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Psychobiological Effects of Music Therapy and Structured Musical Interventions on Biomarkers in Mental Disorders: A Systematic Review and Meta-analysis

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Psychobiological Effects of Music Therapy and Structured Musical Interventions on Biomarkers in Mental Disorders: A Systematic Review and Meta-analysis

Short Title: Music Therapy & Psychoneuroimmunologic Biomarkers

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Abstract

Objective: To systematically synthesize evidence on the psychobiological effects of music therapy and structured musical interventions on biomarkers in individuals with mental disorders, within a psychoneuroimmunological framework.

Methods This systematic review and meta-analysis followed PRISMA 2020 guidelines. Searches were performed in PubMed, LILACS, PsycINFO, and Cochrane Library up to October 2025. Studies with individuals aged ≥16 years, psychiatric diagnoses, and both psychological and biomarker outcomes were eligible. Ten studies met inclusion criteria. Random-effects meta-analysis was conducted for sufficient, comparable data.

Results: Cortisol was the only biomarker with sufficient data for meta-analysis (n=4). Results showed no significant effect on cortisol levels (SMD = -0.18; 95% CI = -0.96 to 0.59), with substantial heterogeneity (I^2 = 88.7%). Exploratory analyses indicated more consistent responses in autonomic and inflammatory biomarkers than endocrine markers. Psychological outcomes showed greater improvement consistency across

studies, even without short-term physiological changes. Findings must be interpreted cautiously due to the limited number of studies and high heterogeneity.
Conclusion: Psychobiological effects of music therapy and musical interventions vary by intervention, design, and population. Despite heterogeneity and limited quantitative data, findings support the clinical relevance of these interventions. More standardized, biomarker-informed research is needed to clarify underlying mechanisms.
Keywords: biomarkers; music therapy; mental disorders; psychoneuroimmunology.

Introduction

More than one billion people worldwide live with mental disorders, which rank among the leading causes of global disability and premature mortality, particularly in severe conditions, underscoring the need for complementary therapeutic approaches[1]. Although pharmacological therapies are fundamental in mental health care, their limitations, such as side effects, treatment discontinuation, and partial medication response, have driven increasing demand for non-pharmacological interventions that expand care options[2].

Music therapy has emerged as an evidence-based practice associated with psychological benefits and measurable physiological responses, including changes in biomarkers[3]. Defined by the World Federation of Music Therapy as the professional use of music to promote health and quality of life through ethical and scientific standards[4], these interventions vary between active approaches, involving sound production, and receptive approaches, centered on listening. Despite these advances, systematic reviews systematically synthesizing the effects of music therapy on biomarkers in mental disorders remain scarce, as current literature often focuses on non-psychiatric contexts or isolated psychological outcomes, presenting substantial heterogeneity in measurement methods that hinders the consolidation of comparable evidence in the field.

Music therapy and music-based interventions modulate the HPA (Hypothalamic–Pituitary–Adrenal) axis by reducing cortisol[5], influence the autonomic nervous system by increasing heart rate variability[6], and impact inflammatory processes by modulating cytokines such as IL-6[7]. Furthermore, these interventions promote neuroplasticity

through sensorimotor engagement and the modulation of neurotrophic factors such as BDNF (Brain-Derived Neurotrophic Factor)[8], justifying the use of endocrine, autonomic, inflammatory, and neurotrophic biomarkers as system-level indicators in clinical research.

Accordingly, the overall aim of this study is to systematically review the effects of music therapy and structured musical interventions on biomarkers in individuals with mental disorders. The biomarkers considered in this review include parameters related to the HPA axis, autonomic function, inflammatory processes, and neurotrophic activity. This study contributes to the integration of biomarkers into psychiatric music therapy research by systematically synthesizing evidence across multiple physiological systems, addressing a gap in previous literature that has primarily focused on psychological outcomes or non-psychiatric populations.

Specifically, this review sought to: (1) identify which biomarkers were assessed in the included studies; (2) describe the effects of music therapy and structured musical interventions on endocrine, autonomic, inflammatory, and neurotrophic markers; (3) compare effects across different psychiatric diagnoses and types of intervention; and (4) conduct meta-analyses of eligible outcomes and qualitatively synthesize the remaining results.

Methods

Protocol and Guidelines

This study followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[9]. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO)[10] under registration number CRD420251162903. Study screening and selection were conducted using the Rayyan (rayyan.ai) software[11]. Quantitative analyses were performed in R software[12], including the implementation of meta-analytic models[13]. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB-2)[14] tool for randomized clinical trials and the ROBINS-I[15] tool for non-randomized studies.

Search Strategy

The search strategy was conducted across PubMed, LILACS, PsycINFO, and the Cochrane Library, with the most recent update performed in October 2025, without date restrictions and without language restrictions. Searches retrieved a total of 352 records, including 186 from PubMed, 140 from PsycINFO, 5 from LILACS, and 21 from the Cochrane Library. By combining controlled descriptors (MeSH and DeCS) with free-text terms, the strategy was segmented by specific psychiatric diagnoses to enhance conceptual precision and improve comprehensiveness. Different biomarker-related terms were selected according to the psychiatric condition investigated, reflecting the biomarkers most commonly explored in the corresponding literature. While the intervention (music therapy or structured musical interventions) and biomarker axes (endocrine, autonomic, inflammatory, and neurotrophic) were applied consistently, the search strings were adapted to the specific indexing systems and scope of each database. In biomedical databases, more specific biomarker terms were prioritized; in broader databases, more general terms were applied to increase sensitivity and minimize the risk of missing relevant evidence. The complete search strategies are presented in Appendix A. No forward or backward citation searching was performed.

Eligibility Criteria

The eligibility criteria for this systematic review were defined based on the PICO framework. The population included individuals aged 16 years and older with psychiatric diagnoses established according to international criteria (DSM or ICD), as well as individuals presenting clinically relevant psychological symptoms (e.g., stress, anxiety, or emotional dysregulation), even in the absence of a formal diagnosis, encompassing depressive disorders, anxiety disorders, bipolar disorder, schizophrenia and other psychotic disorders, obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and stress-related disorders.

The intervention comprised music therapy and/or structured musical interventions with therapeutic purposes. Studies were included if they concurrently assessed psychological outcomes and biomarkers. Comparators included control groups, treatment as usual, wait-list controls, or active control conditions. Outcomes

encompassed biomarkers, including endocrine, autonomic, inflammatory, and neurotrophic parameters.

Studies involving neurodevelopmental conditions, such as autism spectrum disorder, were excluded not only due to developmental differences but also because of the limited comparability of psychological outcomes, which are often assessed using indirect or non–self-reported measures. This limitation would compromise the integrated analysis of psychological changes and biomarkers, which constitutes the central focus of this review.

Study Selection Process

The study selection was conducted using Rayyan (rayyan.ai). All retrieved records were imported into the platform, and duplicate records were identified using the software's automatic detection tools and manually verified before removal to ensure accuracy.

Initially, titles and abstracts were screened by one reviewer based on the predefined eligibility criteria. Subsequently, potentially relevant articles were assessed in full text to confirm inclusion. One reviewer performed the initial screening, and a second reviewer independently verified all decisions. Any discrepancies were resolved through discussion and consensus.

The complete flow of study identification, screening, eligibility, and inclusion is presented in Figure 1.

Data Extraction

Data extraction was performed using Rayyan, with a structured spreadsheet specifically developed for this study. For each included article, the following information was collected: author, year of publication, country, journal, title, study design, clinical diagnosis, population characteristics, psychological assessment instruments, biomarkers investigated, biomarker collection methods, type of musical intervention (active, receptive or mixed), medication use at baseline, as well as psychological and biological outcomes and the main conclusion reported by the authors.

Quantitative data required for the calculation of effect sizes were subsequently organized and analyzed using R software[12]. Not all studies reported sufficient information to estimate standardized mean differences (SMDs), and among the 10 studies initially eligible, only four provided complete data for meta-analysis based on continuous measures. Among the different biomarkers identified, cortisol was the only biomarker with a sufficient number of studies to support the primary quantitative synthesis.

To broaden the analysis and enable further exploration of the findings, biomarkers and psychological outcomes were subsequently recoded into binary/ordinal variables (0, 1, or 2), allowing the performance of complementary exploratory meta-analyses. This procedure made it possible to examine general trends of improvement or non-improvement, even in studies that did not report metrics compatible with SMD calculation. Although this approach allowed the inclusion of studies with heterogeneous reporting formats, it may reduce sensitivity to differences in effect magnitude and should be interpreted as exploratory.

Initial data extraction was conducted by one reviewer and subsequently verified independently by a second reviewer to ensure consistency of the records. Any discrepancies were resolved through discussion and consensus. Studies that did not provide sufficient data for SMD calculation were excluded from the primary meta-analysis but were included in the complementary exploratory analyses when possible. Data standardization, conversion, and harmonization procedures followed the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.

Risk of Bias Assessment

Risk of bias assessment was conducted using the official Cochrane tools. Individually randomized controlled trials were assessed with the Risk of Bias 2.0 (RoB 2) tool, while cluster randomized trials were evaluated using the specific RoB 2 version for cluster-randomized studies. Non-randomized studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. Judgments considered all domains recommended by each instrument, including bias arising from

the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting, resulting in an overall risk of bias classification for each study. Graphical visualizations of the risk of bias judgments are presented in the Results section.

Data Synthesis and Statistical Analysis

The analysis was conducted systematically, taking into account the methodological heterogeneity of the studies and the variability inherent to the different biomarkers assessed. The deliberate inclusion of heterogeneous psychiatric diagnoses aimed to enable the investigation of shared psychobiological processes across mental disorders, particularly in a context of limited available studies combining music-based interventions and biomarkers. Statistical analyses and quantitative synthesis were performed using R (version 4.5.2)[12], adopting random-effects models due to the expected heterogeneity across populations, psychiatric diagnoses, musical interventions, and biomarkers evaluated. Meta-analyses conducted using the “meta” (version 7.0-0) and “metafor” (version 4.4-0) packages. Additional support for data manipulation and visualization was provided by “dmetar” (version 0.1.0), “ggplot2” (version 3.4.4), and “readxl” (version 1.4.3).

Standardized effect sizes (Standardized Mean Difference, SMD) were calculated using post-intervention means, standard deviations, and sample sizes of the groups, or, when available and reported in the original studies, based on pre–post change scores, according to the data structure provided in each study. This approach was necessary due to differences in reporting across studies and may introduce limitations in comparability between effect estimates.

Between-study heterogeneity was quantified using the I^2 and τ^2 statistics, which were used to support the interpretation of variability in the pooled effects. In addition, clinical and methodological variables, such as type of musical intervention, psychiatric diagnosis, and baseline medication use, were examined in an exploratory and descriptive manner to identify potential patterns of variation across studies.

Additionally, a complementary exploratory analysis using dichotomous variables was conducted, classifying studies according to biological response as “improved” (1) or

“not improved” (0), with the aim of identifying overall response patterns among the included studies. These analyses were purely descriptive and exploratory in nature and were not used for statistical inference, hypothesis testing, or formal group comparisons.

Continuous meta-analyses were considered the primary quantitative approach of the study, whereas analyses based on binary data were interpreted as exploratory support for identifying general response patterns. The results of these analyses are presented using forest plots and summary tables in the Results section.

Pooled effects were estimated with 95% confidence intervals, and result interpretation considered point estimates, confidence interval width, and heterogeneity statistics (I^2 and τ^2), without the a priori adoption of a fixed p-value threshold for statistical significance. The continuous meta-analysis of cortisol (SMD = −0.18; 95% CI = −0.96 to 0.59) indicated no pooled effect of musical interventions on this biomarker, as the confidence interval included zero.

The complementary analyses using binary data were conducted exclusively for exploratory and descriptive purposes, aiming to identify general response patterns according to clinical and methodological characteristics of the studies, and were not used for statistical inference or hypothesis testing.

Results

A total of 352 records were identified through database searches (PubMed: 186; PsycINFO: 140; LILACS: 5; Cochrane Library: 21). After removal of 113 duplicate records, 239 studies were screened based on titles and abstracts. Of these, 192 were excluded, and 47 reports were assessed for full-text eligibility. A total of 10 studies met the inclusion criteria and were included in the qualitative synthesis. The study selection process is presented in Figure 1.

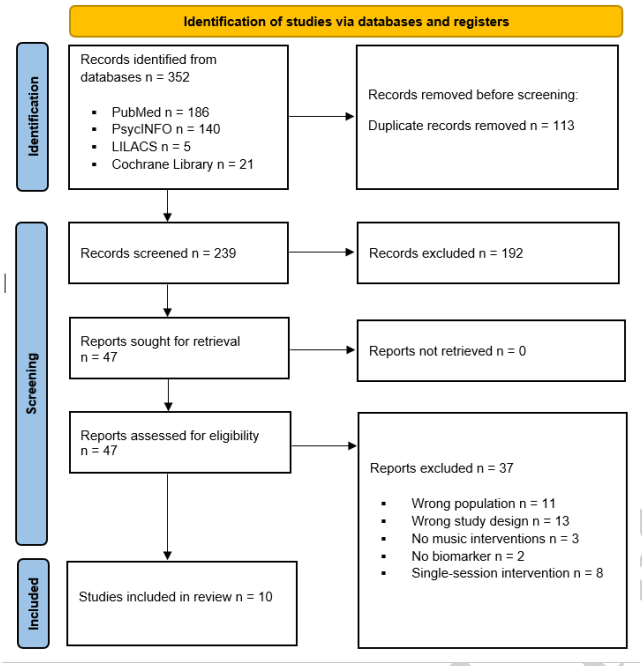


Figure 1. PRISMA 2020 flow diagram of the study selection process.

In this review, 10 studies were considered eligible for qualitative synthesis, encompassing different psychiatric diagnoses, musical intervention methods, and biomarkers, including studies with mixed or partially non-diagnostic populations, in accordance with the predefined inclusion criteria. Of these studies, seven assessed cortisol outcomes, making cortisol the most frequently investigated biomarker across publications and supporting its selection as the primary outcome for the meta-analysis. However, only four studies provided sufficient continuous and comparable data to allow the calculation of standardized mean differences (SMDs) and were therefore included in the meta-analysis. The remaining studies were incorporated into descriptive and exploratory analyses, according to the availability of variables and the format of the reported data.

Table 1. Methodological characteristics and integrated biological and psychological outcomes of the included studies

Study	Country	Population Diagnosis	Sample Size	Intervention Type	Duration	Biomarkers	Measurement	System	Results
Yu et al., 2022[16]	Taiwan	Depressive symptoms	238	Receptive	10 weeks	Cortisol	Saliva	Endocrine	↔ Cortisol; ↓ depressive symptoms
Rasing et al., 2025[17]	Germany	Depression and dementia	183	Active/ Receptive	6 months	Cortisol, amylase	Saliva	Endocrine	↔ Cortisol; ↓ amylase; ↓ perceived stress
Beck et al., 2015[18]	Denmark	Occupational stress	20	Receptive	9 weeks	Cortisol	Saliva	Endocrine	↓ Cortisol; ↑ well-being; ↓ anxiety
Gaebel et al., 2025[19]	Germany	Major Depressive Disorder	102	Active	10 weeks	Cortisol, HRV	Saliva	Autonomic	↓ stress; ↑ coping; ↑ adaptive thinking
Fancourt et al., 2016[6]	United Kingdom	Mild–moderate depression and anxiety	59	Active/ Receptive	10 weeks	IL-4, MCP-1, cortisol	Blood	Inflammatory Endocrine	↑ IL-4; ↓ MCP-1; ↔ Cortisol; ↓ anxiety; ↓ depression; ↑ well-being; ↑ resilience
Finnerty et al., 2023[20]	United Kingdom	Stress and anxiety	83	Active/ Receptive	6 weeks	Cortisol	Hair	Endocrine	↔ Cortisol; ↓ anxiety; ↓ stress
Pabilang et al., 2023[21]	Indonesia	Schizophrenia	45	Receptive	4 weeks	BDNF	Blood	Neurotrophic	↑ BDNF; ↑ cognition
Gantt et al., 2017[22]	USA	PTSD	74	Receptive	4 weeks	HR, HRV	Physiological measurement	Autonomic	↓ HR; ↑ HRV; ↓ anxiety; ↓ stress
Rudstam et al., 2023[23]	Sweden	PTSD	45	Receptive	12 weeks	HR, HRV, SCL	Physiological measurement	Autonomic	↓ HR/SCL; ↑ HRV; ↓ PTSD; ↓ distress; ↑ self-regulation
Chen et al., 2015[24]	Taiwan	Anxiety disorders	71	Receptive	10 weeks	Cortisol	Saliva	Endocrine	↔ Cortisol; ↓ anxiety

The RoB 2 and ROBINS-I tools were used to assess the risk of bias of the included studies. Figure 3 presents the judgments across the evaluated domains, with Panel A corresponding to randomized trials assessed using the RoB 2 tool and Panel B corresponding to non-randomized studies assessed using ROBINS-I. Randomized trials were classified as low risk of bias across all evaluated domains (Figure 3, Panel A). Specifically, Pabilang et al.[21], also exhibited moderate risk in participant selection (D2) and missing data (D5), whereas Fancourt et al.[6], demonstrated low risk in these specific domains. Furthermore, all included studies demonstrated a low risk of bias regarding selective reporting (D5 in RoB 2 and D7 in ROBINS-I), which is consistent with high reporting transparency.

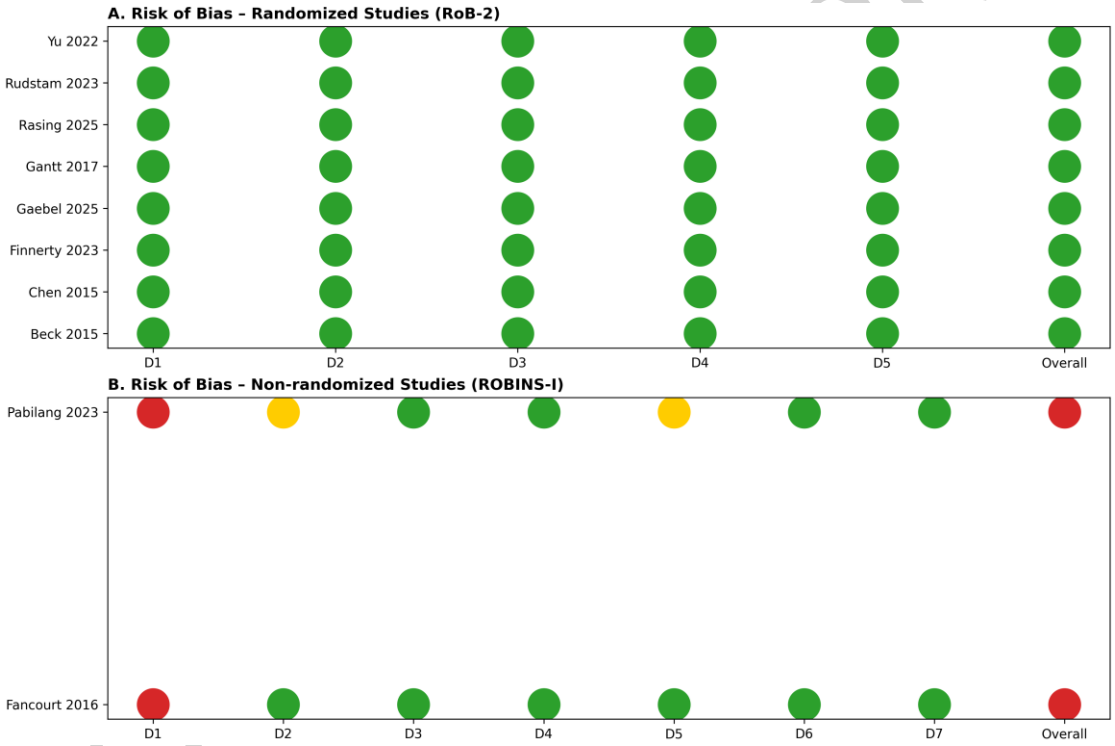


Figure 2. Risk of bias assessment of the included studies using RoB 2 and ROBINS-I tools.

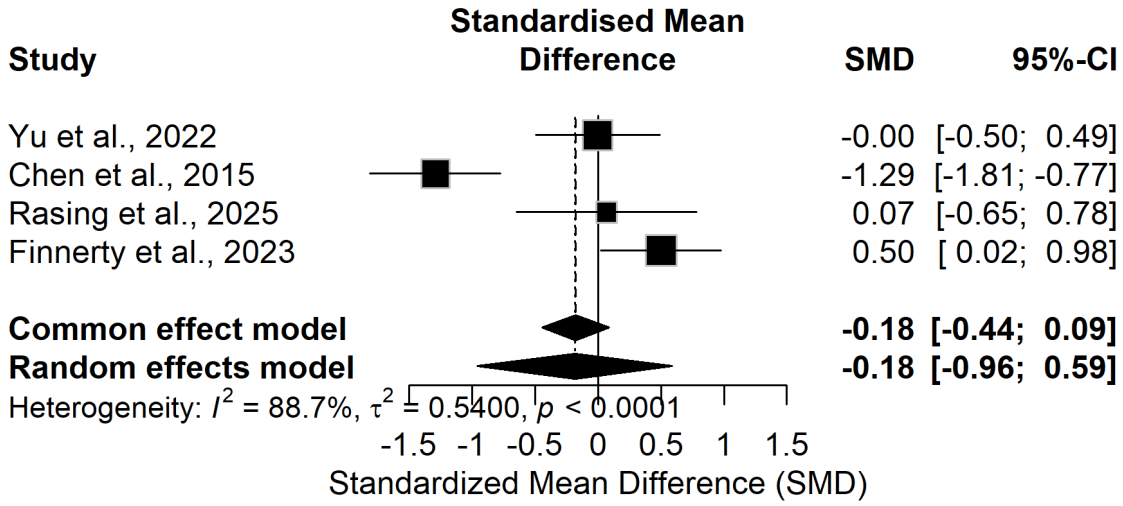
(A) Randomized studies assessed using the RoB 2 tool
D1: Bias arising from the randomization process;
D2: Bias due to deviations from intended interventions;
D3: Bias due to missing outcome data;
D4: Bias in measurement of the outcome;
D5: Bias in selection of the reported result

(B) Non-randomized studies assessed using the ROBINS-I tool
D1: Bias due to confounding;

D2: Bias in selection of participants into the study;
D3: Bias in classification of interventions;
D4: Bias due to deviations from intended interventions;
D5: Bias due to missing data;
D6: Bias in measurement of outcomes;
D7: Bias in selection of the reported result

The meta-analysis was conducted using the four studies that reported sufficient continuous data on cortisol. The random-effects model did not indicate a statistically significant effect of music therapy on cortisol levels (SMD = −0.18; 95% CI = −0.96 to 0.59), with substantial heterogeneity among studies (I^2 = 88.7%). The corresponding forest plot is presented in Figure 3, showing that the confidence interval of the pooled effect crosses the line of no effect.

Figure 3. Effects of music-based interventions on cortisol level



Within the exploratory analyses, a higher frequency of reported biological improvement was observed in studies employing active musical interventions, followed by mixed and receptive interventions. Among the biomarkers assessed, autonomic and inflammatory markers showed more consistent responses, whereas endocrine markers exhibited greater variability. Intervention duration and concomitant medication use did not display consistent patterns of association with the presence of biological improvement. Psychological outcomes showed more consistent positive effects across

studies. A summary of biological responses across physiological systems is presented in Table 2.

Table 2. Analytical framework and sources of heterogeneity across studies of music-based interventions and biological biomarkers.
Note: *Meta-analysis for cortisol included 4 of 7 studies with sufficient continuous data (SMD = −0.18, 95% CI = −0.96 to 0.59, I^2 = 88.7%; see Figure 2). Total N = 10 studies; some assessed multiple biomarkers

Biomarker (System)	Studies (n)	Meta-analysis	Biological Response	Psychological Outcomes Reported
Cortisol (Endocrine)	7	Yes (4 studies)*	↓ in 5 studies; ↔ in 2 studies	↓ stress (5), ↓ anxiety (3), ↓ depression (2)
Amylase (Endocrine)	1	No	↓	↓ perceived stress
HRV (Autonomic)	3	No	↑ in 3/3 studies	↓ anxiety (2), ↑ self-regulation (1), ↓ PTSD (1)
HR (Autonomic)	2	No	↓ in 2/2 studies	↓ anxiety (2), ↓ stress (1)
SCL (Autonomic)	1	No	↓	↓ PTSD symptoms, ↓ distress
IL-4, MCP-1 (Inflammatory)	1	No	↑ IL-4; ↓ MCP-1	↓ depression, ↑ well-being
BDNF (Neurotrophic)	1	No	↑	↑ cognition (MoCA-Ina)

Discussion

This study synthesized the available evidence on the effects of music therapy and structured musical interventions on biomarkers in individuals with mental disorders. Although the continuous meta-analysis did not demonstrate a statistically significant effect of the intervention on cortisol levels, exploratory findings indicated consistent physiological patterns in other biological systems, particularly within the autonomic, inflammatory, and neurotrophic domains. These included increases in neurotrophic markers associated with plasticity and cognitive function, such as BDNF[21]. Studies assessing autonomic parameters, such as heart rate, heart rate variability, and skin conductance, reported consistent reductions in physiological activation, which were associated with decreases in anxiety, stress, and PTSD symptoms [19,22,23].

Although cortisol was selected as the sole biomarker for quantitative synthesis, this decision reflects a methodological requirement rather than a theoretical prioritization. Among the seven studies that assessed cortisol outcomes, only four reported sufficient continuous and comparable data to allow the calculation of standardized mean differences. Other biological markers, including autonomic, inflammatory, and neurotrophic outcomes, were reported with substantial heterogeneity regarding measurement protocols, sampling procedures, and outcome metrics, precluding their inclusion in a meta-analytic model without introducing excessive bias. This limited number of studies included in the meta-analysis (n = 4) should be considered when interpreting the findings, as it may reduce the robustness and generalizability of the pooled estimates.

The findings of this review should be interpreted in light of important sources of heterogeneity. Variability was observed across studies in terms of the types of biomarkers assessed, biological sampling methods (e.g., saliva, blood, hair, and physiological measures), population characteristics, and intervention protocols. The included populations encompassed diverse clinical profiles, including individuals with PTSD (both military personnel and civilian women), young people with anxiety, and older adults with depression, which may influence psychological and physiological responses to the interventions. Additionally, some studies included populations with broader or mixed clinical definitions, as permitted by the PROSPERO protocol, which may have contributed to the observed heterogeneity.

Although musical interventions could be categorized into relatively defined approaches (active, receptive, or mixed), the lack of standardization in biomarker selection and biological assessment methods limited comparability across studies and reduced the number of studies eligible for quantitative synthesis. This limitation is particularly relevant given the still limited number of studies investigating both psychological and biological outcomes in music-based interventions.

Taken together, the studies included in this review indicate that the biological effects of musical interventions do not manifest uniformly across the different systems assessed. While autonomic and inflammatory biomarkers showed more consistent responses aligned with psychological outcomes, the studies contributing to the cortisol

meta-analysis exhibited substantial methodological and clinical variability, including differences in intervention duration, population characteristics, types of musical intervention, and biological sampling protocols (e.g., salivary, blood, and hair cortisol, which assess distinct temporal profiles of HPA axis activity). This heterogeneity may have influenced both the magnitude and direction of the observed effects, contributing to the absence of a statistically significant pooled effect for cortisol.

In addition, the interpretation of the findings should consider that non-randomized studies were classified as having a serious risk of bias, particularly due to confounding, whereas randomized trials were classified as low risk of bias across all evaluated domains. Importantly, all included studies demonstrated a low risk of bias regarding selective reporting (D5 in RoB 2 and D7 in ROBINS-I), which is consistent with high reporting transparency. However, specific findings require additional caution: the single study reporting increases in BDNF[21] was classified as having moderate risk of bias due to concerns about participant selection and missing data, which limits the strength of conclusions regarding neurotrophic effects.

As shown in Table 2, autonomic biomarkers demonstrated greater consistency compared with endocrine biomarkers such as cortisol. Among the studies contributing to the meta-analysis, substantial heterogeneity was observed in cortisol-related findings, with no significant changes detected across different clinical populations despite relevant psychological improvements[16,17,18]. In contrast, reductions in cortisol levels were observed in specific contexts, such as occupational stress or longer-duration interventions, as well as divergent responses across different endocrine markers, including cortisol and amylase[20,24]. These findings reinforce the highly sensitive and variable nature of cortisol as a biomarker, which is influenced by multiple methodological, clinical, and environmental factors.

Reported symptoms of anxiety, stress, and depression were reduced even in studies where endocrine or autonomic markers did not show significant changes, particularly those assessing cortisol[16,17,18]. This pattern suggests that the psychological benefits of musical interventions may not depend on short-term detectable physiological responses, but may instead emerge from subjective processes such as emotional regulation, affective engagement, and cognitive reorganization. These findings support

the potential role of music therapy as a non-pharmacological intervention capable of promoting meaningful psychological benefits despite heterogeneous biological responses, and reinforce the need for integrative models that consider both biological markers and subjective clinical outcomes.

These findings highlight the need for future studies with more standardized protocols, including consistent biomarker selection, comparable biological sampling methods, and more homogeneous study designs, which may contribute to a clearer understanding of the biological mechanisms underlying music-based interventions.

Limitations

This review has several limitations that should be considered when interpreting its findings. The inclusion of studies with different psychiatric diagnoses, types of musical intervention, and biomarkers represented a deliberate methodological choice, guided by the objective of exploring the biological and psychological effects of music therapy in mental disorders from an integrated perspective. Although this transdiagnostic approach is conceptually aligned with the RDoC[25] framework and allowed for the examination of multiple relevant physiological systems, it resulted in substantial methodological heterogeneity across the included studies. The variability in populations, intervention characteristics, and biomarker assessment protocols represents a substantive limitation that may have constrained the comparability and synthesis of findings.

The conduct of the meta-analysis was constrained by the limited availability of comparable continuous data across the included studies. Although ten studies were eligible for qualitative synthesis, only four provided sufficient information for effect size calculation, restricting the meta-analysis to a specific subset of outcomes. This limitation reflects persisting gaps in the literature, particularly regarding the standardization of biomarker measurement and the systematic reporting of biomarker data in music therapy research, and may reduce the reliability of the pooled estimates and limit the strength of conclusions regarding biological effects.

The interpretation of findings should also consider differences in study quality and risk of bias. Non-randomized studies were classified as having serious risk of bias, particularly due to confounding, whereas randomized controlled trials demonstrated low

risk of bias across all evaluated domains. Notably, all included studies showed low risk of selective reporting bias (D5 in RoB 2 and D7 in ROBINS-I), indicating transparent outcome reporting. However, the single study reporting neurotrophic outcomes (BDNF) was assessed as having moderate risk of bias due to concerns about participant selection and missing data, which limits the strength of conclusions regarding neurotrophic effects of musical interventions.

Additionally, the relatively recent emergence of studies combining music-based interventions with biological outcomes reflects a developing field and may explain both the limited number of available studies and the variability in methodological approaches.

Final Considerations

The findings of this review, interpreted through the lens of the psychoneuroimmunological model, suggest that music-based interventions are associated with consistent improvements in psychological outcomes, while effects on biomarkers are not uniform and depend on multiple factors, including the type of musical engagement, methodological design, population characteristics, and the biomarkers selected. The heterogeneity identified across studies represents a relevant methodological limitation; however, it also reflects the complexity of psychobiological responses to music.

Despite the variability and imprecision observed in biomarker-related results, these findings do not diminish the relevance of investigating biological markers within the field of music therapy. On the contrary, they reinforce the need for research that systematically incorporates biomarkers alongside methodologically rigorous protocols. The absence of consistent effects in certain markers should not be interpreted as evidence of ineffectiveness, but rather as an indication that methodological variability, rather than true intervention inefficacy, may be influencing results. Future studies should prioritize more homogeneous protocols regarding the type of musical intervention, duration, context of application, selection of biological markers, and transparent data reporting to strengthen the evidence base for biological mechanisms underlying music-based interventions.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Appendix A. Detailed Search Strategy

PROSPERO Registration: CRD420251162903

Last Search Update: October 2025

PubMed

The PubMed search strategy combined controlled descriptors (MeSH terms) and free-text terms.

Search 1 – Bipolar Disorder

("Bipolar Disorder"[MeSH] OR "Bipolar Affective Disorder"[Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR BDNF[Title/Abstract] OR cytokine*[Title/Abstract] OR IL-6[Title/Abstract] OR TNF-alpha [Title/Abstract])

Search 2 – Post-Traumatic Stress Disorder

("Stress Disorders, Post-Traumatic"[MeSH] OR PTSD[Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR IL-6[Title/Abstract] OR TNF-alpha [Title/Abstract] OR BDNF[Title/Abstract])

Search 3 – Obsessive-Compulsive Disorder

("Obsessive-Compulsive Disorder"[MeSH] OR OCD[Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR serotonin [Title/Abstract] OR cortisol [Title/Abstract] OR BDNF[Title/Abstract] OR cytokine*[Title/Abstract])

Search 4 – Schizophrenia

("Schizophrenia"[MeSH] OR "Psychotic Disorders"[MeSH] OR schizophrenia [Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR oxytocin [Title/Abstract] OR BDNF[Title/Abstract] OR IL-6[Title/Abstract] OR IL-10[Title/Abstract] OR TNF-alpha [Title/Abstract] OR "C-Reactive Protein"[Title/Abstract])

Search 5 – Anxiety Disorders

("Anxiety Disorders"[MeSH] OR anxiety [Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR IL-6[Title/Abstract] OR TNF-alpha [Title/Abstract] OR BDNF[Title/Abstract] OR "C-Reactive Protein"[Title/Abstract])

Search 6 – Depressive Disorders

("Depressive Disorder"[MeSH] OR depression [Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR serotonin [Title/Abstract] OR "C-Reactive Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

Search 7 – Psychotic Disorders

("Psychotic Disorders"[MeSH]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR serotonin [Title/Abstract] OR "C-Reactive Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

Search 8 – Panic Disorder

("Panic Disorder"[MeSH]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR serotonin [Title/Abstract] OR "C-Reactive Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

Search 9 – Borderline Personality Disorder

("Borderline Personality Disorder"[MeSH]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol [Title/Abstract] OR oxytocin [Title/Abstract] OR serotonin [Title/Abstract] OR "C-Reactive Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

Search 9 – Dissociative Disorders (PubMed)

("Dissociative Disorders"[MeSH] OR "dissociative disorder*"[Title/Abstract] OR "dissociation"[Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol[Title/Abstract] OR oxytocin[Title/Abstract] OR serotonin[Title/Abstract] OR "C-Reactive Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

Search 11 – Eating Disorders (PubMed)

("Feeding and Eating Disorders"[MeSH] OR "eating disorder*"[Title/Abstract] OR "anorexia"[Title/Abstract] OR "bulimia"[Title/Abstract] OR "binge eating"[Title/Abstract]) AND ("Music Therapy"[MeSH] OR music therap*[Title/Abstract] OR "music intervention*"[Title/Abstract]) AND ("Biomarkers"[MeSH] OR cortisol[Title/Abstract] OR oxytocin[Title/Abstract] OR serotonin[Title/Abstract] OR "C-Reactive

Protein"[Title/Abstract] OR "Interleukin-6"[Title/Abstract] OR "Tumor Necrosis Factor-alpha"[Title/Abstract] OR BDNF[Title/Abstract])

LILACS

In the LILACS database, DeCS-based descriptors were combined with Portuguese free-text terms.

Search 1 – Bipolar Disorder

("Transtorno Bipolar") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 2 – Post-Traumatic Stress Disorder

("Transtorno de Estresse Pós-Traumático") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 3 – Obsessive-Compulsive Disorder

("Transtorno Obsessivo Compulsivo" OR "TOC") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 4 – Schizophrenia

("Esquizofrenia") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 5 – Anxiety Disorders

("Transtorno de Ansiedade") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 6 – Depressive Disorders

("Depressão") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 7 – Psychotic Disorders

("Transtorno Psicótico")
AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música")
AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 8 – Panic Disorder

("Transtorno do Pânico") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol"

OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 9 – Borderline Personality Disorder

("Transtorno de Personalidade Borderline") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 10 – Dissociative Disorder

("Transtorno Dissociativo" OR "Transtornos Dissociativos" OR "Dissociação") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

Search 11 – Eating Disorders

("Transtornos Alimentares" OR "Anorexia" OR "Bulimia" OR "Transtorno da Compulsão Alimentar") AND ("Musicoterapia" OR "Intervenção Musical" OR "Terapia baseada em música") AND ("Biomarcadores" OR "Marcadores Biológicos" OR "Cortisol" OR "Fator Neurotrófico Derivado do Cérebro" OR "BDNF" OR "Marcadores Neurobiológicos" OR "Testes Fisiológicos" OR "Exames de Sangue" OR "Testes Salivares")

PsyINFO and Cochrane Library

In the PsycINFO and Cochrane Library databases, free-text terms were employed and adapted to the specificities of each database.

Search 1 – Bipolar Disorder

("bipolar disorder" OR "bipolar affective disorder" OR "mania" OR "manic depression") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 2 – Post-Traumatic Stress Disorder

("post-traumatic stress disorder" OR "PTSD" OR "posttraumatic stress disorder" OR "traumatic stress") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 3 – Obsessive-Compulsive Disorder

("obsessive-compulsive disorder" OR "OCD" OR "obsessive compulsive") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 4 – Schizophrenia

("schizophrenia" OR "schizophrenic disorder*" OR "schizoaffective disorder" OR "first-episode psychosis") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 5 – Anxiety Disorders

("anxiety disorder*" OR "anxiety" OR "generalized anxiety disorder" OR "GAD") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 6 – Depressive Disorders

("depressive disorder" OR "depression" OR "major depressive disorder" OR "dysthymia") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 7 – Psychotic Disorders

("psychotic disorder*" OR "psychosis" OR "schizophrenia" OR "schizoaffective disorder") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 8 – Panic Disorder

("panic disorder" OR "panic attack*" OR "agoraphobia") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 9 – Borderline Personality Disorder

("borderline personality disorder" OR "borderline personality" OR "emotionally unstable personality disorder" OR "BPD") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 10 – Dissociative Disorder

("dissociative disorder*" OR "dissociative identity disorder" OR "depersonalization" OR "derealization") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")

Search 11 – Eating Disorder

("eating disorder*" OR "anorexia nervosa" OR "bulimia nervosa" OR "binge eating" OR "feeding disorder*") AND ("music therapy" OR "musical intervention*" OR "music-based therapy") AND ("biomarker*" OR "cortisol" OR "BDNF" OR "neurobiological marker*" OR "physiological measure*" OR "blood test" OR "salivary test")