statistics ("mass of the cluster"). For the permutation runs, 1,000 permutations were used where in each permutation, the order of connectivity measures during the entire music

TABLE 2 | Intervention theory.

Rationale for music selection Preferred music according to parental recommendation and documentation of music by previous music therapists who had worked with the child (if applicable); further selections of songs similar in genre, artist and style to those familiar to child; improvisation introduced at discretion

Accompanying instruments:

- Hand Sonic 10 electric drum (child 8)
- Piano (child 12)
- Violin (child 7)
- Small djembe drum (child 9)
- Wind chimes (child 2)
- Cymbals (child 4)
- Wrist bells, Cabassa, Mallets

* Some instruments were selected more frequently for certain children as shown in brackets

Expected impact: Encourage engagement, alertness/wakefulness, and music participation

TABLE 3 | Sample intervention content.

Instrument	Musical piece
Piano	"Ave Maria" (Franz Schubert)
	"A Whole New World" (Alan Menken)
	"Banana Phone" (Raffi)
	"Feliz Navidad" (Jose Feliciano)
	"I Got Rhythm" (George Gershwin)
	"I Have a Dream (ABBA)"
	"Lean on Me" (Bill Withers)
	"Oh Canada"
	"White Christmas" (Irving Berlin)
	"Yankee Doodle"
Guitar	"Baby Beluga" (Raffi)
	"Black Hole Sun" (Soundgarden)
	"Down by the Bay"
	"Something in the Way" (Nirvana)
	"Stand by Me" (Ben E. King)
	"Sweet Home Alabama" (Lynyrd Skynyrd)
	"The Lion Sleeps Tonight (George David Weiss, Hugo Peretti, and Luigi Creatore)"
	"Where Did You Sleep Last Night" (anonymous; as performed by Nirvana)
	"Yellowž (Coldplay)
	"Yellow Submarine" (Raffi)
	"Yellow Submarine" (The Beatles)
	"You are My Sunshine"
	"3 AM" (Matchbox 20)
	"Fallout" (Marianas Trench)
	"Good Bye Song" (therapist)
	"Have You Ever Seen the Rain?" (John Fogerty; as performed by Credence Clearwater Revival)
	"Hey Jude" (The Beatles)
	"Last Kiss" (W. Cochran et al.; as performed by Pearl Jam)
	"Let it Be" (The Beatles)
	"Mr. Sun" (Raffi)
	"Never Too Late" (Three Days Grace)
	"Ob-la-di Ob-la-da" (The Beatles)
	"Oh Susanna" (Stephen Foster)
	"Over the Rainbow" (E.Y. Harburg (lyrics) and Harold Arlen (music))
	"Proud Mary" (John Fogerty; as performed by Credence Clearwater Revival)
Guitar + electric drum	"La Bamba" (Mexican folk song; written by Ritchie Valens)
Violin	"Por una Cabeza" (Argentine Tango; Carlos Gardel)
	"Salut d'Amour" (Edward Elgar)
Drum	"Kumbaya", "The Ants Go Marching One by One", "When the Saints Go Marching In" (anonymous)
	"Fungalafia"

therapy recording (15−min) was randomized. The baseline connectivities remained unchanged during the permutation test. Cluster masses were computed for the 1,000 randomized permutations as described above.

Subsequently, a connectivity value was identified as significant at $p < 0.05$ if its z-statistic was higher than the 97.5 th percentile of the cluster-based permutation z-statistics, after correcting for multiple comparisons across 16 brain-region pairs and 5 frequency bands. The multiple comparison correction was done by comparing the rank sum z-statistics against the maximum 97.5 th percentile of the randomized z-statistics for 5 (frequency bands) × 16 (brain regions) clusters (Bosman et al., 2012).

Post-hoc analysis (a separate linear mixed-effect regression model) was performed to examine the effects of child sex and residential status (inpatient, outpatient), along with brain region and frequency bands, on coherence and Granger influences (dependent variables). Additionally for Granger values, the effect of the direction of analysis (i.e., parent to child or child to parent) was also tested. While sex, residential status, brain region, frequency band and directionality were included as fixed effects, subjects, sessions, and child age were represented in the model as random effects. Type III Wald F tests with Kenward Roger degrees-of-freedom approximation were used for testing the fixed effects. SPSS statistical package was used to run the *post-hoc* analysis.

3. RESULTS

Figure 5 depicts the proportion of child-parent dyads who exhibited significant inter-brain coherence during music therapy sessions, indexed by frequency band (vertical axis) and pairing of brain quadrants (horizontal axis). In this figure, a red shaded square means that all the child-parent dyads had significant coherence at the given frequency band and pairing of brain regions. Significant coherences were found to occur most often in the β and lower γ bands, between child frontal right and parental frontal left brain regions. Over successive sub-intervals of music therapy sessions, a significant increase in coherence over time (**Figure 6**) was observed in β and lower γ bands in almost all

TABLE 4 | Intervention checklist.

Music delivery method	Interventionist only; one-on-one; live
Intervention materials	Therapist's voice (for every musical excerpt) and instruments mentioned above. No non-music materials were used.
Intervention strategies	Incorporation of child's name and vowel sounds into therapist's vocalizations through improvised music
	Various percussion instruments as accompaniment
	Use of dynamics to match child's apparent alertness
	Variation in rhythm, tempo, pitch and dynamics often applied to promote engagement and alertness
	Mirroring and mimicking of child motion or vocalization to promote engagement
Intervention delivery schedule	Ten 15-min sessions (except for child 1: six 15-min sessions); no more than 2 weeks apart
Interventionist	Qualified music therapist at Holland Bloorview.)
Treatment fidelity	Clinician had a Certified Music Therapist (MTA) designation from the Canadian Association for Music Therapists, which indicates they have met the guidelines and standards for professional competence set out by the Association.
Setting	Complex Continuing Care Activity Room or Music Therapy Room at Holland Bloorview; private; ambient sound was negligible
Unit of delivery	One-on-one

dyads, again between the child's frontal right and parental frontal left brain regions. Frontal left brain regions of parent and child also showed significant increases in coherence over the session for the majority of dyads.

When comparing Granger influences (i.e., direction and magnitude of influence from child to parent and vice versa) during music therapy sessions with those of corresponding baselines, no prominent pattern was observed (**Figure 7**). Granger influences, however, significantly increased over the course of the music therapy session bidirectionally between child and parent, as indicated in **Figures 8A,B**. Similar to coherence measures, significant Granger influences between the oscillations deriving from the child's frontal right and parent's frontal left brain regions in the β and lower γ frequency bands were the most frequently observed.

As seen in **Table 5**, the mixed model analysis revealed significant effects of brain regions (**Figure 4**) and frequency bands on the observed coherence. Coherence however was not affected by the child's sex or residential condition at $p < 0.05$. In addition, there were significant two-way interactions on the observed coherence values: (1) child's sex and frequency band, (2) residential status and frequency band, and (3) brain region and frequency band. Inspecting the marginal means revealed that outpatient participants demonstrated higher coherence with their parents in the α band and female participants demonstrated lower coherence in the α band. Similarly, brain region and frequency band had significant effects on Granger influence (**Figure 4**). Furthermore, the direction of analysis (child to parent vs. parent to child) significantly affected Granger values. However, there was no significant effect of child's sex or residential status on Granger influence ($p < 0.05$). The interactions of (1) direction and frequency band, and (2) residential status and brain region exerted significant effects on Granger influences (**Table 6**).

4. DISCUSSION

We documented contemporaneous brain signals and their directional influences in non-speaking children with severe disabilities and one of their cognate parents, during music therapy.

4.1. Synchronous Brain Regions

The observed interpersonal brain couplings were primarily concentrated in the prefrontal and frontal areas that are often implicated in empathic function (Shamay-Tsoory et al., 2003, 2009; Mitchell et al., 2005; Schulte-Rüther et al., 2007; Nummenmaa et al., 2008). The children were not able to see or hear their parents during the sessions. Thus, synchronized activation of empathy-related areas in both the children and parents suggest that the latter vicariously experienced the child-therapist interaction. In particular, there was significant coupling between Broca's area (parental brain), which is associated with emotional empathy (Schulte-Rüther et al., 2007; Nummenmaa et al., 2008) and dorsolateral prefrontal cortex (child's brain), which is linked to cognitive empathy (Shamay-Tsoory et al., 2003, 2009). This contralateral, regional interbrain coupling implies that while the children were cognitively engaged with their music therapist, the parents were emotionally attuned to their child's experience (Rankin et al., 2006; Decety and Ickes, 2009).

The ventrolateral frontal areas (including Broca's area) putatively support emotional empathy (Schulte-Rüther et al., 2007; Nummenmaa et al., 2008), a supposition corroborated by lesion studies where localized frontal damage leads to impaired emotional contagion (Shamay-Tsoory et al., 2009). The notion that the parents were attuned in an emotionally empathic manner to their children is further supported by the apparent association between Broca's area and the mirror neuron system (Fadiga et al., 2009), which is believed to be critical to social-cognitive processing (Schmidt, 2020).

The observation of synchronous involvement of the right frontal side of the children's brains may suggest invocation of non-verbal intuition, cognition, and creativity. Importantly, activity in the right prefrontal regions is affiliated with cognitive empathy, where one evaluates the mental states of others with reference to oneself (Shamay-Tsoory et al., 2003, 2009). Thus, the right prefrontal brain activity in the children might reflect some degree of allocentric perspective-taking, i.e., understanding of the therapist's thoughts, feelings and perceptions. In similar vein, the instances of significant ipsilateral (left-side) coupling between frontal areas of children and parents (at β and lower γ bands in the final sub-intervals of music therapy) suggest

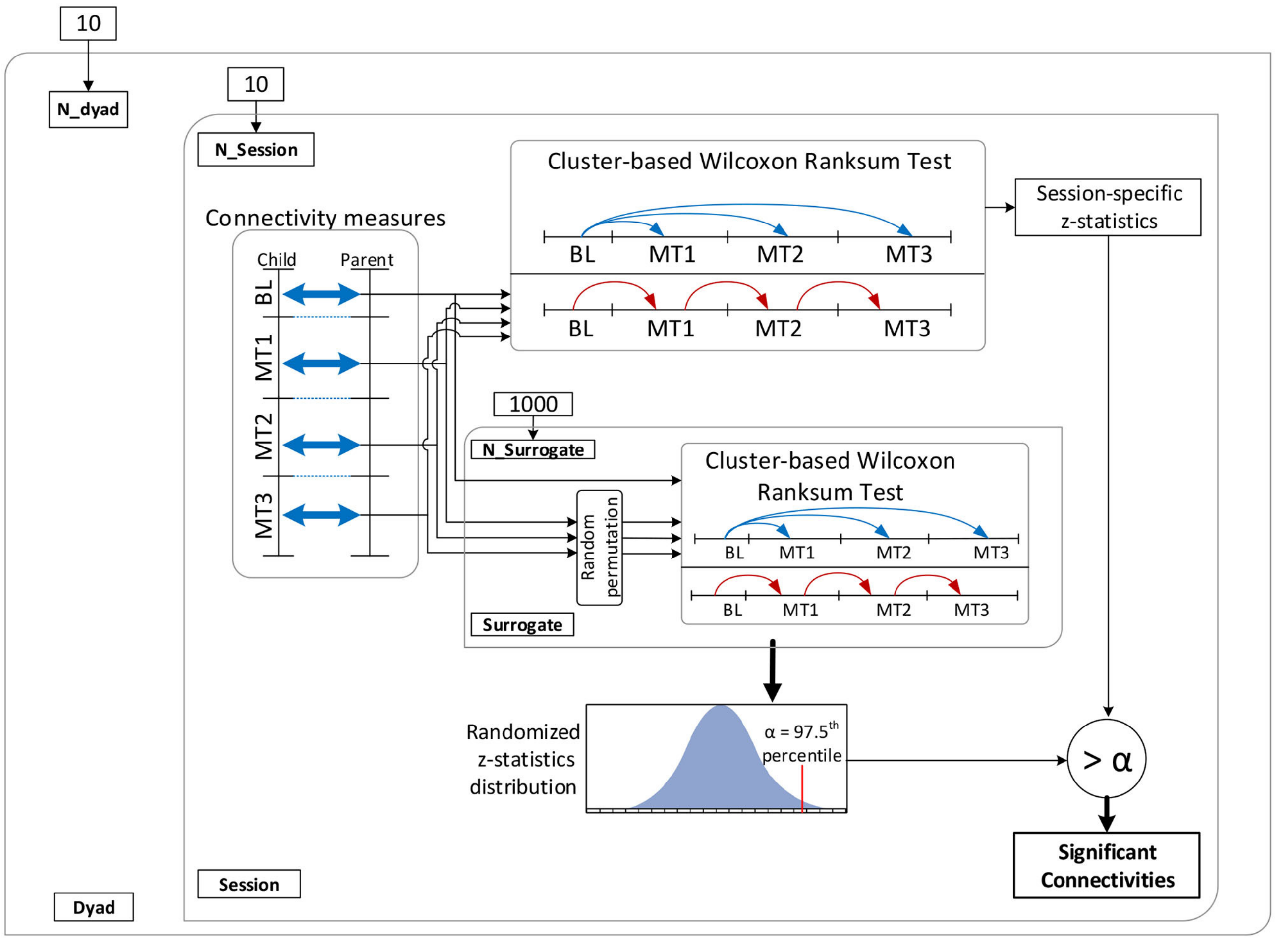

FIGURE 3 | Schematic of the connectivity analysis. BL, baseline; MT1, first 5 min of music therapy; MT2, second 5 min of music therapy; MT3, last 5 min of music therapy.

that both parents and children alike were harmonized with the emotional disposition of their counterpart (children and therapists, respectively), possibly as a consequence of observing facial expressions (Kesler-West et al., 2001) and affective prosody (Wildgruber et al., 2005).

4.2. Frequency Bands With Greatest Synchrony

Prefrontal and frontal activity in the β and γ bands is known to increase parametrically with working memory load (Howard et al., 2003; Spitzer et al., 2010; von Lautz et al., 2017). Thus, increased coupling in these bands might indicate synchronized active engagement in the music therapy sessions by both children and parents. Interestingly, we observed a paucity of α synchrony. This observation may in fact support the speculation that β and γ synchrony may have been indicative of empathic connection. In particular, Frenkel-Toledo et al. (2014) have reported associations between μ suppression (sensorimotor EEG signal power in the α frequency range) and mirror neuron system activation, which is putatively involved in cognitive empathy. Lübke et al. (2020) went further to report associations between μ suppression and a measure of state empathy while Babiloni et al. (2012) linked task-related α band power decrease to emotional empathy. Further, the lower α coherence in female participants during *post-hoc* analyses may suggest that the degree of empathic experiences varied depending on the child's sex. Indeed, many studies have reported generally heightened empathic traits in females (for an extensive review, see Christov-Moore et al., 2014): superior nonverbal emotion recognition (McClure, 2000; Schirmer et al., 2007), greater susceptibility to emotional contagion (Doherty et al., 1995; Magen and Konasewich, 2011), and advantages in mentalizing (perspective-taking) (Gardner et al., 2012).

4.3. Increase in Inter-brain Synchrony

Both coherence and Granger influence exhibited significant increases over the course of a 15-min music therapy session in frontal brain regions, in the β and low γ bands. In other words, the majority of parent and child dyads became more neurophysiologically "in sync" during a music therapy session. This is an interesting finding as it indicates that

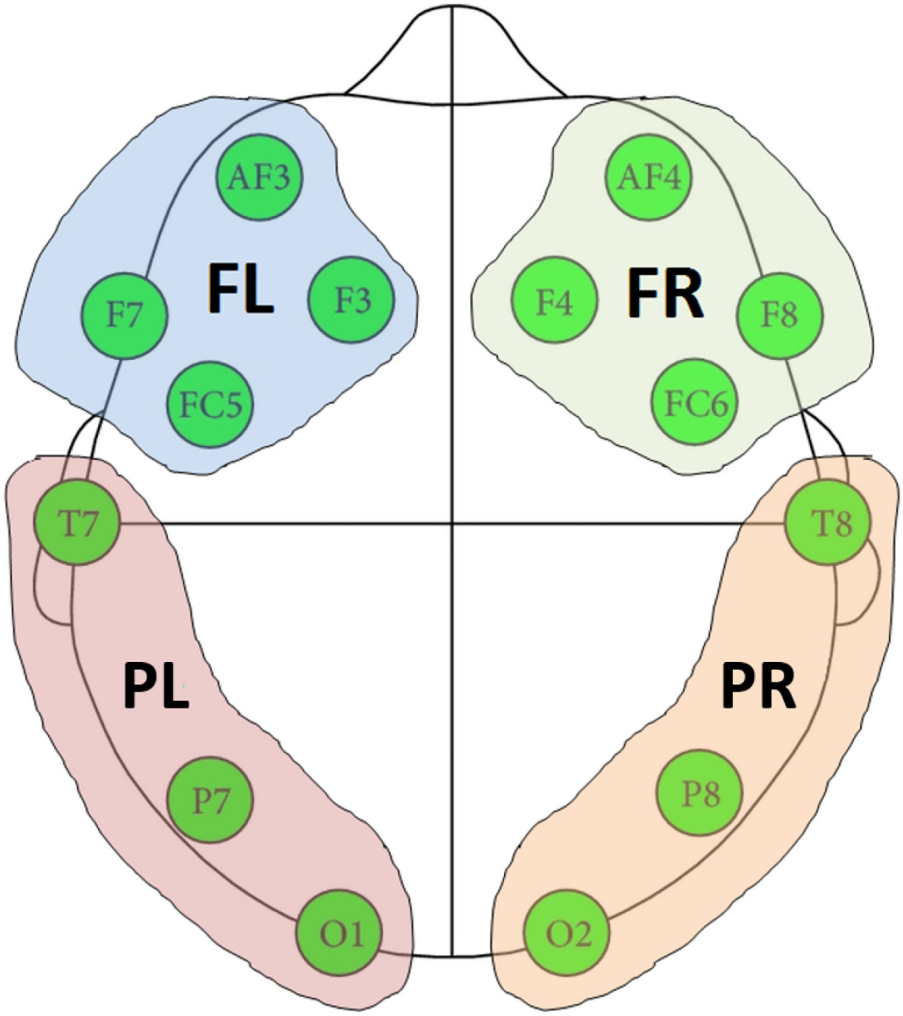

FIGURE 4 | Four regions formed based on the location of EEG channels. FR, frontal right; FL, frontal left; PR, posterior right; PL, posterior left.

not only are the sample of non-speaking children with severe disabilities capable of physiologically influencing their parents (i.e., significant directional Granger values from child to parent), but that this influence is dynamic and labile. Indeed, studies of infants and mothers have reported that their interpersonal bio-behavioral synchrony can fluctuate with episodic gaze, vocalizations and touch (Feldman, 2012). Further, Davis et al. (2018) draw attention to proximal (such as the shared task at hand) and distal (such as family risk) contexts that may impact physiological synchrony. Our data would seem to suggest that a music therapy experience is a facilitatory context which can promote child-parent neural synchrony.

The parent-to-child Granger influence may appear odd at first glance, since the child was not able to see or interact with the parent. However, it is important to remember that the Granger measure in this case ascertains the contribution of previous values of the parent's brain signals to the prediction of current values of the child's brain signals. As such, the measure ought to be considered a quantification of the predictability of the child's signals on the basis of recent past values of the parent's signals. Alternatively, one might think of the Granger measure as capturing the strength with which the parent's signals lead the child's signals. In our study, it is indeed conceivable that the parent tended to anticipate the response of the child, given that the selected songs were familiar and personalized to each dyad. Recent literature has demonstrated that interpersonal autonomic synchrony between people may arise in the absence of face-to-face interaction, while jointly watching a positively or negatively valenced movie clip (Golland et al., 2015) or attending a live monolog performance (Ardizzi et al., 2020). In the former study, the degree of synchronization was further correlated with the level of convergence of subjective emotional experience. In terms of neural synchrony, Azhari et al. (2019) observed heightened prefrontal cortex hemodynamic signal alignment between spouses when attending to salient infant and adult vocalizations

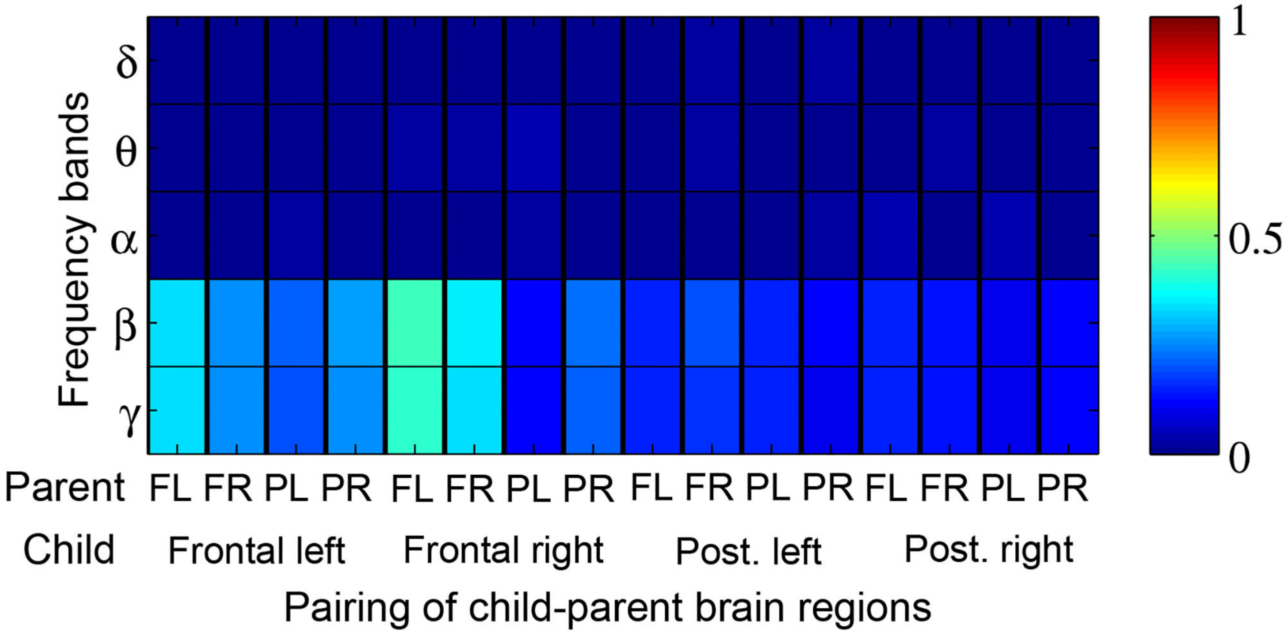

FIGURE 5 | Proportion of child-parent dyads exhibiting significant music therapy coherences with respect to their corresponding baseline segments. Red shading thus denotes 100% of dyads with significant coherence. The proportions are tabulated by frequency band (rows) and pairings of child-parent brain regions i.e., frontal left (FL), frontal right (FR), posterior left (PL), and posterior right (PR).

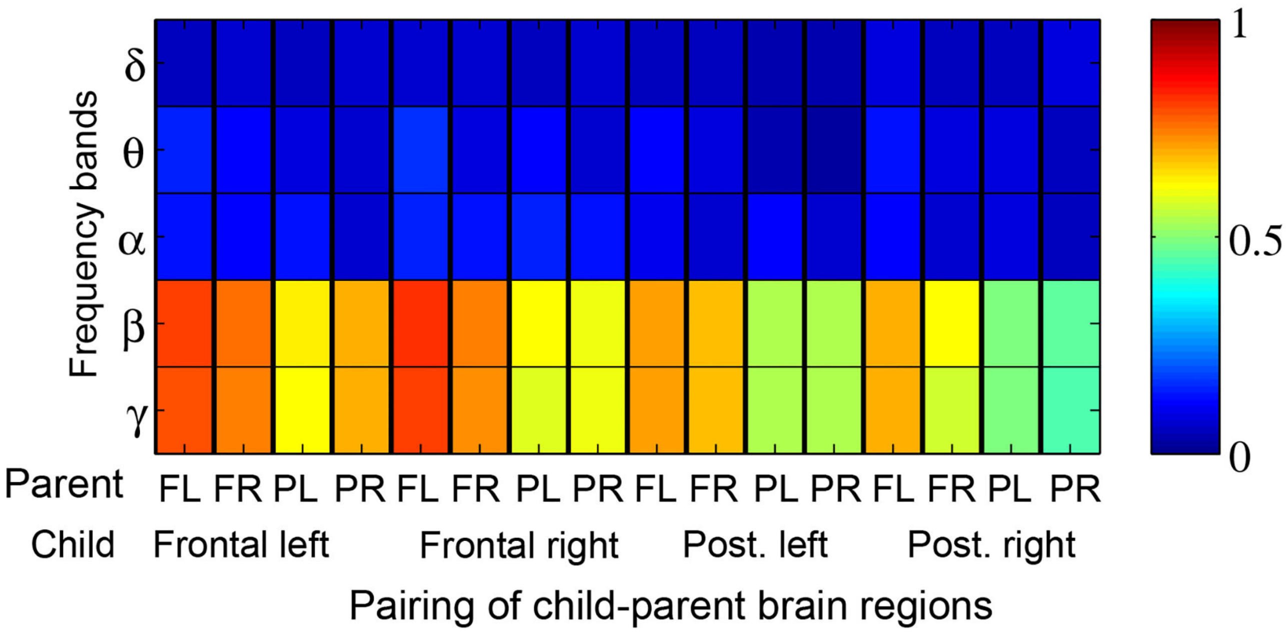

FIGURE 6 | Proportion of child-parent dyads exhibiting significant increases in coherence over the course of a music therapy session. Red shading thus denotes 100% of dyads with significant increases in coherence. The proportions are tabulated by frequency band (rows) and pairing of child-parent brain regions i.e., frontal left (FL), frontal right (FR), posterior left (PL), and posterior right (PR).

in each other's presence compared to experiencing the same alone or with a non-spousal control. Collectively, these studies suggest that "co-presence" (Golland et al., 2015) may be a critical contributor to physiological synchrony, ushering its emergence among people, without interpersonal communication, but simply through a joint sensory experience. In our study, the parent

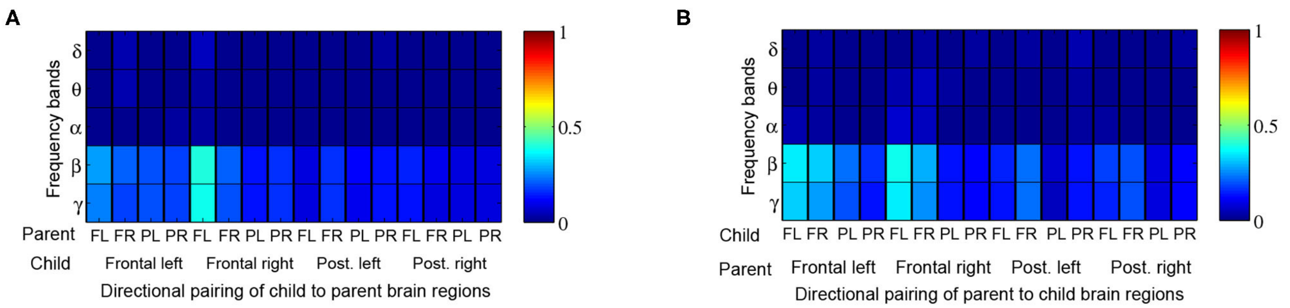

FIGURE 7 | Proportion of child→parent and parent→child directional analyses exhibiting significant Granger influences during music therapy compared to preceding baseline values. Red shading thus denotes 100% of dyads with significant Granger influence. The proportions are tabulated by frequency band (rows) and directional pairing of brain regions, i.e., frontal left (FL), frontal right (FR), posterior left (PL) and posterior right (PR) from **(A)** child to parent, and **(B)** parent to child.

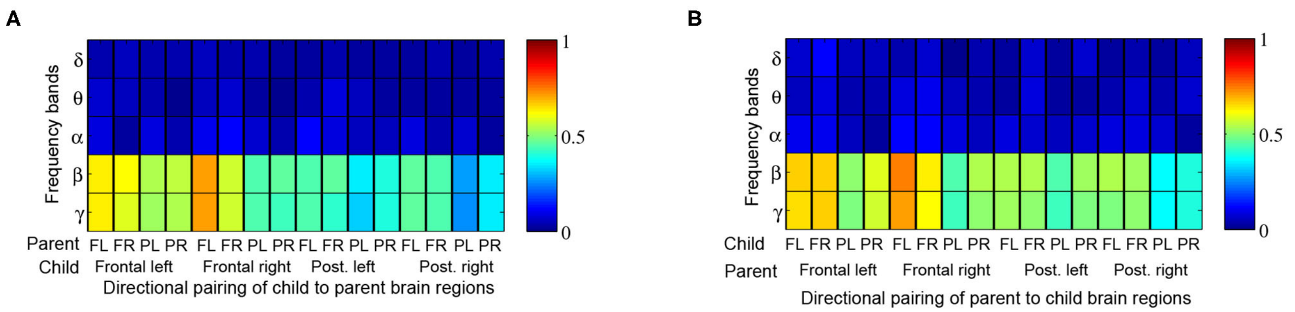

FIGURE 8 | Proportion of child→parent and parent→child directional analyses exhibiting significant increases in Granger influences over the course of a music therapy session. The proportions are tabulated by frequency band (rows) and brain region, i.e., frontal left (FL), frontal right (FR), posterior left (PL), and posterior right (PR) from **(A)** child to parent, and **(B)** parent to child.

and child contemporaneously experienced, proximal to each other, salient musical stimuli presented by the therapist, without face-to-face interaction, and hence the observed parent-to-child synchrony may in part be attributable to their co-presence.

4.4. Music Therapy Context

The observed neurological correspondence between children and their parents in β and low γ bands may reflect neurophysiological responsiveness of the non-speaking children to the music therapy sessions. Indeed, Thompson and McFerran (2015) contend that music therapy "creates engaging and motivating conditions for interactions with others" and Mendelson et al. (2016) found that music therapy promoted verbal responsiveness in children with autism and other developmental disabilities.

Our findings suggest that music therapy seems to support the emergence of interbrain synchrony between parent and child. This may not be surprising given that one of the fundamental goals of music therapy is the establishing or re-establishing of interpersonal relationships (Meadows, 1997). Moreover, in a review of music therapy interventions with children with disabilities, Brown and Jellison (2012) reported that pediatric studies most often reported effective or partially effective treatment of social behaviors while Pavlicevic et al. (2014) found that music therapy afforded opportunities for developing and sustaining friendships in adults with disabilities. The latter study also lends credence to the choice of music therapy as a setting for studying interpersonal synchrony as families and young adults with severe learning disabilities ascribed relational and social values to long-term music therapy (Pavlicevic et al., 2014).

The interpretation that the observed spectral coherence may reflect mutual engagement may in part be supported by the fact that functional outcomes of music therapy often include children's ability to participate in turn-taking, maintain attention (Perry, 2003) and learn social reciprocity (Hussey et al., 2008). That music therapy affords a propitious setting for neural synchrony may be germane to the theoretical perspective that affective attunement between child and parent is musical and improvisational in nature (Lindstrøm et al., 2016).

4.5. Clinical Implications

The present study, while based on a modest sample, does have important implications for understanding the capacity of non-speaking children with severe disabilities for bio-behavioral neurophysiological synchrony. Our findings suggest that parent-child dyads can possess the ability to synchronize physiologically, in face of severe disability and without the need for making any vocal or gestural interactions. This tendency may be

TABLE 5 | F-statistics and *p*-values from the linear mixed model of the effect of child's sex, residential status, brain region, frequency band, and interactions thereof, on the observed coherence measures.

Effects		***p*-value**
Sex	F(1, 6.4): 0.10	0.762
Residential status	$F_{(1,1.9)}$: 3.13	0.228
Brain region	$F_{(15,\ 7088.2)}$: 3.70	< 0.001
Frequency band	$F_{(4,\ 7088.2)}$: 1989.25	< 0.001
Sex × Region	$F_{(15,\ 7088.2)}$: 0.59	0.886
Sex × Frequency band	$F_{(4,\ 7088.2)}$: 12.66	< 0.001
Residential status × Brain region	$F_{(15,\ 7088.2)}$: 1.43	0.121
Residential status × Frequency band	$F_{(4,\ 7088.2)}$: 55.04	< 0.001
Brain region × Frequency band	$F_{(60,\ 7088.2)}$: 1.83	< 0.001

TABLE 6 | F-statistics and *p*-values from the linear mixed model of the effect of direction of influence, child's sex, condition, brain region, frequency band, and interactions thereof, on the observed Granger influences.

Effects		***p*-value**
Direction	$F_{(1,14345.9)}$: 19.42	< 0.001
Sex	$F_{(1,\ 5.8)}$: 0.02	0.881
Residential status	$F_{(1,\ 1.1)}$: 0.02	0.917
Brain region	$F_{(15,\ 14345.9)}$: 23.59	< 0.001
Frequency band	$F_{(4,\ 14345.9)}$: 283.58	< 0.001
Direction × Child's sex	$F_{(1,\ 14345.3)}$: 0.62	0.43
Direction × Participant's condition	$F_{(1,\ 14345.9)}$: 0.73	0.393
Direction × Brain region	$F_{(15,\ 14345.9)}$: 0.01	0.998
Direction × Frequency band	$F_{(4,\ 14345.9)}$: 7.11	< 0.001
Sex × Brain region	$F_{(15,\ 14345.9)}$: 1.51	0.092
Sex × Frequency band	$F_{(4,\ 14345.9)}$: 45.76	< 0.001
Residential status × Brain region	$F_{(15,\ 14345.2)}$: 1.88	0.02
Residential status × Band	$F_{(4,\ 14345.9)}$: 52.85	< 0.001
Brain region × Frequency band	$F_{(60,\ 14345.9)}$: 6.24	< 0.001

an instantiation of what Golland et al. (2015) termed "co-presence," where they found that the mere fact of being in the presence of another, in the absence of direct communication, can nonetheless lead to autonomic (heart rate and electrodermal activity) synchronization between people. While the participants in Golland et al. (2015) watched emotional movies, our findings suggest that music therapy with personalized content may also serve as a scaffold for physiological co-regulation.

The surprising finding that the outpatient dyads tended to exhibit stronger synchrony than their inpatient counterparts, albeit on the basis of small subsamples, supports the notion that the nature of familial relationships has a role in determining the levels of parent-child physiological co-regulation (Davis et al., 2018). Finally, our findings provide preliminary evidence that while caring for a child with severe disability is a known familial stressor (Burke et al., 2020), parent-child neurophysiological synchrony can be preserved and in fact, labile in a facilitatory, music therapy context. Future research may nonetheless consider documenting the mental health of caregivers as parental stress can diminish brain-to-brain synchrony between mothers and their young children (Azhari et al., 2019). Conversely, the presence of physiological synchrony may not always connote positive experiences and can in fact be maladaptive in response to negative interactions (Oshri et al., 2020).

4.6. Limitations

While we observed significant contralateral coupling of prefrontal and frontal brain regions, these regions are also critical to many other functional brain networks. For instance, Broca's area is commonly involved in language processing and one could surmise that coupling in this region could have simply indicated a synchronization of linguistic processing in response to music therapy. Therefore, we cannot definitively attribute the observed coherence and Granger influences to emotional empathy between parent and child. Future studies may yoke brain measurement with self-reported empathy scores throughout music therapy to shed light on the relationship between interbrain coupling and empathic function.

We did not control for time of day in our data collection but had to accommodate the schedules of our participants, many of whom had complex care needs. Nonetheless, diurnal rhythms can influence the level of physiological synchronization (Davis et al., 2018), and thus future studies may consider standardizing data collection times across participant where feasible.

Our participants ranged in developmental stage and clinical diagnoses. The propensity for synchrony with parents may depend on the developmental stage of the child (Harrist and Waugh, 2002) and in particular, their level of independence, e.g., more or less reliant on parental support, and time spent in co-habitation. Likewise, the lability of certain physiological responses and hence capacity for synchrony, may be blunted in certain clinical populations (Blain-Moraes and Chau, 2012). Future research may thus consider a narrower developmental and diagnostic sample.

A wealth of literature exists on rhythmic auditory stimulation and auditory-motor entrainment (Ghai et al., 2018). From our study data, we were not able to discriminate the contribution of synchrony due strictly to the rhythmic components of the music from that due to physical presence and shared emotional experiences. A future study may seek to quantify brain coupling due exclusively to listening to a common piece of music where dyadic participants are physically isolated from one another.

We did not have a balanced sample of males and females. From childhood through to adolescence, females are found to express more prosocial, sympathetic, and empathetic traits than males (Rose and Rudolph, 2006; Chaplin and Aldao, 2013). Future studies with larger, balanced samples of both males and females are required. Furthermore, both mothers and fathers of children should be recruited in future studies and parental demographic characteristics should be recorded to compare respective levels of neurophysiological coherence with their children and explore potential association with personal attributes. Gender-based differences in child-parent dyadic interactional synchrony have been previously noted (De Mendonça et al., 2019).

5. CONCLUSION

We observed significant neurophysiological synchrony as measured by coherence and Granger influence in a dyadic sample of non-speaking children with severe physical disabilities and cognate parents during music therapy sessions where the musical content was tailored to the child's preferences. Coherence was most prominent in contralateral frontal brain regions (child right and parent left) in the β and low γ bands. Further, both coherence and Granger influence increased significantly over the course of a music therapy session. Collectively, these findings suggest a cognitive-emotional alignment between child and parent that is responsive to music therapy. Further investigations on the facilitative effect of music therapy on interbrain synchrony and empathic connection between children and their familial caregivers are warranted.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of ethical constraints. Requests to access the datasets should be directed to tchau@hollandbloorview.ca.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Holland Bloorview Kids Rehabilitation Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SK and TC designed the study. SK collected the data. AS and SK performed the data analyses. JM and KK edited the manuscript and wrote parts of the discussion. TC, KK, and AS made substantive revisions to the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Altshuler, I. (1948). *The Past, Present, and Future of Musical Therapy*. PODOLSKY, Edward. Music Therapy. New York, NY: Philosophical Library.

Ardizzi, M., Calbi, M., Tavaglione, S., Umiltà, M. A., and Gallese, V. (2020). Audience spontaneous entrainment during the collective enjoyment of live performances: physiological and behavioral measurements. *Sci. Rep.* 10, 1–12. doi: 10.1038/s41598-020-60832-7

Azhari, A., Leck, W., Gabrieli, G., Bizzego, A., Rigo, P., Setoh, P., et al. (2019). Parenting stress undermines mother-child brain-to-brain synchrony: a hyperscanning study. *Sci. Rep.* 9, 1–9. doi: 10.1038/s41598-019-47810-4

Azhari, A., Lim, M., Bizzego, A., Gabrieli, G., Bornstein, M. H., and Esposito, G. (2020). Physical presence of spouse enhances brain-to-brain synchrony in co-parenting couples. *Sci. Rep.* 10, 1–11. doi: 10.1038/s41598-020-63596-2

Babiloni, C., Buffo, P., Vecchio, F., Marzano, N., Del Percio, C., Spada, D., et al. (2012). Brains "in concert": frontal oscillatory alpha rhythms and empathy in professional musicians. *Neuroimage* 60, 105–116. doi: 10.1016/j.neuroimage.2011.12.008

Bendat, J. S., and Piersol, A. G. (2011). *Random Data: Analysis and Measurement Procedures*. Vol. 729. Hoboken, NJ: John Wiley & Sons.

Bernieri, F. J., and Rosenthal, R. (1991). "Interpersonal coordination: Behavior matching and interactional synchrony," in *Stuides in Emotion & Social Interaction: Fundamentals of Nonverbal Behavior*, eds R. S. Feldman and B. Rimé (New York, NY: Cambridge University Press; Editions de la Maison des Sciences de l'Homme), 401–432.

Bispham, J. C. (2009). Music's "design features": Musical motivation, musical pulse, and musical pitch. *Music. Sci.* 13(2 Suppl.), 41–61. doi: 10.1177/1029864909013002041

Blain-Moraes, S., and Chau, T. (2012). Challenges of developing communicative interaction in individuals with congenital profound intellectual and multiple disabilities. *J. Intellect. Dev. Disabil.* 37, 348–359. doi: 10.3109/13668250.2012.721879

Bosman, C. A., Schoffelen, J.-M., Brunet, N., Oostenveld, R., Bastos, A. M., Womelsdorf, T., et al. (2012). Attentional stimulus selection through selective synchronization between monkey visual areas. *Neuron* 75, 875–888. doi: 10.1016/j.neuron.2012.06.037

Brown, L. S., and Jellison, J. A. (2012). Music research with children and youth with disabilities and typically developing peers: a systematic review. *J. Music Ther.* 49, 335–364. doi: 10.1093/jmt/49.3.335

Burke, M. M., Rios, K., and Aleman-Tovar, J. (2020). Identifying child, parent, and school correlates of stress among parents of children with intellectual and developmental disabilities. *Res. Pract. Intellect. Dev. Disabil.* 7, 5–16. doi: 10.1080/23297018.2019.1647552

Chaplin, T. M., and Aldao, A. (2013). Gender differences in emotion expression in children: a meta-analytic review. *Psychol. Bull.* 139:735. doi: 10.1037/a0030737

Christov-Moore, L., Simpson, E. A., Coudé, G., Grigaityte, K., Iacoboni, M., and Ferrari, P. F. (2014). Empathy: gender effects in brain and behavior. *Neurosci. Biobehav. Rev.* 46, 604–627. doi: 10.1016/j.neubiorev.2014.09.001

Coutinho, J., Oliveira-Silva, P., Fernandes, E., Gonçalves, O. F., Correia, D., Perrone Mc-Govern, K., et al. (2019). Psychophysiological synchrony during verbal interaction in romantic relationships. *Fam. Process* 58, 716–733. doi: 10.1111/famp.12371

Cui, X., Bryant, D. M., and Reiss, A. L. (2012). Nirs-based hyperscanning reveals increased interpersonal coherence in superior frontal cortex during cooperation. *Neuroimage* 59, 2430–2437. doi: 10.1016/j.neuroimage.2011.09.003

Davis, M., West, K., Bilms, J., Morelen, D., and Suveg, C. (2018). A systematic review of parent–child synchrony: it is more than skin deep. *Dev. Psychobiol.* 60, 674–691. doi: 10.1002/dev.21743

Davis, W. B., Gfeller, K. E., and Thaut, M. H. (2008). *An Introduction to Music Therapy: Theory and Practice*. Silver Spring, MD: American Music Therapy Association.

De Mendonça, J. S., Bussab, V. S. R., and Kärtner, J. (2019). Interactional synchrony and child gender differences in dyadic and triadic family interactions. *J. Fam. Issues* 40, 959–981. doi: 10.1177/0192513X19832938

Decety, J. E., and Ickes, W. E. (2009). *The Social Neuroscience of Empathy*. Cambridge, MA: MIT Press.

Dikker, S., Wan, L., Davidesco, I., Kaggen, L., Oostrik, M., McClintock, J., et al. (2017). Brain-to-brain synchrony tracks real-world dynamic group interactions in the classroom. *Curr. Biol.* 27, 1375–1380. doi: 10.1016/j.cub.2017.04.002

Doherty, R. W., Orimoto, L., Singelis, T. M., Hatfield, E., and Hebb, J. (1995). Emotional contagion: gender and occupational differences. *Psychol. Women Q.* 19, 355–371. doi: 10.1111/j.1471-6402.1995.tb00080.x

Dvir, T., Lotan, N., Viderman, R., and Elefant, C. (2020). The body communicates: movement synchrony during music therapy with children diagnosed with ASD. *Arts Psychother.* 69:101658. doi: 10.1016/j.aip.2020.101658

Ebisch, S. J., Aureli, T., Bafunno, D., Cardone, D., Romani, G. L., and Merla, A. (2012). Mother and child in synchrony: thermal facial imprints of autonomic contagion. *Biol. Psychol.* 89, 123–129. doi: 10.1016/j.biopsycho.2011.09.018

Errante, A., Di Cesare, G., Pinardi, C., Fasano, F., Sghedoni, S., Costi, S., et al. (2019). Mirror neuron system activation in children with unilateral cerebral palsy during observation of actions performed by a pathological model. *Neurorehabil. Neural Repair* 33, 419–431. doi: 10.1177/1545968319847964

Fachner, J. C., Maidhof, C., Grocke, D., Nygaard Pedersen, I., Trondalen, G., Tucek, G., et al. (2019). "... telling me not to worry" hyperscanning and neural dynamics of emotion processing during guided imagery in music. *Front. Psychol.* 10:1561. doi: 10.3389/fpsyg.2019.01561

Fadiga, L., Craighero, L., and D'Ausilio, A. (2009). Broca's area in language, action, and music. *Ann. N. Y. Acad. Sci.* 1169, 448–458. doi: 10.1111/j.1749-6632.2009.04582.x

Feldman, R. (2007). Parent–infant synchrony and the construction of shared timing; physiological precursors, developmental outcomes, and risk conditions. *J. Child Psychol. Psychiatry* 48, 329–354. doi: 10.1111/j.1469-7610.2006.01701.x

Feldman, R. (2012). Parent–infant synchrony: a biobehavioral model of mutual influences in the formation of affiliative bonds. *Monogr. Soc. Res. Child Dev.* 77, 42–51. doi: 10.1111/j.1540-5834.2011.00660.x

Feldman, R., Magori-Cohen, R., Galili, G., Singer, M., and Louzoun, Y. (2011). Mother and infant coordinate heart rhythms through episodes of interaction synchrony. *Infant Behav. Dev.* 34, 569–577. doi: 10.1016/j.infbeh.2011.06.008

Fitch, W. T. (2006). The biology and evolution of music: a comparative perspective. *Cognition* 100, 173–215. doi: 10.1016/j.cognition.2005.11.009

Freeman, W. J. (1998). "A neurobiological role of music in social bonding," in *The Origins of Music*, eds N. L. Wallin, B. Merker, and S. Brown (Cambridge, MA: MIT Press), 411–424.

Freitas, C., Manzato, E., Burini, A., Taylor, M. J., Lerch, J. P., and Anagnostou, E. (2018). Neural correlates of familiarity in music listening: a systematic review and a neuroimaging meta-analysis. *Front. Neurosci.* 12:686. doi: 10.3389/fnins.2018.00686

Frenkel-Toledo, S., Bentin, S., Perry, A., Liebermann, D. G., and Soroker, N. (2014). Mirror-neuron system recruitment by action observation: effects of focal brain damage on mu suppression. *Neuroimage* 87, 127–137. doi: 10.1016/j.neuroimage.2013.10.019

Fries, P. (2005). A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn. Sci.* 9, 474–480. doi: 10.1016/j.tics.2005.08.011

Gallese, V. (2001). The'shared manifold'hypothesis. from mirror neurons to empathy. *J. Conscious. Stud.* 8, 33–50.

Gardner, M. R., Sorhus, I., Edmonds, C. J., and Potts, R. (2012). Sex differences in components of imagined perspective transformation. *Acta Psychol.* 140, 1–6. doi: 10.1016/j.actpsy.2012.02.002

Ghai, S., Ghai, I., Schmitz, G., and Effenberg, A. O. (2018). Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. *Sci. Rep.* 8, 1–19. doi: 10.1038/s41598-017-16232-5

Golland, Y., Arzouan, Y., and Levit-Binnun, N. (2015). The mere co-presence: synchronization of autonomic signals and emotional responses across co-present individuals not engaged in direct interaction. *PLoS ONE* 10:e0125804. doi: 10.1371/journal.pone.0125804

Gordon, I., Gilboa, A., Cohen, S., and Kleinfeld, T. (2020). The relationship between physiological synchrony and motion energy synchrony during a joint group drumming task. *Physiol. Behav.* 224:113074. doi: 10.1016/j.physbeh.2020.113074

Granger, C. W. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica* 37, 424–438. doi: 10.2307/1912791

Groppe, D. M., Urbach, T. P., and Kutas, M. (2011a). Mass univariate analysis of event-related brain potentials/fields I: a critical tutorial review. *Psychophysiology* 48, 1711–1725. doi: 10.1111/j.1469-8986.2011.01273.x

Groppe, D. M., Urbach, T. P., and Kutas, M. (2011b). Mass univariate analysis of event-related brain potentials/fields II: simulation studies. *Psychophysiology* 48, 1726–1737. doi: 10.1111/j.1469-8986.2011.01272.x

Harrist, A. W., and Waugh, R. M. (2002). Dyadic synchrony: its structure and function in children's development. *Dev. Rev.* 22, 555–592. doi: 10.1016/S0273-2297(02)00500-2

Heiderscheit, A., and Madson, A. (2015). Use of the iso principle as a central method in mood management: a music psychotherapy clinical case study. *Music Ther. Perspect.* 33, 45–52. doi: 10.1093/mtp/miu042

Hickok, G. (2009). Eight problems for the mirror neuron theory of action understanding in monkeys and humans. *J. Cogn. Neurosci.* 21, 1229–1243. doi: 10.1162/jocn.2009.21189

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., et al. (2003). Gamma oscillations correlate with working memory load in humans. *Cereb. Cortex* 13, 1369–1374. doi: 10.1093/cercor/bhg084

Hussey, D. L., Reed, A. M., Layman, D. L., and Pasiali, V. (2008). Music therapy and complex trauma: a protocol for developing social reciprocity. *Resident. Treat. Children Youth* 24, 111–129. doi: 10.1080/08865710802147547

Jospe, K., Flöel, A., and Lavidor, M. (2020). The interactive effect of empathy and motor cortex stimulation on hand gesture comprehension. *Neuropsychologia* 141:107412. doi: 10.1016/j.neuropsychologia.2020.107412

Kasari, C., Freeman, S. F., and Bass, W. (2003). Empathy and response to distress in children with down syndrome. *J. Child Psychol. Psychiatry* 44, 424–431. doi: 10.1111/1469-7610.00132

Kesler-West, M. L., Andersen, A. H., Smith, C. D., Avison, M. J., Davis, C., Kryscio, R. J., et al. (2001). Neural substrates of facial emotion processing using fMRI. *Cogn. Brain Res.* 11, 213–226. doi: 10.1016/S0926-6410(00)00073-2

Kim, S., Gaebel, C., Aguilar-Raab, C., Hillecke, T. K., and Warth, M. (2018). Affective and autonomic response to dynamic rhythmic entrainment: mechanisms of a specific music therapy factor. *Arts Psychother.* 60, 48–54. doi: 10.1016/j.aip.2018.06.002

Koelsch, S. (2014). Brain correlates of music-evoked emotions. *Nat. Rev. Neurosci.* 15:170. doi: 10.1038/nrn3666

Lamm, C., and Majdandžić, J. (2015). The role of shared neural activations, mirror neurons, and morality in empathy–a critical comment. *Neurosci. Res.* 90, 15–24. doi: 10.1016/j.neures.2014.10.008

Leclère, C., Viaux, S., Avril, M., Achard, C., Chetouani, M., Missonnier, S., and Cohen, D. (2014). Why synchrony matters during mother-child interactions: a systematic review. *PLoS ONE* 9:e113571. doi: 10.1371/journal.pone.0113571

Lindstrøm, S., Oscarsson, S., Ridder, H. M., Haslbeck, F., Oldfield, A., Teggelove, K., et al. (2016). *Music Therapy With Families: Therapeutic Approaches and Theoretical Perspectives*. London: Jessica Kingsley Publishers.

Liu, N., Mok, C., Witt, E. E., Pradhan, A. H., Chen, J. E., and Reiss, A. L. (2016). Nirs-based hyperscanning reveals inter-brain neural synchronization during cooperative jenga game with face-to-face communication. *Front. Hum. Neurosci.* 10:82. doi: 10.3389/fnhum.2016.00082

Lübke, K. T., Sachse, C., Hoenen, M., and Pause, B. M. (2020). Mu-suppression as an indicator of empathic processes in lesbian, gay, and heterosexual adults. *Arch. Sex. Behav.* 49, 635–644. doi: 10.1007/s10508-019-01491-2

Magen, E., and Konasewich, P. A. (2011). Women support providers are more susceptible than men to emotional contagion following brief supportive interactions. *Psychol. Women Q.* 35, 611–616. doi: 10.1177/0361684311423912

Marci, C. D., Ham, J., Moran, E., and Orr, S. P. (2007). Physiologic correlates of perceived therapist empathy and social-emotional process during psychotherapy. *J. Nerv. Ment. Dis.* 195, 103–111. doi: 10.1097/01.nmd.0000253731.71025.fc

McClure, E. B. (2000). A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol. Bull.* 126:424. doi: 10.1037/0033-2909.126.3.424

McCoy, E. J., Walden, A. T., and Percival, D. B. (1998). Multitaper spectral estimation of power law processes. *IEEE Trans. Signal Process.* 46, 655–668. doi: 10.1109/78.661333

Meadows, T. (1997). Music therapy for children with severe and profound multiple disabilities: a review of literature. *Aust. J. Music Ther.* 8:3.

Mendelson, J., White, Y., Hans, L., Adebari, R., Schmid, L., Riggsbee, J., et al. (2016). A preliminary investigation of a specialized music therapy model for children with disabilities delivered in a classroom setting. *Autism Res. Treat.* 2016:1284790. doi: 10.1155/2016/1284790

Mitchell, J. P., Banaji, M. R., and MacRae, C. N. (2005). The link between social cognition and self-referential thought in the medial prefrontal cortex. *J. Cogn. Neurosci.* 17, 1306–1315. doi: 10.1162/0898929055002418

Novembre, G., Mitsopoulos, Z., and Keller, P. E. (2019). Empathic perspective taking promotes interpersonal coordination through music. *Sci. Rep.* 9, 1–12. doi: 10.1038/s41598-019-48556-9

Nummenmaa, L., Hirvonen, J., Parkkola, R., and Hietanen, J. K. (2008). Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *Neuroimage* 43, 571–580. doi: 10.1016/j.neuroimage.2008.08.014

Oostenveld, R., Fries, P., Maris, E., and Schoffelen, J.-M. (2011). Fieldtrip: open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput. Intell. Neurosci.* 2011:156869. doi: 10.1155/2011/156869

Oshri, A., Liu, S., Huffman, L. G., and Koss, K. J. (2020). Firm parenting and youth adjustment: stress reactivity and dyadic synchrony of respiratory sinus arrhythmia. *Dev. Psychobiol.* 23, 945–959. doi: 10.1002/dev.22019

Papp, L. M., Pendry, P., and Adam, E. K. (2009). Mother-adolescent physiological synchrony in naturalistic settings: within-family cortisol associations and moderators. *J. Fam. Psychol.* 23, 882–894. doi: 10.1037/a0017147

Pauly, T., Michalowski, V. I., Drewelies, J., Gerstorf, D., Ashe, M. C., Madden, K. M., et al. (2020). Cortisol synchrony in older couples: daily socio-emotional correlates and interpersonal differences. *Psychosom. Med.* 82, 669–677. doi: 10.1097/PSY.0000000000000838

Pavlicevic, M., O'Neil, N., Powell, H., Jones, O., and Sampathianaki, E. (2014). Making music, making friends: long-term music therapy with young adults with severe learning disabilities. *J. Intellect. Disabil.* 18, 5–19. doi: 10.1177/1744629513511354

Perry, M. M. R. (2003). Relating improvisational music therapy with severely and multiply disabled children to communication development. *J. Music Ther.* 40, 227–246. doi: 10.1093/jmt/40.3.227

Quiñones-Camacho, L. E., Fishburn, F. A., Camacho, M. C., Hlutkowsky, C. O., Huppert, T. J., Wakschlag, L. S., et al. (2020). Parent–child neural synchrony: a novel approach to elucidating dyadic correlates of preschool irritability. *J. Child Psychol. Psychiatry* 61, 1213–1223. doi: 10.1111/jcpp.13165

Rankin, K. P., Gorno-Tempini, M. L., Allison, S. C., Stanley, C. M., Glenn, S., Weiner, M. W., et al. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain* 129, 2945–2956. doi: 10.1093/brain/awl254

Reindl, V., Gerloff, C., Scharke, W., and Konrad, K. (2018). Brain-to-brain synchrony in parent-child dyads and the relationship with emotion regulation revealed by fNIRS-based hyperscanning. *Neuroimage* 178, 493–502. doi: 10.1016/j.neuroimage.2018.05.060

Robb, S. L., Carpenter, J. S., and Burns, D. S. (2011). Reporting guidelines for music-based interventions. *J. Health Psychol.* 16, 342–352. doi: 10.1177/1359105310374781

Rose, A. J., and Rudolph, K. D. (2006). A review of sex differences in peer relationship processes: potential trade-offs for the emotional and behavioral development of girls and boys. *Psychol. Bull.* 132:98. doi: 10.1037/0033-2909.132.1.98

Ryan, N. P., Catroppa, C., Beare, R., Silk, T. J., Hearps, S. J., Beauchamp, M. H., et al. (2017). Uncovering the neuroanatomical correlates of cognitive, affective and conative theory of mind in paediatric traumatic brain injury: a neural systems perspective. *Soc. Cogn. Affect. Neurosci.* 12, 1414–1427. doi: 10.1093/scan/nsx066

Salomon-Gimmon, M., and Elefant, C. (2019). Development of vocal communication in children with autism spectrum disorder during improvisational music therapy. *Nordic J. Music Ther.* 28, 174–192. doi: 10.1080/08098131.2018.1529698

Schirmer, A., Simpson, E., and Escoffier, N. (2007). Listen up! processing of intensity change differs for vocal and nonvocal sounds. *Brain Res.* 1176, 103–112. doi: 10.1016/j.brainres.2007.08.008

Schmidt, S. N. L. (2020). *Neural mechanisms of social cognition–the mirror neuron system and beyond* (Ph.D. thesis). Heidelberg: Ruprecht-Karls-Universitt.

Schulte-Rüther, M., Markowitsch, H. J., Fink, G. R., and Piefke, M. (2007). Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *J. Cogn. Neurosci.* 19, 1354–1372. doi: 10.1162/jocn.2007.19.8.1354

Shamay-Tsoory, S. G., Aharon-Peretz, J., and Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain* 132, 617–627. doi: 10.1093/brain/awn279

Shamay-Tsoory, S. G., Tomer, R., Berger, B. D., and Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *J. Cogn. Neurosci.* 15, 324–337. doi: 10.1162/089892903321593063

Spitzer, B., Wacker, E., and Blankenburg, F. (2010). Oscillatory correlates of vibrotactile frequency processing in human working memory. *J. Neurosci.* 30, 4496–4502. doi: 10.1523/JNEUROSCI.6041-09.2010

Stegemann, T., Geretsegger, M., Phan Quoc, E., Riedl, H., and Smetana, M. (2019). Music therapy and other music-based interventions in pediatric health care: an overview. *Medicines* 6:25. doi: 10.3390/medicines6010025

Stephens, G. J., Silbert, L. J., and Hasson, U. (2010). Speaker listener neural coupling underlies successful communication. *Proc. Natl. Acad. Sci. U.S.A.* 107, 14425–14430. doi: 10.1073/pnas.1008662107

Stupacher, J., Wood, G., and Witte, M. (2017). Synchrony and sympathy: social entrainment with music compared to a metronome. *Psychomusicol. Music Mind Brain* 27:158. doi: 10.1037/pmu0000181

Thaut, M., and Hoemberg, V. (2014). *Handbook of Neurologic Music Therapy*. Oxford: Oxford University Press.

Thompson, G. A., and McFerran, K. S. (2015). Music therapy with young people who have profound intellectual and developmental disability: four case studies exploring communication and engagement within musical interactions. *J. Intellect. Dev. Disabil.* 40, 1–11. doi: 10.3109/13668250.2014.965668

Tononi, F. (2020). Aesthetic response to the unfinished: empathy, imagination and imitation learning. *Aisthesis* 13, 135–153. doi: 10.13128/Aisthesis-10737

Trehub, S. E. (2003). The developmental origins of musicality. *Nat. Neurosci.* 6:669. doi: 10.1038/nn1084

Tschacher, W., and Meier, D. (2020). Physiological synchrony in psychotherapy sessions. *Psychother. Res.* 30, 558–573. doi: 10.1080/10503307.2019.1612114

von Lautz, A. H., Herding, J., Ludwig, S., Nierhaus, T., Maess, B., Villringer, A., et al. (2017). Gamma and beta oscillations in human meg encode the contents of vibrotactile working memory. *Front. Hum. Neurosci.* 11:576. doi: 10.3389/fnhum.2017.00576

Voorman, J. M., Dallmeijer, A. J., Van Eck, M., Schuengel, C., and Becher, J. G. (2010). Social functioning and communication in children with cerebral palsy: association with disease characteristics and personal and environmental factors. *Dev. Med. Child Neurol.* 52, 441–447. doi: 10.1111/j.1469-8749.2009.03399.x

Wallmark, Z., Deblieck, C., and Iacoboni, M. (2018). Neurophysiological effects of trait empathy in music listening. *Front. Behav. Neurosci.* 12:66. doi: 10.3389/fnbeh.2018.00066

Wildgruber, D., Riecker, A., Hertrich, I., Erb, M., Grodd, W., Ethofer, T., et al. (2005). Identification of emotional intonation evaluated by fmri. *Neuroimage* 24, 1233–1241. doi: 10.1016/j.neuroimage.2004.10.034

Wyart, V., and Tallon-Baudry, C. (2008). Neural dissociation between visual awareness and spatial attention. *J. Neurosci.* 28, 2667–2679. doi: 10.1523/JNEUROSCI.4748-07.2008

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