

# Alpha-Music Entrainment Combined with Physiotherapy Improves Inflammatory and Functional Outcomes in Osteoarthritis of Knee : A Randomized Trial

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**Abstract.** Background: Osteoarthritis of the knee is a chronic degenerative condition characterized by pain, inflammation, stiffness, and functional limitations. Conventional physiotherapy plays a central role in its management; however, complementary neurosensory approaches such as alpha-music entrainment may enhance therapeutic outcomes by influencing pain perception, relaxation, and neurophysiological processes that regulate inflammation. Objective: To evaluate the effects of alpha-music entrainment, when combined with physiotherapy, on inflammatory markers and functional outcomes among individuals with knee osteoarthritis. Methods: A randomized controlled trial was conducted on 40 participants diagnosed with chronic osteoarthritis of the knee (Kellgren–Lawrence grade 2–3). Participants were randomly assigned to Group I (alpha-music entrainment + physiotherapy + electrical modalities) or Group II (physiotherapy + electrical modalities). Interventions were delivered five days a week for eight weeks. Outcome measures included FLIR infrared thermography, Visual Analogue Scale (VAS), Manual Muscle Testing (quadriceps and hamstrings), girth measurement, knee flexion range of motion, and Musculoskeletal Health Questionnaire (MSK-HQ). Assessments were recorded at baseline, 2 weeks, 4 weeks, and 8 weeks. Results: Both groups demonstrated statistically significant improvements over eight weeks ( $p < 0.05$ ). However, Group I showed markedly greater reductions in surface temperature (mean difference  $5.61^{\circ}\text{C}$ ), VAS (mean difference 8.95), swelling (mean difference 8.81 cm), and significantly higher gains in knee flexion, quadriceps and hamstring strength, and MSK-HQ scores compared to the control group ( $p < 0.001$ ). Conclusion: Alpha-music entrainment combined with physiotherapy produced superior improvements in inflammation, pain reduction, muscle strength, and functional capacity than physiotherapy alone. Incorporating alpha-rhythm auditory stimulation may provide an effective adjunctive approach in the rehabilitation of knee osteoarthritis.

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## 1 Introduction

Osteoarthritis (OA) of the knee is one of the most prevalent and disabling musculoskeletal disorders worldwide, representing a major cause of pain, impaired mobility, and diminished quality of life among older adults. It is a chronic, progressive condition characterized by degeneration of articular cartilage, subchondral bone remodeling, synovial inflammation, and periarticular muscle dysfunction—pathological processes that collectively contribute to persistent pain and functional decline.[1-3] As life expectancy increases and sedentary behavior becomes more common, the global burden of knee OA is expected to rise significantly, posing substantial clinical, social, and economic challenges. [1-2]

A growing body of evidence highlights the role of inflammation in mediating the onset and progression of OA. Although traditionally viewed as a “non-inflammatory” arthropathy, contemporary research demonstrates that low-grade synovitis, cytokine activation, and metabolic dysregulation are central to symptom severity and structural deterioration. [3-5] Circulating inflammatory markers such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and C-reactive protein have been correlated with heightened pain, accelerated cartilage loss, and radiographic progression, suggesting that interventions capable of modulating inflammation may influence clinical outcomes. [4-5]

Physiotherapy remains a cornerstone of knee OA management, with strong evidence supporting strengthening exercises, proprioceptive training, stretching, joint mobilization, and task-oriented functional rehabilitation for reducing pain and improving mobility. [12-18] Adjunct electrotherapeutic modalities such as transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound further contribute to symptom relief, particularly in individuals with moderate to severe pain. [17-18] Yet, despite these established approaches, the persistence of pain and the multifactorial biological drivers of OA highlight the need for multimodal, complementary interventions that address not only musculoskeletal impairments but also underlying neurophysiological mechanisms associated with pain perception.

Music-based therapeutic interventions have emerged as a promising adjunct in chronic pain management.[22-25] Among these, **alpha-music stimulation**, designed to entrain brain oscillations within the 8–12 Hz alpha frequency band, has attracted increasing scientific interest. Alpha-wave entrainment is associated with modulations in cortical excitability, improved sensory gating, enhanced emotional regulation, and attenuation of perceived pain. [19-21,28-30] Neurophysiological studies indicate that alpha rhythms influence thalamocortical circuits and inhibitory control networks implicated in nociception, suggesting a plausible mechanism through which rhythmic auditory stimulation may reduce pain intensity and autonomic arousal. [20,21,28,29] Additionally, alpha-music has been shown to induce relaxation responses, decrease sympathetic activation, and potentially modulate inflammatory pathways, thereby offering a biopsychosocial complement to conventional physiotherapy. [22-25]

Although previous investigations have examined music therapy in chronic musculoskeletal pain, evidence specifically evaluating **alpha-music entrainment** in

combination with physiotherapeutic exercise for knee OA is extremely limited. The potential synergistic interaction—wherein alpha-state relaxation may prime neuromuscular responsiveness, enhance exercise tolerance, and support favourable inflammatory modulation—remains underexplored. This gap provides a strong rationale for rigorous clinical evaluation.

Therefore, the present randomized controlled trial was designed to investigate the **effects of alpha-music entrainment combined with conventional physiotherapy** on inflammatory and functional outcomes in individuals with osteoarthritis of the knee. By employing multimodal outcome measures—including infrared thermography for inflammation assessment, pain intensity, muscle strength, joint range of motion, anthropometric changes, and musculoskeletal health-related quality of life—this study aims to offer comprehensive insight into the clinical utility of integrating neuroacoustic stimulation with physiotherapeutic rehabilitation. The findings are expected to contribute meaningful evidence toward developing holistic, non-pharmacological treatment strategies for knee OA.

## 2 Methods

### 2.1 Study Design and Ethical Approval

This investigation was conceptualized as a parallel-group, randomized controlled trial designed to elucidate the therapeutic influence of alpha-music entrainment combined with structured physiotherapy on inflammatory and functional outcomes in individuals diagnosed with osteoarthritis of the knee. The study adhered to the ethical principles set forth in the Declaration of Helsinki and followed the methodological standards recommended for clinical research in rehabilitation *sciences*. Ethical approval for the study protocol was obtained from the Institutional Human Ethics Committee prior to participant enrolment. All participants were informed regarding the nature, purpose, and procedural requirements of the study and provided written informed consent [23–25].

### 2.2 Participants

#### 2.2.1 Recruitment Procedures

Participants were recruited from outpatient physiotherapy clinics and community orthopedic centres through clinician referrals and public notices. Screening was performed by a trained physiotherapist to ensure adherence to eligibility criteria. Individuals presenting with chronic knee pain attributable to osteoarthritis were evaluated for radiographic confirmation, symptom chronicity, functional limitations, and the absence of competing diagnoses.

#### 2.2.2 Inclusion Criteria

1. Were aged between 45 and 75 years.
2. Fulfilled the American College of Rheumatology clinical criteria for knee osteoarthritis.

3. Demonstrated Kellgren–Lawrence (KL) radiographic grade II–III changes.
4. Reported persistent knee pain for >1 year.
5. Exhibited functional limitation in activities requiring lower-limb weight-bearing.
6. Scored  $\geq 8$  on the Visual Analogue Scale (VAS) at baseline.
7. Were able to comply with the full intervention schedule and follow-up assessments [26–28].

### **2.2.3 Exclusion Criteria**

1. Prior knee surgery or intra-articular injections within the past six months.
2. Rheumatologic, neurologic, or metabolic disorders influencing joint function.
3. Cardiovascular or systemic conditions contraindicating physiotherapy or music-based interventions;
4. Cognitive impairments limiting procedural comprehension.
5. Concurrent participation in other physiotherapy or pharmacological clinical trials [29–31].

### **2.2.4 Baseline Characteristics**

#### **Enrollment**

- Assessed for eligibility (n = 52)
- Excluded (n = 12): Not meeting inclusion criteria (n = 7); Declined (n = 3); Other reasons (n = 2)

#### **Randomisation**

- Randomized (n = 40)

#### **Allocation**

- Experimental Group (n = 20): Alpha-music entrainment + Physiotherapy + Electrical modalities
- Control Group (n = 20): Physiotherapy + Electrical modalities

#### **Follow-Up**

- Experimental Group: Lost to follow-up (n = 0); Discontinued (n = 0)
- Control Group: Lost to follow-up (n = 0); Discontinued (n = 0)

#### **Analysis**

- Experimental Group: Included in analysis (n = 20)
- Control Group: Included in analysis (n = 20)

Forty participants meeting the eligibility criteria were enrolled and randomized into two equal groups (n = 20 each). Demographic and clinical characteristics, including age, gender distribution, chronicity, KL grading, side involvement, and baseline severity measures—were recorded to ensure comparability between groups. The two groups demonstrated no statistically significant baseline differences, supporting methodological equivalence and unbiased allocation.

## **2.3 Randomization and Blinding**

### **2.3.1 Randomization Procedure**

Participants were allocated using a computer-generated random sequence employing permuted blocks to ensure balanced distribution across intervention arms. Allocation

was concealed using sequentially numbered, opaque, sealed envelopes prepared by an independent researcher not involved in recruitment or assessment [32].

### 2.3.2 Blinding

Given the nature of the interventions, participant blinding was not feasible. However, outcome assessments and data entry were performed by evaluators blinded to group assignment to minimize assessment-related bias. Statistical analysis was conducted by an independent biostatistician similarly blinded to group identity.

## 2.4 Intervention Procedures

### 2.4.1 Experimental Group: Alpha-Music Entrainment + Physiotherapy

Participants in the experimental group received a structured therapeutic protocol beginning with **20 minutes of alpha-music entrainment** delivered through calibrated headphones in a quiet treatment environment. Music selection was guided by predefined, evidence-based criteria. Musical pieces were selected to exhibit a dominant rhythmic structure within the alpha frequency range (8–12 Hz), which has been shown to facilitate cortical alpha-band entrainment. Only instrumental, non-lyrical compositions with a low-tempo and stable rhythmic pattern were included to minimize cognitive load and language-related cortical activation. The selection framework was informed by prior EEG-based entrainment studies and music-induced analgesia literature, supporting the role of rhythmic auditory stimulation in modulating pain perception, relaxation, and attentional states.

The musical composition was selected to promote neurophysiologic entrainment within the alpha frequency range (8–12 Hz), which has been associated with modulating pain perception, autonomic balance, and inflammatory processes. Participants were positioned supine with verbal instructions to maintain diaphragmatic breathing and to remain relaxed throughout the session. Immediately following entrainment, individuals underwent a multimodal physiotherapy program consisting of:

- **PNF stretching** of hamstrings and calf musculature (30-second holds; 3 repetitions);
- **Isometric strengthening** for quadriceps and gluteal muscles (10-second holds × 10 repetitions)
- **Open-chain knee flexion–extension** active exercises (10-second holds × 10 repetitions)
- **Progressive resistance strengthening** of hip and ankle musculature (10-second holds × 10 repetitions)
- **Proprioceptive tasks**, such as partial squats, single-leg stance (eyes open/closed), heel-to-toe gait, and cross-body leg swings.
- **Mulligan mobilization with movement (MWM)** focusing on medial/lateral glides (6–10 repetitions)
- **Task-oriented exercises**, including step-up/step-down training and functional walking drills.

Therapeutic intensity was progressively increased by narrowing the base of support, lengthening lever arms, increasing movement resistance, or advancing proprioceptive demands. Rest was provided as needed to avoid fatigue.

### 2.4.2 Control Group: Physiotherapy Without Alpha-Music Entrainment

Participants in the control group underwent identical physiotherapeutic procedures but **without** exposure to alpha-music entrainment. Instead, they received standardized **TENS (80 Hz, 10–30 mA)** and **continuous-mode therapeutic ultrasound (1 MHz, 1 W/cm<sup>2</sup>)** before exercises. This served as a conventional physiotherapy comparison arm aligned with current clinical practice guidelines for knee osteoarthritis.

## 2.5 Outcome Assessment

### 2.5.1 Primary Outcomes

Primary outcomes were assessed at baseline (Day 1), 2 weeks, 4 weeks, and 8 weeks:

1. **FLIR Infrared Thermography** (surface temperature as an inflammation marker);
2. **Visual Analogue Scale (VAS)** for pain intensity.
3. **Musculoskeletal Health Questionnaire (MSK-HQ)** for global musculoskeletal function.

### 2.5.2 Secondary Outcomes

- **Quadriceps and hamstring muscle strength** measured using the standard Manual Muscle Testing (MMT) scale;
- **Girth measurement** of the peripatellar region using a tape gauge to assess effusion;
- **Range of motion (ROM) of knee flexion** measured using a universal goniometer.

### 2.5.3 Measurement Reliability and Standardization

All measurements were conducted by a single experienced therapist to reduce inter-rater variability. The FLIR E8-series thermographic camera was calibrated before each use. Standardized measurement protocols ensured consistent positioning, anatomical landmark identification, and environmental temperature control during assessments.

## 2.6 Statistical Analysis

Data were analyzed using SPSS (version 22.0). Normality was verified using the Shapiro–Wilk test. Repeated-measures ANOVA assessed within-group changes across time points, with Greenhouse–Geisser or Huynh–Feldt corrections applied based on sphericity violations. Between-group differences were examined using independent sample t-tests. A significance level of  $p < 0.05$  was considered statistically meaningful.

## 3. Results

### 3.1 Participant Flow and Baseline Characteristics

A total of 40 participants meeting the eligibility criteria were enrolled and randomized into two groups (Experimental:  $n = 20$ ; Control:  $n = 20$ ). All participants completed the full 8-week intervention and follow-up assessments, with no attrition recorded. Baseline demographic and clinical characteristics were comparable between groups, indicating successful randomization.

**Table 1.** Baseline Demographic and Clinical Characteristics (OA Knee)

Variable	Group I (Experimental) Mean $\pm$ SD / n	Group II (Control) Mean $\pm$ SD / n	p-value
Age (years)	62.80 $\pm$ 7.30	58.70 $\pm$ 9.29	0.112

Gender (M/F)	9 / 11	5 / 15	0.180
KL Grade	2.30 ± 0.47	2.25 ± 0.44	0.742
Involved Side (R/L)	15 / 5	14 / 6	0.723
Chronicity (years)	1.57 ± 0.45	1.77 ± 1.03	0.451
VAS (baseline)	9.35 ± 0.74	9.20 ± 0.76	0.512

**Interpretation:**

Both groups were statistically comparable at baseline, confirming that any subsequent change can be attributed to the intervention effect rather than pre-existing differences.

**3.2 Normality Testing**

Shapiro–Wilk and Kolmogorov–Smirnov tests confirmed that all outcome data for both groups were normally distributed ( $p > 0.05$ ), justifying the use of parametric statistics.

3.3 Within-Group Changes Over Time (Repeated-Measures ANOVA)

3.3.1 Control Group (Group II)

A significant improvement was observed across all outcomes over time ( $p < 0.001$ ), although the magnitude of change was moderate.

3.3.2 Experimental Group (Group I)

Participants receiving Alpha-Music Entrainment + Physiotherapy demonstrated markedly greater improvements, with large effect sizes, especially for:

- **Pain reduction (VAS)**
- **Thermography-derived inflammation reduction**
- **Knee flexion ROM**
- **Functional improvement (MSK-HQ)**

3.2 Between-Group Comparisons (Independent t-Tests)

- 3.3 At each time-point (2, 4, 8 weeks), the experimental group showed statistically superior outcomes compared to the control group

TABLE SET 2 — Mean ± SD at 2, 4, and 8 Weeks

**Table 2.** Outcomes After 2 Weeks

Outcome	Group I Mean ± SD	Group II Mean ± SD	p-value
FLIR Temperature (°C)	31.565 ± 0.954	33.025 ± 0.552	<0.001
VAS	6.35 ± 1.27	8.00 ± 0.86	<0.001
MMT Quadriceps	3.325 ± 0.634	2.475 ± 0.443	<0.001
MMT Hamstring	2.925 ± 0.568	2.475 ± 0.343	0.005
Girth (cm)	40.300 ± 1.318	42.485 ± 1.708	<0.001
ROM Knee Flexion (°)	111.95 ± 3.48	97.15 ± 6.03	<0.001
MSK-HQ	32.55 ± 4.57	22.00 ± 3.71	<0.001

**Table 3.** Outcomes After 4 Weeks

Outcome	Group I Mean ± SD	Group II Mean ± SD	p-value
FLIR Temperature (°C)	29.825 ± 0.870	32.840 ± 0.563	<0.001
VAS	3.30 ± 1.08	6.10 ± 1.65	<0.001
MMT Quadriceps	3.700 ± 0.637	3.000 ± 0.459	<0.001
MMT Hamstring	3.825 ± 0.520	2.600 ± 0.308	<0.001
Girth (cm)	37.355 ± 1.863	41.050 ± 2.803	<0.001
ROM Knee Flexion (°)	125.10 ± 3.04	98.90 ± 6.56	<0.001
MSK-HQ	44.45 ± 2.61	25.65 ± 4.27	<0.001

**Table 4.** Outcomes After 8 Weeks

Outcome	Group I Mean ± SD	Group II Mean ± SD	p-value
FLIR Temperature (°C)	27.660 ± 0.817	32.590 ± 0.533	<0.001
VAS	0.40 ± 0.50	5.90 ± 1.48	<0.001
MMT Quadriceps	4.625 ± 0.358	3.250 ± 0.526	<0.001
MMT Hamstring	4.350 ± 0.462	2.900 ± 0.308	<0.001
Girth (cm)	34.980 ± 1.859	40.165 ± 3.573	<0.001
ROM Knee Flexion (°)	130.50 ± 1.91	107.40 ± 4.49	<0.001
MSK-HQ	52.90 ± 2.20	33.20 ± 5.92	<0.001

### 3.5 Summary of Key Statistical Findings

#### Inflammation (FLIR Thermography)

- Significant reductions in surface temperature in both groups ( $p < 0.001$ )
- Greater reduction in the experimental group by Week 8 ( $\Delta = 5.61$  °C vs.  $0.61$  °C)

#### Pain (VAS)

- Experimental group: reduction from 9.35 → 0.40
- Control group: reduction from 9.20 → 5.90
- Week 8  $p < 0.001$

#### Muscle Strength (MMT)

- Quadriceps and hamstring strength improved significantly more in the experimental arm ( $p < 0.001$ )

#### Girth (Effusion)

- Larger reduction in swelling in the experimental group
- Week 8: 34.98 vs. 40.165 cm ( $p < 0.001$ )

#### Range of Motion

- Experimental group:  $93.75^\circ \rightarrow 130.50^\circ$
- Control group:  $96.65^\circ \rightarrow 107.40^\circ$
- Meaningful clinical and statistical superiority

#### Functional Status (MSK-HQ)

- Experimental group improved from 19.3 → 52.9
- Control group improved from 17.75 → 33.20

- $p < 0.001$  across all time-points

## 4. DISCUSSION

The present randomized trial examined the therapeutic efficacy of alpha-music entrainment combined with physiotherapy in individuals with knee osteoarthritis (OA), with outcomes systematically assessed across inflammatory, neuromuscular, and functional domains. The findings demonstrate that the addition of alpha-music entrainment produces superior improvements in pain, inflammatory markers (thermography and girth), muscle strength, joint mobility, and global functional health compared to conventional physiotherapy alone. These results highlight the growing importance of neurophysiological modulation in musculoskeletal rehabilitation, particularly in conditions characterized by chronic pain and persistent inflammation.

### 4.1. Impact on Inflammation: Thermography and Edema Reduction

Infrared thermography demonstrated a substantial decline in knee surface temperature in the experimental group, suggesting a robust modulation of the local inflammatory response. Surface temperature is a well-established correlate of synovial inflammation and microvascular activity in OA [6]. The reduction from 33.27°C to 27.66°C aligns with literature showing that effective rehabilitation diminishes peripheral inflammatory activity by improving joint biomechanics and reducing nociceptive drive

The reduction in girth also indicates decreased effusion, consistent with improved lymphatic clearance, reduced synovial congestion, and lowered cytokine activity—mechanisms central to OA pathophysiology[5-7]. Together, thermal and volumetric improvements strengthen the argument that entrainment-based interventions exert a meaningful regulatory effect on inflammatory pathways.

### 4.2. Superior Analgesic Response Through Alpha-Music Entrainment

Pain reduction was markedly greater in the alpha-music group, decreasing from 9.35 to 0.40 on the VAS scale. This dramatic response is consistent with the analgesic mechanisms described in music-induced neurophysiology, including:

#### 4.2.1 *Alpha-wave enhancement and cortical gating*

Alpha-band oscillations (8–12 Hz) are known to suppress irrelevant sensory inputs and reduce pain perception by modulating thalamocortical communication and excitatory–inhibitory balance [19-21,28-30].

#### 4.2.2 *Activation of emotional and reward networks*

Music stimulates dopaminergic pathways and limbic areas associated with emotional reappraisal, reducing catastrophization and fear of movement crucial determinants of OA disability [24,25].

#### 4.2.3 *Attenuation of autonomic arousal*

Music has been shown to downregulate sympathetic activity and lower inflammatory cytokines [22,23], thereby complementing the physical effects of physiotherapy.

The deeper and faster pain decline observed in this trial indicates that entrainment enhances both neurophysiological inhibition of nociception and psychophysiological relaxation, positioning it as a valuable non-pharmacological adjunct for chronic pain management in OA.

### **4.3 Enhancements in Muscle Strength and Motor Performance**

Significant gains in quadriceps and hamstring muscle strength were observed in the experimental group, surpassing those seen with routine physiotherapy. Pain is a major contributor to arthrogenic muscle inhibition in OA; thus, reducing nociception allows more efficient recruitment of motor units. Muscle strengthening is the cornerstone of OA rehabilitation, improving joint stability, shock absorption, and functional tolerance[12-15]

The pronounced strength improvement in this study suggests that alpha entrainment optimizes motor learning through:

- improved cortical readiness and attentional focus
- reduced fear-avoidance and movement inhibition
- better neuromuscular control from enhanced proprioceptive feedback

These neurobiological pathways help explain why the entrainment group demonstrated a steeper strength-gain trajectory, highlighting a synergistic interaction between sensory modulation and motor adaptation.[19-21]

### **4.4 Range of Motion and Joint Mobility Improvements**

Knee flexion ROM increased significantly in the entrainment group, far exceeding improvements observed in the control group. Pain reduction, reduced effusion, and improved muscle activation collectively facilitate greater joint excursion. Furthermore, Mulligan mobilization and open and closed strengthening components present in both groups—are known to restore arthrokinematics and reduce movement-related discomfort.[12,16]

However, only the entrainment group showed a complete normalization trend, suggesting that reduced central sensitization and improved muscle tone contributed to greater mobility gains.

### **4.5 Functional Outcomes: A Multi-Domain Recovery Effect**

The MSK-HQ functional scores revealed robust improvements, indicating enhanced participation, reduced disability, and better global musculoskeletal health. Such gains are aligned with literature showing that reducing pain catastrophization and emotional distress contributes to functional restoration beyond what exercise alone can achieve. The magnitude of functional gain observed in this study (from 19.3 to 52.9) is clinically meaningful and exceeds typical improvements seen in exercise-only OA interventions.[11]

This supports the notion that alpha entrainment enhances rehabilitation by simultaneously targeting sensory, emotional, motor, and cognitive domains—a multimodal recovery profile rarely achieved with traditional physiotherapy alone.

### **4.6 Comparison with Previous Literature**

The present findings complement earlier studies showing beneficial effects of:

- meditation and music-based intervention in chronic pain.
- physiotherapy and strengthening programs in OA
- proprioceptive and task-oriented training

However, this study is among the first to systematically combine alpha-music entrainment with a structured physiotherapy protocol and measure outcomes using thermography, MMT, ROM, and MSK-HQ, thereby extending the evidence base for integrative rehabilitation models.[12-18,22-25]

#### **4.7 Mechanistic Interpretation**

A conceptual model emerges from these findings: Alpha-Music Entrainment → Reduced Cortical Hypervigilance → Lower Pain Sensitivity → Improved Motor Recruitment → Enhanced Physiotherapy Response → Reduced Peripheral Inflammation. This pathway aligns with contemporary frameworks of chronic pain integrating central modulation, emotional processing, peripheral biomechanics, and neuroimmune interactions.[19-21,28-31]

#### **4.8 Strengths of the Study**

- use of objective inflammatory assessment (thermography)
- comprehensive multimodal outcomes
- standardized exercise protocol
- integration of a neurophysiological intervention rarely examined in OA
- strong internal validity through random allocation

#### **4.9 Limitations**

Despite the promising findings, several limitations of the present study should be acknowledged. First, although alpha-music entrainment was designed based on established neurophysiological principles of alpha-band modulation, direct EEG verification of cortical alpha entrainment was not performed during the intervention sessions. Therefore, while the clinical and functional outcomes support the efficacy of the intervention, the neurophysiological mechanisms remain inferred rather than directly measured. Second, the sample size, although adequately powered to detect significant between-group differences, was relatively modest and limited to individuals with Kellgren–Lawrence grade 2–3 knee osteoarthritis. This may restrict the generalizability of the findings to patients with very early or advanced disease stages. Third, the study employed infrared thermography as a surrogate marker of inflammation, which reflects changes in surface temperature rather than direct biochemical inflammatory markers. While thermography is a validated, non-invasive tool for assessing inflammatory activity, future studies incorporating serological or synovial biomarkers would provide a more comprehensive evaluation of inflammatory modulation. Fourth, the absence of long-term follow-up limits conclusions regarding the durability of treatment effects after cessation of the intervention. The sustained impact of alpha-music entrainment on pain, function, and inflammatory parameters warrants further longitudinal investigation. Finally, although efforts were made to standardize the physiotherapy protocol, individual variability in pain perception, psychological responsiveness to auditory stimulation, and adherence to exercises may have influenced outcomes.

### **5. Conclusion**

Alpha-music entrainment combined with physiotherapy produces superior clinical and inflammatory outcomes compared to physiotherapy alone in knee osteoarthritis. The intervention demonstrates a powerful synergistic effect, simultaneously improving pain, inflammation, muscle strength, joint mobility, and functional health. These findings position alpha-music entrainment as a promising, low-cost, non-invasive adjunct capable of enhancing conventional rehabilitation outcomes in chronic degenerative musculoskeletal conditions.

## References

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* 2008;58(1):15–25.
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet.* 2011;377(9783):2115–26.
3. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol.* 2011;7(1):33–42.
4. Jin X, Beguerie JR, Zhang W, et al. Circulating C-reactive protein in osteoarthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2015;74(4):703–10.
5. Stannus O, Jones G, Cicuttini F, et al. Circulating levels of IL-6 and TNF- $\alpha$  are associated with knee radiographic OA and cartilage loss. *Osteoarthritis Cartilage.* 2010;18(11):1441–7.
6. Schiavon G, Capone G, Frize M, Zaffagnini S, Candrian C, Filardo G. Infrared thermography for the evaluation of inflammatory and degenerative joint diseases: a systematic review. *CARTILAGE.* 2021;13(2 Suppl):1790S–1801S.
7. Silva AEL, Martimbianco ALC, Pontin JCB, Lahoz GL, Carneiro Filho M, Chamlian TR. Reproducibility analysis of knee circumference in individuals with osteoarthritis. *Acta Fisiátrica.* 2014;21(2).
8. Norkin CC, White DJ. Measurement of Joint Motion: A Guide to Goniometry. 5th ed. Philadelphia: F.A. Davis; 2016.
9. Seeder L. Muscle strength grading. *Ann Emerg Med.* 1983;12:407.
10. Cuthbert SC, Goodheart GJ. On the reliability and validity of manual muscle testing: a literature review. *Chiropr Man Therap.* 2007;15:4.
11. Hill JC, et al. Development and validation of the MSK-HQ for use across musculoskeletal care pathways. *BMJ Open.* 2016;6:e012331.
12. Alkhawajah HA, Alshami AM. Effect of mobilization with movement on pain and function in knee osteoarthritis: a randomized double-blind controlled trial. *BMC Musculoskelet Disord.* 2019;20:452.
13. Weng MC, Lee CL, Chen CH, Hsu JJ, Lee WD, Huang MH, Chen TW. Effects of different stretching techniques on isokinetic outcomes in knee OA. *Kaohsiung J Med Sci.* 2009;25(6):306–15.
14. Nazari A, Moezy A, Nejati P, Mazaherinezhad A. Efficacy of high-intensity laser therapy vs. conventional physiotherapy in knee OA. *Lasers Med Sci.* 2019;34:505–16.
15. Ojoawo AO, Olaogun MO, Hassan MA. Comparative effects of proprioceptive vs isometric exercises in knee OA. *Technol Health Care.* 2016;24(6):853–63.

16. Lalnunpuii A, Sarkar B, Alam S, Equebal A, Biswas A. Efficacy of Mulligan mobilisation vs Maitland mobilisation in female OA knee patients. *Int J Ther Rehabil Res.* 2017;6(2):37.
17. Wu Y, Zhu F, Chen W, Zhang M. Effects of TENS in people with knee OA: systematic review and meta-analysis. *Clin Rehabil.* 2021;36.
18. Dantas LO, Osani MC, Bannuru RR. Therapeutic ultrasound for knee osteoarthritis: systematic review & meta-analysis. *Braz J Phys Ther.* 2021;25(6):688–97.
19. Busch NA, Dubois J, VanRullen R. The phase of ongoing EEG oscillations predicts visual perception. *J Neurosci.* 2009;29:7869–76.
20. Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: Gating by inhibition. *Front Hum Neurosci.* 2010;4:186.
21. Pfurtscheller G, Stancák A, Neuper C. Event-related synchronization in the alpha band as a correlate of cortical idling. *Int J Psychophysiol.* 1996;24:39–46.
22. Innes KE, Selfe TK, Kandati S, Wen S, Huysmans Z. Mantra meditation vs music listening in knee OA: RCT findings. *Evid Based Complement Alternat Med.* 2018;2018:76838.
23. Khan SH, Kitsis M, Golovyan D, et al. Effects of music intervention on inflammatory markers in critically ill patients. *Heart Lung.* 2018;47:489–96.
24. Garza-Villarreal EA, Wilson AD, Vase L, Brattico E, Barrios FA, et al. Music reduces pain and increases functional mobility in fibromyalgia. *Front Psychol.* 2014;5:90.
25. Garza-Villarreal EA, Pando-Naude V, Vuust P, Parsons C. Music-induced analgesia in chronic pain: systematic review & meta-analysis. *Pain Physician.* 2017;20:597–610.
26. Singh V, Rana RK, Singhal R. Analysis of repeated measurement data in clinical trials. *J Ayurveda Integr Med.* 2013;4:77–81.
27. Kim TK. T-test as a parametric statistic. *Korean J Anesthesiol.* 2015;68:540–6.
28. Thut G, Schyns PG, Gross J. Entrainment of perceptually relevant brain oscillations by non-invasive rhythmic stimulation of the human brain. *Front Psychol.* 2011;2:170. doi:10.3389/fpsyg.2011.00170.
29. Klimesch W, Sauseng P, Hanslmayr S. EEG alpha oscillations: the inhibition–timing hypothesis. *Brain Res Rev.* 2007;53(1):63–88. doi:10.1016/j.brainresrev.2006.06.003.
30. Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain.* 2006;129(Pt 1):55–64. doi:10.1093/brain/awh631.
31. Arendsen LJ, Hugh-Jones S, Lloyd DM. Entraining alpha activity using visual stimulation in patients with chronic musculoskeletal pain: a feasibility study. *Front Neurosci.* 2020;14:558115. doi:10.3389/fnins.2020.558115.
32. Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci.* 2010;4:186. doi:10.3389/fnhum.2010.00186.