Principles and Practice of Clinical Research
A GLOBAL JOURNAL OF CLINICAL RESEARCH

Design Considerations for Clinical Trials Combining Music Therapy and Physical Activity in Alzheimer's Disease: Lessons from Designing a Multicenter Randomized Protocol

Alice Liriano[1], Ana Isabella Bencosme[2], Angélica Furzán[3], Bruno Cateb[4], Carla Arias[5], Carolina Matté Dagostini[6*], Claudia Meireles[7], Daniel Musse Gomes[8], Daniela Jorquera[9], David Moros[10], Erlando Mendez[11], Giovanna Oliveira dos Santos[12], Hanan Alshareef[13], Jazmin Insfran[14], Jorge Pastrana[15], Komwudh Konchalard[16], Lucas Koji Uchiyama[17], Marcos Brioschi[13], Marcos Ramirez[13], Mario Diego Teles Correia[18], Matheus Machado Rech[19], Mayra Muñoz[20], Natalia Rodriguez[21], Nelia Sanchez-Crespo[22], Nicole Mannis[23], Olumide Adeniyi[24], Pascal Gaechter[25], Rodrigo Mariano[13], Silvia Castro Piedra[26], Tatiana Dus[13]

[1] Pontificia Universidad Católica Madre y Maestra, Santiago, Dominican Republic; [2] Pontificia Universidad Católica Madre y Maestra, Santiago, Dominican Republic; [3] Universidad de Ciencias Médicas (UCIMED), San José, Costa Rica; [4] Faculdade de Medicina São Leopoldo Mandic (SLMandic), Campinas, Brazil; [5] Eugenio Espejo Specialty Hospital (HEEE); [6] Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, Brazil; [7] Universidade de São Paulo (USP), São Paulo, Brazil; [8] Instituto D'Or de Ensino e Pesquisa, Rio de Janeiro, Brazil; [9] Clínica Alemana Santiago, Chile. Facultad de medicina UDD Santiago, Chile; [10] Heart, Vascular and Thoracic Institute, Cleveland clinic, Ohio, USA; [11] Instituto Tecnológico de Santo Domingo (INTEC), Santo Domingo, Dominican Republic; [12] Núcleo de Pesquisa e Ensino IBCC Oncologia, São Paulo, Brazil; [13] Principles and Practice of Clinical Research, Harvard T. H. Chan School, USA; [14] Universidad del Pacífico, Asuncion, Paraguay; [15] Instituto Politécnico Nacional, Ciudad de México, Mexico; [16] Queen Savang Vadhana Memorial Hospital, Thai Red Cross Society, Thailand; [17] Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [18] Real Hospital Português, Recife, Brazil; [19] University of Caxias do Sul (UCS), Caxias do Sul, Brazil; [20] Universidad San Martín de Porres (USMP) - Facultad de Medicina, Lima, Perú; [21] Transplant surgery, Massachusetts General Hospital, MA, USA; [22] CenexelRCA, Florida, USA; [23] Faculdade São Leopoldo Mandic, Campinas, Brazil; [24] Obafemi Awolowo University Teaching Hospitals Complex, Ile-lfe, Nigeria; [25] University of Basel, Basel, Switzerland; [26] Instituto Tecnológico de Costa Rica, Cartago, Costa Rica.

Abstract

Non-pharmacological interventions targeting cognitive decline are increasingly important in aging and Alzheimer's disease (AD). Music therapy and physical activity have both demonstrated neurocognitive and emotional benefits, but few studies have systematically explored their combined effects or the methodological challenges in implementing such interventions. This brief report discusses key design considerations for clinical trials integrating music and exercise in individuals with subjective cognitive decline (SCD), drawing on lessons from a multicenter, two-arm randomized controlled trial currently evaluating the addition of active music therapy to physical activity in older adults. Core design elements include careful population selection within the pre-dementia spectrum, standardized intervention delivery, culturally adapted musical stimuli, cluster randomization to reduce contamination, and the use of sensitive, multidomain cognitive outcomes. Methodological recommendations address standardization, adherence, control conditions, and statistical strategies appropriate for multicountry behavioral interventions. Integrating multimodal interventions such as music and exercise provides a novel framework for preventive neuroscience and rehabilitation, fostering cognitive resilience through synergistic engagement of motor, emotional, and memory circuits.

*Corresponding author: carolina.dagostini-2024@ppcr.org
Received: November 27, 2024 **Accepted:** February 15, 2026
Published: April 26, 2026
Editor: Felipe Fregni
Reviewers: Tomas Pablos, Karen Bedirian, Johan A. De La Rosa, Claudia Lopez
Keywords: Alzheimer's disease, cognitive decline, music therapy, physical activity, trial design
DOI: https://doi.org/10.21801/ppcrj.2025.114.1

Introduction

Cognitive decline is an inevitable aging natural process. Age-related changes include brain volume reduction (Murman, 2015), affecting the overall cognitive function and possibly leading to a progressive development of dementia, which is a term that includes several diseases that affect memory, thinking, and ability to perform daily activities (WHO, 2023); diminishment of autonomy and overall health depending on the severity of disease. Subjective Cognitive Decline is (SCD) involved in persistent self-reported concerns about worsening cognitive abilities, even when objective testing does not show deficits. It is not caused by acute events and can sometimes signal early changes linked to neurodegenerative diseases like dementia (Munro et al., 2023). SCD has been linked to an accelerated deterioration of cognitive function with and increased risk for progression of 4.5 times and a 2 to 6.5 increased risk of progression for Alzheimer's disease (AD) and a reported annual conversion rate of 7-10% to mild cognitive impairment (MCI) or dementia (Innes et al., 2021). According to the World Health Organization, in 2019 dementia had a societal cost around US$ 1.3 trillion. Last year, there were 55.2 million living with dementia, and Alzheimer's disease (AD) and other dementias were ranked as the 7th leading cause of death worldwide. A systematic review evaluating the economic burden of AD until August 2022 showed that the annual cost of AD per capita ranged from US$468.28 in mild to US$171 283.80 in severe AD. For 2030, the global cost of dementia is expected to reach US $2 trillion (Tay et al., 2024).

Scientific evidence indicates that non-pharmacological interventions can potentially improve cognitive impairment in adults with subjective cognitive decline (SCD), preventing or delaying the progression from SCD and mild cognitive impairment to dementia (NIA, 2024). The SCD period, when the burden of neurodegenerative changes is still relatively low, may represent a crucial therapeutic window for addressing cognitive decline and associated neuropathogenic changes. Music therapy (MT) and physical activity (PA) are among these interventions. Incorporating these practices into daily routines can have a cumulative effect, supporting brain function both in the present and over time (NIA, 2024).

Previous studies have demonstrated a relationship between physical exercise and cognition. Cassilhas et al. (2016) show that physical activity can induce hippocampal plasticity. Aerobic exercise increases brain-derived neurotrophic factor (BDNF), promoting neurogenesis and cell proliferation. These effects positively influence spatial learning and memory improvement (Cassilhas et al., 2016). Similarly, Erickson et al. (2011) found that aerobic exercise training appears to increase gray and white matter volume in the prefrontal cortex and temporal lobe, areas responsible for executive control and spatial memory, particularly in older adults.

Music therapy (MT) is a non-pharmacological complementary strategy that has been gaining strength in management of cognitive decline and dementia due to engaging different brain areas responsible for language, memory, motor function, and hearing (Barradas et al., 2021; François et al., 2015; Guetin et. al, 2013; Harrison et al., 2022; Romero et al., 2014; Särkämö et al., 2014; Warren et al., 2003). Studies have shown the effect of MT in different modalities of intervention. Active interventions as clapping, singing, and dancing could reduce agitation, anxiety, depression, and behavioral symptoms of dementia (Clément et al., 2012; Holmes et al., 2006; Narme et al., 2014; Sakamoto et al., 2013; Sung et al., 2006). Figure 1 summarizes the effects of MT in the brain. Singing involves many processes such as short-term memory, long-term planning, control of errors, and engages several brain areas of the prefrontal cortex (Sakamoto et al., 2014). Listening to familiar melodies activates the bilateral and superior temporal regions and the parahippocampal gyrus, which plays a role in recovery of remote memory, verbal and emotional processing (Biasutti & Mangiacotti, 2017; Satoh et al., 2006).

With the increasing elderly population, degenerative diseases such as dementia present growing challenges. MT has shown promising results for these patients by inducing plastic changes in brain networks, facilitating cognitive recovery, modulating emotions, and promoting social communication, making it a potential approach for rehabilitation (Bleibel et al., 2023). While studies have demonstrated MT's impact on mild cognitive impairment and dementia, its effects on SCD as the earliest stage of dementia is less clear.

The combination of PA and active music therapy MT could enhance cognitive outcomes by simultaneously stimulating different brain areas. Researchers in neuroplasticity suggest that integrating multiple modalities can strengthen neural connectivity, particularly in the frontal and temporal lobes as well as the hippocampus—regions essential for memory and executive functions (Sanders et al., 2020). This clinical trial has the innovative objective to investigate whether adding active MT to PA provides superior cognitive benefits compared to PA alone. The study will control for group interactions,

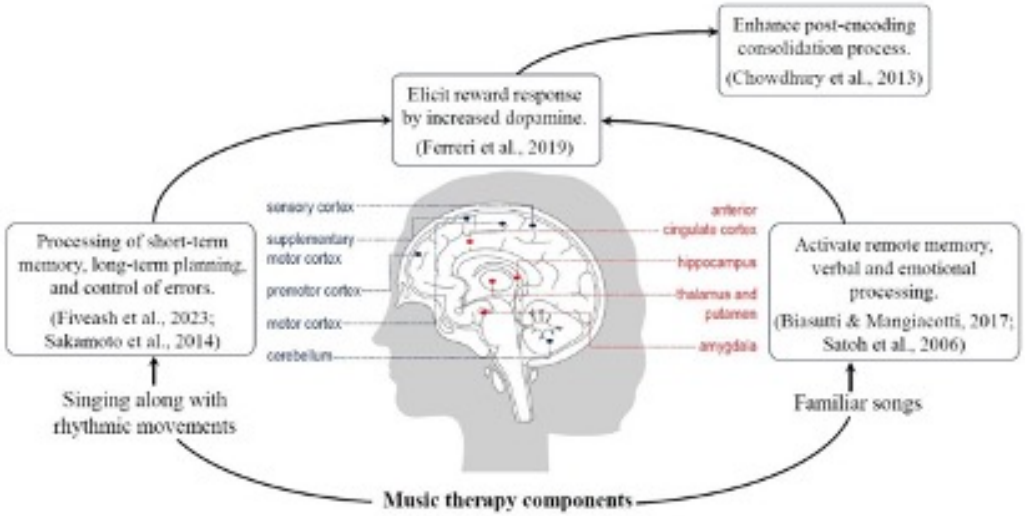

Figure 1: *Mechanism and brain structures involved in two distinct components of music therapy intervention in this study: familiar songs and singing along with rhythmic movements.*

employ optimal dosing strategies, and identify key neural pathways involved in recovery.

As there is no pharmacological standard of care for SCD, the usual care recommended to improve quality of life and well-being includes being physically active and taking part in social interactions that stimulate the brain and maintain daily function (WHO, 2023). Physical activity as regular exercises have been shown to improve outcomes in this subset and is recommended as part of an overall non-pharmacological approach to manage SCD to maintain and improve memory (Ismail et al., 2020; Gomes-Osman et al., 2018). Studies that combined PA and MT reported challenges, such as the difficulty in isolating the specific effects of physical exercise from those of music (Satoh et al., 2017).

This report summarizes methodological insights and design recommendations for trials integrating music and physical activity in preclinical cognitive decline. As an illustrative example, we draw on a multicenter randomized controlled trial evaluating active music therapy combined with exercise in adults over 65 with SCD.

Mechanistic Rationale

Physical activity and neuroplasticity

Regular aerobic exercise promotes hippocampal plasticity and upregulates the expression of brain-derived neurotrophic factor (BDNF), a key mediator of synaptic growth and long-term potentiation. Increased BDNF levels facilitate neurogenesis, dendritic arborization, and synaptic efficacy, particularly in the hippocampus and prefrontal cortex—regions vulnerable to early Alzheimer's pathology (Cassilhas et al., 2016). Experimental and clinical studies have shown that both acute and chronic aerobic training enhance BDNF availability and modulate signaling cascades involving TrkB and CREB, which are essential for learning and memory consolidation. Neuroimaging evidence supports these findings: exercise interventions lead to measurable increases in gray matter volume in the hippocampus and prefrontal cortex, as well as improvements in white matter integrity and connectivity within default mode and executive control networks (Erickson et al., 2011; Sanders et al., 2020). In addition to structural benefits, physical activity improves cerebral perfusion and oxygenation, mitigates oxidative stress, and reduces peripheral and central inflammation (REF)—factors implicated in AD pathogenesis. Exercise also promotes vascular endothelial growth factor (VEGF) expression and angiogenesis, contributing to enhanced metabolic support for neuronal function (REF). Collectively, these biological adaptations illustrate that aerobic exercise exerts multimodal neuroprotective effects capable of counteracting early degenerative processes and sustaining cognitive function in aging populations.

Music therapy and multisensory engagement

Music therapy (MT) engages widespread cortical and subcortical networks implicated in emotion, attention, motor planning, and autobiographical memory (François et al., 2015; Guetin et al., 2013; Warren et al., 2003). Active interventions such as singing, clapping, and rhythmic movement have been associated with reductions in anxiety,

depression, and behavioral symptoms in dementia (Clément et al., 2012; Särkämö et al., 2014). Listening to familiar melodies activates the superior temporal and parahippocampal regions, supporting emotional regulation and memory retrieval (Biasutti & Mangiacotti, 2021; Satoh et al., 2006).

Potential synergy

Combining MT with physical exercise may leverage complementary neurobiological pathways. Rhythmic entrainment can enhance motor coordination and executive functioning, while emotionally rewarding musical stimuli may strengthen adherence and motivation. Dopaminergic activation during music exposure (Ferreri et al., 2019) may further augment the cognitive effects of exercise by enhancing reward-driven learning. This multimodal activation of motor, limbic, and cognitive networks provide a strong theoretical basis for integrative interventions targeting early neurodegeneration.

Design and Methodological Considerations

Population and Disease Stage

Trials should target individuals at the SCD or MCI stage, when neurodegenerative burden is still limited but compensatory mechanisms remain viable. In the illustrative multicenter protocol, inclusion followed SCD-I research criteria (Jessen et al., 2014; Molinuevo et al., 2017), combining self-reported decline with preserved test performance (MoCA $>$ 21). Exclusion of participants with major depression or significant hearing impairment helps ensure interpretability of cognitive outcomes and engagement in music-based tasks.

Intervention

Music Intervention

Consistency across centers is critical for ensuring both scientific validity and reproducibility in multisite behavioral trials: In the illustrative multicenter protocol, participants would have to engage in 30-minute sessions of low-intensity cycling immediately followed by 30 minutes of active music therapy, three times per week for four weeks. The music therapy component should integrate three structured modules: (1) universally familiar songs from the 1960s–1970s, (2) regionally adapted selections reflecting each site's cultural background, and (3) participant-selected pieces to enhance personal engagement and emotional salience. This tiered approach allows harmonization across diverse countries while preserving local relevance—a crucial factor in maintaining adherence and emotional connection.

Standardization drew from prior successful paradigms in music-based interventions for cognitive decline: For example, *Särkämö et al.* (2014) demonstrated that regular singing sessions improved memory and mood in early dementia, while *Sakamoto et al.* (2013) and *Sung et al.* (2006) showed that group rhythmic and percussion-based activities reduced agitation and enhanced social interaction in institutionalized elders. Other studies, such as *Narme et al.* (2014) and *Hsu et al.* (2015), have used structured rhythmic entrainment programs—combining clapping, drumming, and synchronized movement—to promote executive functioning and emotional regulation. Drawing from these models, the present trial emphasizes multimodal engagement, where participants are encouraged to sing along, clap, or use simple percussion instruments synchronized to rhythm and tempo.

All instructors could complete at least 12 hours of standardized training including theoretical modules on aging, cognition, and rhythm-based facilitation techniques, followed by supervised practice sessions to ensure delivery fidelity. Fidelity monitoring could include observation checklists, periodic video reviews, and inter-site feedback meetings. Such structured supervision helps to minimize inter-site variability and to ensure that the "active ingredients" of the intervention—rhythmic synchronization, cognitive engagement, and emotional resonance—are delivered consistently. At the same time, controlled flexibility in song choice can allow individualized adaptation, maintaining participant motivation and maximizing therapeutic impact.

Physical Activity Intervention

During the physical activity (PA) sessions, all participants should engage in aerobic exercise using a semi-recumbent cycle ergometer for 30 minutes, three times per week. This frequency and duration are based on prior evidence indicating that moderate-volume aerobic exercise can induce measurable improvements in cognitive performance and brain function in older adults (Zhang et al., 2022; Colcombe & Kramer, 2003). The cycling modality is suggested for its safety, accessibility, and ease of standardization across centers—particularly suitable for older individuals who may present with balance limitations or orthopedic constraints.

We suggest that participants in a trial with exercise in cognitive decline should pedal at a self-selected,

comfortable cadence, with resistance adjusted to maintain a target heart rate (THR) corresponding to approximately 50% of their age-predicted maximum heart rate (MHR), consistent with very light to light exercise intensity (American College of Sports Medicine, 2021). This level was chosen to ensure tolerability and adherence while still engaging cardiovascular and neuromotor systems relevant to cognitive function. The target should be maintained for 25 minutes, followed by a 5-minute cool-down period during which resistance is gradually reduced to the lowest setting. The MHR can be calculated as 220 minus the participant's age, and THR is continuously monitored using Bluetooth-enabled chest straps synchronized with heart rate monitoring applications for real-time feedback.

Sessions should be supervised by physiotherapists or certified exercise physiologists trained in geriatric exercise prescription and safety protocols. Investigators could provide standardized orientation to site-based staff regarding the use of ergometers, calibration, heart rate monitoring, and participant safety monitoring (e.g., perceived exertion, blood pressure, signs of fatigue). Each site should be equipped with an emergency plan, and staff should be trained in basic life support. Pre-session screening could include assessment of vital signs and contraindications to exertion, following established ACSM and WHO recommendations for older adults.

To optimize adherence, sessions might be conducted in small groups (up to six participants) to foster social engagement and peer motivation. Participants could be encouraged to maintain a consistent routine, and adherence logs are completed for every session. Motivational reinforcement strategies—including positive verbal feedback and gradual workload progression for those with higher tolerance—can be applied to sustain engagement throughout the intervention.

This structured yet flexible exercise model ensures feasibility and safety while maintaining sufficient physiological challenge to stimulate neuroplastic and cardiovascular adaptations. The semi-recumbent cycling paradigm also allows seamless integration with the subsequent music therapy session, providing a continuous multimodal intervention that transitions smoothly from physical activation to cognitive–emotional engagement.

Control Conditions

Appropriate comparators are vital to isolate the specific effects of music. A social interaction control (physical activity plus leisure conversation without music) can control for non-specific benefits of attention and socialization. Passive controls, such as wait-list groups, risk overestimating efficacy. Including an active control also enables exploration of additive versus synergistic effects between modalities.

Randomization and Blinding

Cluster randomization by site or group session reduces contamination—particularly in behavioral interventions where participants may interact. In the illustrative study, an interactive response technology system generated allocation sequences stratified by site and age group. While participants and facilitators could not be blinded, outcome assessors and data analysts remained masked. This design balances practical feasibility with methodological rigor.

Outcome Measures

Selecting sensitive, multidomain outcomes is essential. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is suggested to be chosen as the primary measure for its objectivity and granularity across memory, attention, and executive domains (Cognition, 2006). Secondary outcomes may include the Montreal Cognitive Assessment (MoCA) for global cognition, the Positive and Negative Affect Schedule (PANAS) for mood, and the Geriatric Depression Scale (GDS). Follow-up assessments at baseline, four weeks, six months, and twelve months can capture both immediate and sustained effects.

Multicenter Implementation

Multinational trials must harmonize procedures across diverse healthcare and cultural settings. The current suggested design involves centers in Latin America, Asia, and Europe, coordinated through a central hub (Clínica Alemana, Santiago, Chile). Uniform screening, instructor training, and data management via a web-based electronic data capture system may ensure procedural alignment. Cultural adaptation of music content while preserving structure could allow standardization without compromising ecological validity.

Ethical and Practical Considerations

Elderly participants with cognitive complaints constitute a vulnerable population, warranting strict oversight. Although non-pharmacological interventions are low-risk, physical fatigue or emotional distress may occur. An independent Data

Monitoring Committee (DMC) should conduct periodic reviews of safety and adherence. Engagement strategies—such as caregiver involvement, reminder systems, and minor incentives—can reduce dropout rates. Ethical frameworks must emphasize autonomy, informed consent, and cultural sensitivity.

Statistical and Analytical Approaches

Cluster designs necessitate methods that account for intra-site correlation. Linear mixed-effects models with random intercepts allow estimation of group differences while controlling for cluster effects. Sample size calculations should consider expected small effect sizes (Cohen's d $\approx$ 0.2–0.3) and potential attrition. Handling missing data through multiple imputation and sensitivity analyses helps preserve validity. Given the exploratory nature of multimodal interventions, pragmatic rather than explanatory designs may best reflect real-world applicability.

Discussion

This study proposes a blinded, cluster-randomized, two-arm clinical trial to examine whether the addition of structured physical activity to music therapy enhances cognitive outcomes compared with music therapy alone in individuals with subjective cognitive decline (SCD). Designing clinical trials that integrate music therapy and physical activity in AD requires balancing scientific rigor with practical feasibility. The illustrative multicenter RCT demonstrates that structured standardization, appropriate control conditions, and validated cognitive assessments are feasible across international sites. This approach bridges preventive and rehabilitative frameworks by simultaneously engaging physical, emotional, and cognitive systems.

Cluster randomization was chosen to minimize contamination between intervention arms, which is a recognized challenge in behavioral and lifestyle trials conducted in shared environments (Puffer et al., 2005). Individual randomization was considered but rejected due to the high risk of information exchange and behavioral spillover between participants. Cross-over designs were also deemed inappropriate given the potential for lasting cognitive effects of physical activity that could lead to carryover bias. Although full blinding is not feasible in behavioral interventions, this study incorporates blinded outcome assessment to reduce detection bias.

The inclusion of individuals with subjective cognitive decline as the population of the study, rather than patients with Alzheimer's disease, is a deliberate methodological choice aligned with current prevention-oriented models of neurodegenerative research. SCD represents an early, preclinical stage along the Alzheimer's disease continuum, in which individuals experience cognitive complaints despite preserved objective performance (Sperling et al., 2011). Intervening at this stage maximizes the potential impact of lifestyle-based interventions, as neuroplasticity and cognitive reserve are relatively preserved compared with established AD.

The selection of a combined physical activity and music therapy as an intervention is supported by evidence suggesting that multimodal lifestyle approaches may have synergistic cognitive effects. Compared with pharmacologic interventions, behavioral trials face unique challenges—particularly regarding blinding, adherence, and heterogeneity in engagement. However, they offer distinct advantages in safety, accessibility, and cross-cultural adaptability. The integration of music into exercise sessions may enhance motivation and reduce attrition, addressing one of the major limitations of long-term lifestyle interventions. Importantly, cultural musical familiarity should be treated as both a variable and an asset—capable of shaping emotional salience and neural activation patterns.

Cognitive outcomes were suggested to be measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB), because it consists of a validated, computerized tool that offers high sensitivity to subtle cognitive changes in at-risk populations and minimizes assessor-related variability.

A recent published systematic review provided important context for the present study by highlighting the heterogeneity and component-specific effects of non-pharmacological interventions in individuals with subjective cognitive decline. Consistent with our trial rationale, the review suggests that physical activity components—particularly resistance, aerobic, and balance exercises—may be more effective than purely cognitive interventions in reducing subjective memory complaints (Yu et al., 2024). In contrast, interventions such as music therapy and cognitive training appear to exert greater effects on global cognitive function and related domains, including activities of daily living and psychological outcomes (Yu et al., 2024). These results support the hypothesis that combining physical activity with music-based interventions may leverage complementary mechanisms, targeting both subjective cognitive symptoms and objective cognitive performance.

A previous published parallel three-arm randomized controlled trial study protocol evaluating music therapy and physical activity in individuals with Alzheimer's disease, mild cognitive impairment, and subjective memory complaints further supports the relevance of non-pharmacological interventions

across the Alzheimer's disease continuum in clinical trials. Its longitudinal design and inclusion of both active and passive control groups strengthen causal inference regarding the effects of music therapy and physical activity (Flo et at., 2022). In contrast, our presented study protocol focuses on a more homogeneous SCD population and directly tests the added value of physical activity when combined with music therapy, addressing a key gap identified in prior trials.

The ALMUTH study represented a randomized controlled trials to formally investigate music therapy and physical activity as non-pharmacological interventions in individuals with Alzheimer's disease and was conducted as a parallel three-arm RCT (Matziorinis et al., 2023). The study included two active intervention arms and a passive control and provided valuable randomized evidence on both the potential benefits and the feasibility of these approaches. Importantly, despite the methodological rigor inherent to its randomized design, the trial demonstrated significant feasibility challenges in patients with mild-to-moderate Alzheimer's disease, including low adherence, high attrition, and difficulties with recruitment and protocol fidelity (Matziorinis et al., 2023). These findings suggest that, even within an RCT framework, disease severity can substantially limit the successful implementation of long-term behavioral interventions. This evidence supports the rationale for the present RCT focusing on individuals with subjective cognitive decline.

Future studies should extend beyond behavioral outcomes to include biomarkers such as EEG, heart-rate variability, or serum BDNF to elucidate mechanistic pathways. Neuroimaging sub-studies could clarify how combined interventions modulate connectivity within the default mode, motor, and limbic networks. Incorporating digital monitoring tools and adaptive dosing algorithms may further optimize precision in non-pharmacologic intervention trials.

Conclusion

Integrating music therapy with physical activity represents a promising multimodal strategy to enhance cognitive resilience in individuals at risk for Alzheimer's disease. Successful implementation requires thoughtful design addressing population selection, cultural adaptability, outcome sensitivity, and data integrity. The multicenter randomized protocol described here illustrates a scalable model for rigorous evaluation of non-pharmacologic interventions across diverse global settings. Establishing standardized frameworks for such trials will accelerate translation of creative, humanistic therapies into evidence-based clinical practice.

Acknowledgements

We would like to express our gratitude to Prof. Felipe Fregni, Alma Tamara Sanchez Jimenez, Fathima Minisha, Juan Carlos Silva, and Harvard's Faculty whose guidance, encouragement and constant supervision was crucial to elaborate these manuscripts. We also want to thank all the senior, second and first teacher assistants and all the PPCR team for their valuable inputs in the whole process, their patience and encouragement were crucial in the development of this work.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

References

Andrews, J. S., Desai, U., Kirson, N. Y., Zichlin, M. L., Ball, D. E., & Matthews, B. R. (2019). Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 5, 354–363. https://doi.org/10.1016/j.trci.2019.06.005.

Barradas, G. T., Juslin, P. N., & i Badia, S. B. (2021). Emotional Reactions to Music in Dementia Patients and Healthy Controls: Differential Responding Depends on the Mechanism. Music & Science, 4. https://doi.org/10.1177/20592043211010152.

Berg-Weger, M., & Stewart, D. B. (2017). Non-Pharmacologic Interventions for Persons with Dementia. Missouri medicine, 114(2), 116–119.

Biasutti, M., & Mangiacotti, A. (2021). Music Training Improves Depressed Mood Symptoms in Elderly People: A Randomized Controlled Trial. International journal of aging & human development, 92(1), 115–133. https://doi.org/10.1177/0091415019893988.

Bleibel, M., El Cheikh, A., Sadier, N.S. et al. (2023). The effect of music therapy on cognitive functions in patients with Alzheimer's disease: a systematic review of randomized controlled trials. Alz Res Therapy 15, 65. https://doi.org/10.1186/s13195-023-01214-9.

Bredin, S. S. D., Gledhill, N., Jamnik, V. K., & Warburton, D. E. R. (2013). PAR-Q+ and ePARmed-X+. Canadian Family Physician, 59(3), 273–277.

Cassilhas, R. C., Tufik, S., & de Mello, M. T. (2016). Physical exercise, neuroplasticity, spatial learning and memory. Cellular and molecular life sciences : CMLS, 73(5), 975–983.

https://doi.org/10.1007/s00018-015-2102-0.

Cognition, C. (2006). CANTABeclipseTM: Version 3: Software User Guide. Cambridge, UK: Author.

Chowdhury, R., Guitart-Masip, M., Lambert, C., Dayan, P., Huys, Q., Düzel, E., & Dolan, R. J. (2013). Dopamine restores reward prediction errors in old age. Nature neuroscience, 16(5), 648–653. https://doi.org/10.1038/nn.3364.

Chun, C. T., Seward, K., Patterson, A., Melton, A., & MacDonald-Wicks, L. (2021). Evaluation of Available Cognitive Tools Used to Measure Mild Cognitive Decline: A Scoping Review. Nutrients, 13(11), 3974. https://doi.org/10.3390/nu13113974.

Clément, S., Tonini, A., Khatir, F., Schiaratura, L., & Samsony, S. (2012). Short and longer term effects of musical intervention in severe Alzheimer's disease. Music Perception, 29(5), 533–541. https://doi.org/10.1525/mp.2012.29.5.533.

Crawford, J. R., & Henry, J. D. (2004). The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. The British journal of clinical psychology, 43(Pt 3), 245–265. https://doi.org/10.1348/0144665031752934.

Cuddy, L. L., & Duffin, J. (2005). Music, memory, and Alzheimer's disease: is music recognition spared in dementia, and how can it be assessed?. Medical hypotheses, 64(2), 229–235. https://doi.org/10.1016/j.mehy.2004.09.005.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., White, S. M., Wojcicki, T. R., Mailey, E., Vieira, V. J., Martin, S. A., Pence, B. D., Woods, J. A., McAuley, E., & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America, 108(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108.

Ferreri, L., Mas-Herrero, E., Zatorre, R. J., Ripollés, P., Gomez-Andres, A., Alicart, H., Olivé, G., Marco-Pallarés, J., Antonijoan, R. M., Valle, M., Riba, J., & Rodriguez-Fornells, A. (2019). Dopamine modulates the reward experiences elicited by music. Proceedings of the National Academy of Sciences of the United States of America, 116(9), 3793–3798. https://doi.org/10.1073/pnas.1811878116.

Fiveash, A., Bella, S. D., Bigand, E., Gordon, R. L., & Tillmann, B. (2022). You got rhythm, or more: The multidimensionality of rhythmic abilities. Attention, perception & psychophysics, 84(4), 1370–1392. https://doi.org/10.3758/s13414-022-02487-2.

Flo BK, Matziorinis AM, Skouras S, Sudmann TT, Gold C, Koelsch S. (2022). Study protocol for the Alzheimer and music therapy study: An RCT to compare the efficacy of music therapy and physical activity on brain plasticity, depressive symptoms, and cognitive decline, in a population with and at risk for Alzheimer's disease. PLoS One, 17(6), e0270682. doi: 10.1371/journal.pone.0270682.

François, C., Grau-Sánchez, J., Duarte, E., & Rodriguez-Fornells, A. (2015). Musical training as an alternative and effective method for neuro-education and neuro-rehabilitation. Frontiers in psychology, 6, 475. https://doi.org/10.3389/fpsyg.2015.00475.

Freitas, S., Simões, M. R., Alves, L., Vicente, M., & Santana, I. (2012). Montreal Cognitive Assessment (MoCA): validation study for vascular dementia. Journal of the International Neuropsychological Society : JINS, 18(6), 1031–1040. https://doi.org/10.1017/S135561771200077X.

Foster, N. A., & Valentine, E. R. (2001). The Effect of Auditory Stimulation on Autobiographical Recall in Dementia. Experimental Aging Research, 27(3), 215–228. https://doi.org/10.1080/036107301300208664.

Gomes-Osman, J., Cabral, D. F., Morris, T. P., McInerney, K., Cahalin, L. P., Rundek, T., Oliveira, A., & Pascual-Leone, A. (2018). Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose. Neurology. Clinical practice, 8(3), 257–265. https://doi.org/10.1212/CPJ.0000000000000460.

González, D. A., Gonzales, M. M., Resch, Z. J., Sullivan, A. C., & Soble, J. R. (2022). Comprehensive Evaluation of the Functional Activities Questionnaire (FAQ) and Its Reliability and Validity. Assessment, 29(4), 748–763. https://doi.org/10.1177/1073191121991215.

Guetin, S., Charras, K., Berard, A., Arbus, C., Berthelon, P., Blanc, F., Blayac, J. P., Bonte, F., Bouceffa, J. P., Clement, S., Ducourneau, G., Gzil, F., Laeng, N., Lecourt, E., Ledoux, S., Platel, H., Thomas-Anterion, C., Touchon, J., Vrait, F. X., & Leger, J. M. (2013). An overview of the use of music therapy in the context of Alzheimer's disease: a report of a French expert group. Dementia (London, England), 12(5), 619–634. https://doi.org/10.1177/1471301212438290.

Harrison, S., Cooke, M., Moyle, W., Shum, D., and Murfield, J. E. (2010). Development of a music intervention protocol and its effect on participant engagement: experiences from a randomised controlled trial with older people with dementia. Arts Health 2, 125–139. doi: 10.1080/17533015.2010.490839.

Holmes, C., Knights, A., Dean, C., Hodkinson, S., & Hopkins, V. (2006). Keep music live: music and the alleviation of apathy in dementia subjects. International psychogeriatrics, 18(4), 623–630. https://doi.org/10.1017/S1041610206003887.

Hsu, M. H., Flowerdew, R., Parker, M., Fachner, J., & Odell-Miller, H. (2015). Individual music therapy for managing neuropsychiatric symptoms for people with dementia and their carers: a cluster randomised controlled feasibility study. BMC geriatrics, 15, 84.

https://doi.org/10.1186/s12877-015-0082-4.

Innes, K. E., Selfe, T. K., Khalsa, D. S., & Kandati, S. (2017). Meditation and Music Improve Memory and Cognitive Function in Adults with Subjective Cognitive Decline: A Pilot Randomized Controlled Trial. Journal of Alzheimer S Disease, 56(3), 899–916. https://doi.org/10.3233/jad-160867.

Irish, M., Cunningham, C. J., Walsh, J. B., Coakley, D., Lawlor, B. A., Robertson, I. H., & Coen, R. F. (2006). Investigating the enhancing effect of music on autobiographical memory in mild Alzheimer's disease. Dementia and geriatric cognitive disorders, 22(1), 108–120. https://doi.org/10.1159/000093487.

Ismail, Z., Black, S. E., Camicioli, R., Chertkow, H., Herrmann, N., Laforce, R., Jr, Montero-Odasso, M., Rockwood, K., Rosa-Neto, P., Seitz, D., Sivananthan, S., Smith, E. E., Soucy, J. P., Vedel, I., Gauthier, S., & CCCDTD5 participants (2020). Recommendations of the 5th Canadian Consensus Conference on the diagnosis and treatment of dementia. Alzheimer's & dementia : the journal of the Alzheimer's Association, 16(8), 1182–1195. https://doi.org/10.1002/alz.12105.

Jessen, F., Amariglio, R. E., van Boxtel, M., Breteler, M., Ceccaldi, M., Chételat, G., Dubois, B., Dufouil, C., Ellis, K. A., van der Flier, W. M., Glodzik, L., van Harten, A. C., de Leon, M. J., McHugh, P., Mielke, M. M., Molinuevo, J. L., Mosconi, L., Osorio, R. S., Perrotin, A., Petersen, R. C., ... Subjective Cognitive Decline Initiative (SCD-I) Working Group (2014). A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association, 10(6), 844–852. https://doi.org/10.1016/j.jalz.2014.01.001.

Johnson, J. K., Chang, C. C., Brambati, S. M., Migliaccio, R., Gorno-Tempini, M. L., Miller, B. L., & Janata, P. (2011). Music recognition in frontotemporal lobar degeneration and Alzheimer disease. Cognitive and behavioral neurology: official journal of the Society for Behavioral and Cognitive Neurology, 24(2), 74–84. https://doi.org/10.1097/WNN.0b013e31821de326.

Kernan, W. N., Viscoli, C. M., Makuch, R. W., Brass, L. M., Horwitz, R. I. (1999). Stratified randomization for clinical trials. J Clin Epidemiol, 52(1):19-26. doi: 10.1016/s0895-4356(98)00138-3. PMID: 9973070.

Liu X., Liu L., Liu C. (2024). Summary of the effect of an exercise intervention on elderly with mild cognitive impairment: A systematic review and meta-analysis. Medicine (Baltimore), 103(24):e38025. https://doi.org/10.1097/MD.0000000000038025.

Liu, M., Ma, J., Fu, C. Y., Yeo, J., Xiao, S. S., Xiao, W. X., Li, R. R., Zhang, W., Xie, Z. M., Li, Y. J., & Li, Y. X. (2022). Dysfunction of Emotion Regulation in Mild Cognitive Impairment Individuals Combined With Depressive Disorder: A Neural Mechanism Study. Frontiers in aging neuroscience, 14, 884741. https://doi.org/10.3389/fnagi.2022.884741.

Matziorinis AM, Flo BK, Skouras S, Dahle K, Henriksen A, Hausmann F, Sudmann TT, Gold C, Koelsch S. (2023). A 12-month randomised pilot trial of the Alzheimer's and music therapy study: a feasibility assessment of music therapy and physical activity in patients with mild-to-moderate Alzheimer's disease. Pilot Feasibility Stud, 9(1), 61. doi: 10.1186/s40814-023-01287-1.

Mayo Foundation for Medical Education and Research. (2024). Mild cognitive impairment (MCI). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/symptoms-causes/syc-20354578.

Molinuevo, J. L., Rabin, L. A., Amariglio, R., Buckley, R., Dubois, B., Ellis, K. A., Ewers, M., Hampel, H., Klöppel, S., Rami, L., Reisberg, B., Saykin, A. J., Sikkes, S., Smart, C. M., Snitz, B. E., Sperling, R., van der Flier, W. M., Wagner, M., Jessen, F., & Subjective Cognitive Decline Initiative (SCD-I) Working Group (2017). Implementation of subjective cognitive decline criteria in research studies. Alzheimer's & dementia : the journal of the Alzheimer's Association, 13(3), 296–311. https://doi.org/10.1016/j.jalz.2016.09.012.

Munro, C. E., Boyle, R., Chen, X., Coughlan, G., Gonzalez, C., Jutten, R. J., Martinez, J., Orlovsky, I., Robinson, T., Weizenbaum, E., Pluim, C. F., Quiroz-Gaviria, Y. T., Gatchel, J. R., Vannini, P., & Amariglio, R. (2023). Recent contributions to the field of subjective cognitive decline in aging: A literature review. Alzheimer's & dementia (Amsterdam, Netherlands), 15(4), e12475. https://doi.org/10.1002/dad2.12475.

Murman D. L. (2015). The Impact of Age on Cognition. Seminars in hearing, 36(3), 111–121. https://doi.org/10.1055/s-0035-1555115.

Narme, P., Clément, S., Ehrlé, N., Schiaratura, L., Vachez, S., Courtaigne, B., Munsch, F., & Samson, S. (2014). Efficacy of musical interventions in dementia: evidence from a randomized controlled trial. Journal of Alzheimer's disease: JAD, 38(2), 359–369. https://doi.org/10.3233/JAD-130893.

NIH National Institute of Aging, (2024). Cognitive Health and Older Adults. Available at https://www.nia.nih.gov/health/brain-health/cognitive-health-and-older-adults.

Pereira, C. S., Teixeira, J., Figueiredo, P., Xavier, J., Castro, S. L., & Brattico, E. (2011). Music and emotions in the brain: familiarity matters. PloS one, 6(11), e27241. https://doi.org/10.1371/journal.pone.0027241.

Pihlstrom BL, Curran AE, Voelker HT, Kingman A. (2012) Randomized controlled trials: what are they and who needs them? Periodontol 2000, 59(1), 14-31. doi:

10.1111/j.1600-0757.2011.00439.x.

Pinto, E., & Peters, R. (2009). Literature review of the Clock Drawing Test as a tool for cognitive screening. Dementia and geriatric cognitive disorders, 27(3), 201–213. https://doi.org/10.1159/000203344.

Puffer S, Torgerson DJ, Watson J. (2005). Cluster randomized controlled trials. J Eval Clin Pract., 11(5), 479-83. doi: 10.1111/j.1365-2753.2005.00568.x.

Rami, L., Mollica, M. A., García-Sanchez, C., Saldaña, J., Sanchez, B., Sala, I., Valls-Pedret, C., Castellvi, M., Olives, J., & Molinuevo, J. L. (2014). Subjective Cognitive Decline Questionnaire (SCD-Q) [Database record]. APA PsycTests. https://doi.org/10.1037/t62730-000.

Reuben D. B., Kremen S., Maust D.T. (2024). Dementia Prevention and Treatment: A Narrative Review. JAMA Intern Med, 1;184(5):563-572. https://doi.org/10.1001/jamainternmed.2023.8522.

Romero, F. (2014). Body Percussion and Memory for Elderly People Through the BAPNE Method. Procedia - Social and Behavioral Sciences, 132. https://doi.org/10.1016/j.sbspro.2014.04.349.

Sakamoto, M., Ando, H., & Tsutou, A. (2013). Comparing the effects of different individualized music interventions for elderly individuals with severe dementia. International psychogeriatrics, 25(5), 775–784. https://doi.org/10.1017/S1041610212002256.

Sanders, L. M. J., Hortobágyi, T., Karssemeijer, E. G. A., Van der Zee, E. A., Scherder, E. J. A., & van Heuvelen, M. J. G. (2020). Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. Alzheimer's research & therapy, 12(1), 28. https://doi.org/10.1186/s13195-020-00597-3.

Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J. K., & Rantanen, P. (2014). Cognitive, emotional, and social benefits of regular musical activities in early dementia: randomized controlled study. The Gerontologist, 54(4), 634–650. https://doi.org/10.1093/geront/gnt100.

Särkämö T. (2018). Cognitive, emotional, and neural benefits of musical leisure activities in aging and neurological rehabilitation: A critical review. Annals of physical and rehabilitation medicine, 61(6), 414–418. https://doi.org/10.1016/j.rehab.2017.03.006.

Satoh, M., Ogawa, J.-I., Tokita, T., Nakaguchi, N., Nakao, K., Kida, H., & Tomimoto, H. (2017). Physical Exercise with Music Maintains Activities of Daily Living in Patients with Dementia: Mihama-Kiho Project Part 21. Journal of Alzheimer's Disease : JAD, 57(1), 85–96. https://doi.org/10.3233/JAD-161217.

Satoh, M., Takeda, K., Nagata, K., Shimosegawa, E., & Kuzuhara, S. (2006). Positron-emission tomography of brain regions activated by recognition of familiar music. AJNR. American journal of neuroradiology, 27(5), 1101–1106.

Simmons-Stern, N. R., Budson, A. E., & Ally, B. A. (2010). Music as a memory enhancer in patients with Alzheimer's disease. Neuropsychologia, 48(10), 3164–3167. https://doi.org/10.1016/j.neuropsychologia.2010.04.033.

Spenciere, B., Alves, H., & Charchat-Fichman, H. (2017). Scoring systems for the Clock Drawing Test: A historical review. Dementia & neuropsychologia, 11(1), 6–14. https://doi.org/10.1590/1980-57642016dn11-010003.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R., Jr, Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., Wagster, M. V., ... Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association, 7(3), 280–292. https://doi.org/10.1016/j.jalz.2011.03.003.

Sung, H. C., Chang, S. M., Lee, W. L., & Lee, M. S. (2006). The effects of group music with movement intervention on agitated behaviours of institutionalized elders with dementia in Taiwan. Complementary therapies in medicine, 14(2), 113–119. https://doi.org/10.1016/j.ctim.2006.03.002.

Sung, H. C., Lee, W. L., Li, T. L., & Watson, R. (2012). A group music intervention using percussion instruments with familiar music to reduce anxiety and agitation of institutionalized older adults with dementia. International journal of geriatric psychiatry, 27(6), 621–627. https://doi.org/10.1002/gps.2761.

Tay, L. X., Ong, S. C., Tay, L. J., Ng, T., & Parumasivam, T. (2024). Economic Burden of Alzheimer's Disease: A Systematic Review. Value in health regional issues, 40, 1–12. https://doi.org/10.1016/j.vhri.2023.09.008.

Thompson, R. G., Moulin, C. J., Hayre, S., & Jones, R. W. (2005). Music enhances category fluency in healthy older adults and Alzheimer's disease patients. Experimental aging research, 31(1), 91–99. https://doi.org/10.1080/03610730590882819.

Torisson, G., Stavenow, L., Minthon, L., & Londos, E. (2016). Reliability, validity and clinical correlates of the Quality of Life in Alzheimer's disease (QoL-AD) scale in medical inpatients. Health and quality of life outcomes, 14, 90. https://doi.org/10.1186/s12955-016-0493-8.

Venegas-Sanabria, L. C., Cavero-Redondo, I., Martínez-

Vizcaino, V., Cano-Gutierrez, C. A., & Álvarez-Bueno, C. (2022). Effect of multicomponent exercise in cognitive impairment: a systematic review and meta-analysis. BMC geriatrics, 22(1), 617. https://doi.org/10.1186/s12877-022-03302-1.

Warren, J. D., Warren, J. E., Fox, N. C., & Warrington, E. K. (2003). Nothing to say, something to sing: primary progressive dynamic aphasia. Neurocase, 9(2), 140–155. https://doi.org/10.1076/neur.9.2.140.15068.

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The Physical Activity Scale for the Elderly (PASE): development and evaluation. Journal of clinical epidemiology, 46(2), 153–162. https://doi.org/10.1016/0895-4356(93)90053-4.

White, D. K., Wilson, J. C., & Keysor, J. J. (2011). Measures of adult general functional status: SF-36 Physical Functioning Subscale (PF-10), Health Assessment Questionnaire (HAQ), Modified Health Assessment Questionnaire (MHAQ), Katz Index of Independence in activities of daily living, Functional Independence Measure (FIM), and Osteoarthritis-Function-Computer Adaptive Test (OA-Function-CAT). Arthritis care & research, 63 Suppl 11, S297–S307. https://doi.org/10.1002/acr.20638.

Yu XH, Li XR, Du ZR, Zhang Y, Fei Y, Tang WP, Li XW, Zhao Q. (2024). Effects of non-pharmacological interventions for adults with subjective cognitive decline: a network meta-analysis and component network meta-analysis. BMC Med, 22(1), 272. doi: 10.1186/s12916-024-03491-z.

Zhang, S., Zhen, K., Su, Q., Chen, Y., Lv, Y., & Yu, L. (2022). The Effect of Aerobic Exercise on Cognitive Function in People with Alzheimer's Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. International journal of environmental research and public health, 19(23), 15700. https://doi.org/10.3390/ijerph192315700.