



Music and Biomarkers of Stress: A Systematic Review

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Article History

Received: August 15, 2020

Revised: September 3, 2020

Accepted: September 7, 2020

Published: September 10, 2020

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Abstract

Objective: The purpose of this paper is to review literature on music and biomarkers of stress in order to (1) Identify music interventions and (2) Detail the biomarkers of stress associated with music. **Methods:** PRISMA guidelines were followed in performing this systematic review. Studies published from January 1995 to January 2020 that pertain to biomarkers of stress and music were identified through the use of the PubMed database, using the keywords: ‘music’ AND ‘biomarker’ OR ‘marker’ OR ‘hormone’. Two authors independently conducted a focused analysis and reached a final consensus on 16 studies that met the specific selection criteria and passed the study quality checks. **Results:** The reviewed studies were all randomized controlled trials. Reviewed music interventions included Music Listening (ML), Meditative Music (MM), ‘Guided Imagery and Music’ (GIM), and Singing. The studies showed that music is associated with a decreasing trend in cortisol, salivary α -amylase, heart rate, and blood pressure, as well as an increasing trend in Immunoglobulin A (IgA), oxytocin, and EEG theta wave, while testosterone was associated with sex-related differences. **Conclusion:** Music is associated with significant changes in biomarkers of stress, suggesting that it could be utilized for the development of stress reduction tools.

Keywords: Music; Biomarkers; Markers; Therapeutic uses.

1. Introduction

Music is the composition of vocal or instrumental patterns to express artists’ emotions [1]. Music, fostering a universal celebration of emotion and beauty, is proven to impact approximately 90% of all of the world’s population at an average of over thirty-two hours per week [2]. Music therapy is the practice of treating patients with music (usually at the patient’s discretion); although it is casually understood that music may have a positive effect on one’s mood, there is no standing measure of improvement, nor is there a standard treatment as the norm grants patients to pick their musical treatment [3]. In addition, musicologists understand the melodic aspect of feelings associated with certain progressions, while psychologists understand the scientific aspect of chemical reactions involved in emotion, but the two fields have never actually seen eye-to-eye on music for therapeutic purposes [4]. An important question, addressed by Gerra, *et al.* [5], focused on whether all genres of music had the same effect. They found that Techno-music was associated with a significant increase in heart rate, systolic blood pressure and in self-rated emotional states. Contrarily, classical music induced an improvement in a patient’s emotional state. Another important theory explored by Fukui and Yamashita [6] was whether the impact music had on hormones was the same between both sexes.

The most common emotional response associated with music, frisson (colloquially known as the “chills”), is widely known yet not quite scientifically understood; over the course of extensive scientific research, this widely known emotional response has been recorded as “electrodermal activity and subjective arousal” [7]. Psychological frisson as a result of music has biological implications on heart rate and breathing and mimics the human stress response and the return to homeostasis as a result of stress [7]. The purpose of this systematic review is to examine the scientific literature on music and biomarkers of stress in order to (1) Describe music interventions and (2) Detail the biomarkers of stress associated with music.

2. Methods

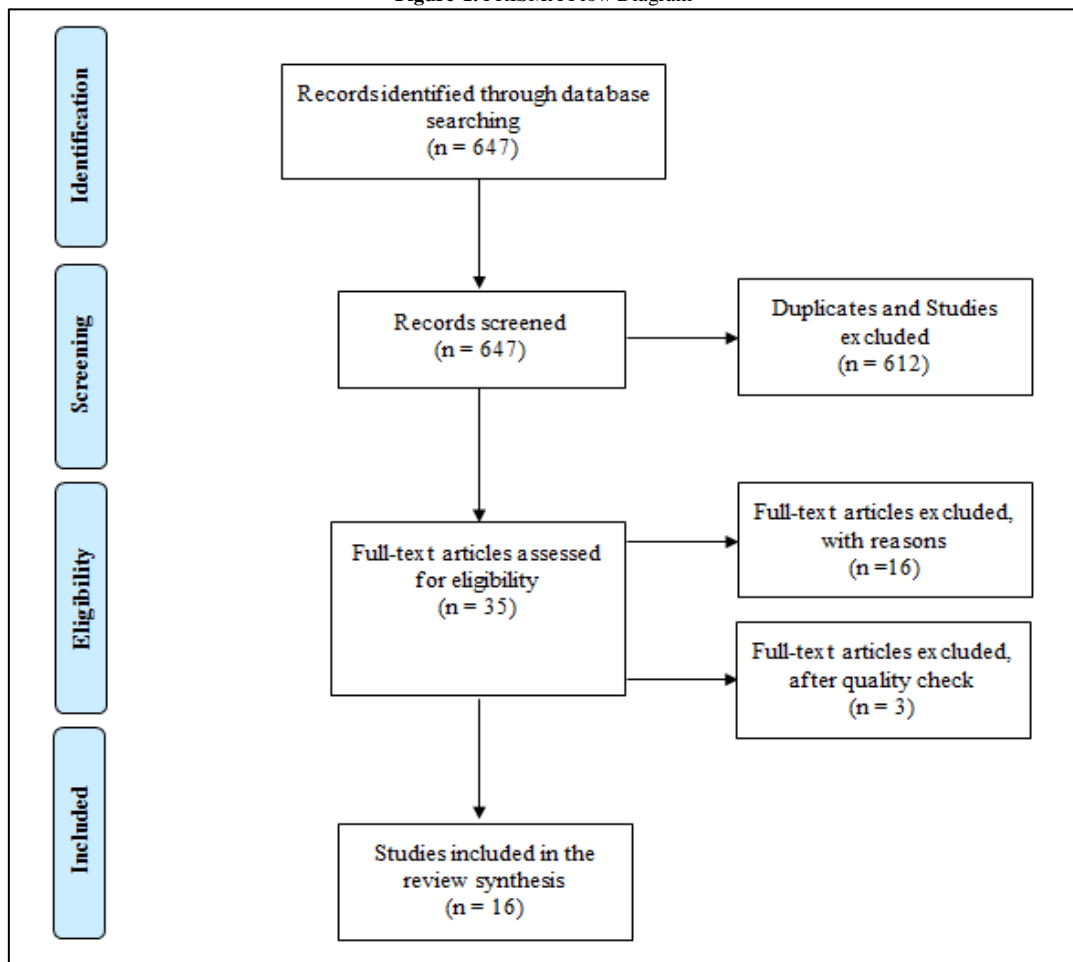
2.1. Search Strategy

We performed this systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. A systematic literature search was conducted on articles in the PubMed database that were published within the past 25 years, from January 1995 to January 2020 using the following keywords: ‘music’ AND ‘biomarker’ OR ‘marker’ OR ‘hormone’ and following the inclusion and exclusion criteria detailed below. More studies were added from the reference lists for identified research studies and reviews of music and biological markers.

2.2. Study Selection Criteria and Methodology

The following inclusion criteria were used: (a) articles published in English or had a published English translation; (b) articles published in a peer reviewed journal; (c) original studies in human adults (no reviews, no animal studies, no studies age<18). Exclusion criteria included studies using music in the medical illness or settings, reviews, editorials, opinion pieces, and case reports. Two authors independently conducted a focused analysis then together reached a consensus on studies that meet the specific selection criteria. The quality of each study was examined by identifying its strengths and limitations using the criteria adapted from Lohr and Carey by the Agency for Healthcare Research and Quality [9], [10]. Quality aspects assessed include sample size, patient selection methods, bias, study groups comparison, blinding, intervention details, outcome measures, and statistical analysis plans. The search method is displayed in a flow diagram in Figure 1.

Figure-1. PRISMA Flow Diagram



2.3. Search Results

Our search strategy identified 647 articles. After elimination of the duplicates and irrelevant abstracts, 35 studies were identified to meet the pre-defined selection criteria. Two authors independently conducted a focused analysis of the gathered 35 full-text articles. The two authors then reached a consensus on what studies to include in this review, which yielded 19 studies. The findings from the study quality check method [8, 9] eventually led to the exclusion of three studies due to inadequate sample size and statistical reporting [5, 11, 12] resulting in a final selection of 16 studies.

2.4. Data Extraction and Yield

Key findings were derived from the full-text and table of the selected studies. The study designs and findings were analyzed for quality and are detailed in Table 1.

Table-1. Reviewed Studies on Music and Biomarkers of Stress

Author, Year, Location	Population and Setting	Sample Size	Cate-gory	Intervention	Compara-tor	Duration of the intervention	Instru-ments used	Biomarkers measured	Outcome	Effect size and/or Significance	Quality Check
Trappe and Voit [13], Germany	Healthy adults	120	ML	ML to instrumental music (Classical, Romantic periods and pop music)	Silence	25 min	None	Serum Cortl, HR, BP	ML to all 3 musical genres showed a notably decrease in HR compared with baseline. The same is true for Cort concentrations. This review found a decrease in Systolic and Diastolic BP when listening to Classical and Romantic music. Biomarkers changes are much more evident in the ML period compared with silence period.	ML intervention demonstrated significant decrease in systolic BP when listening to Mozart and Strauss ($p < 0.001$, $p = 0.003$), respectively. During the ML period, a significant decrease in Diastolic BP was seen as well for Strauss and Mozart ($p = 0.004$) for both. All 3 types of music demonstrated significant decrease in subject's HR when compared with baseline ($p < 0.001$). For all musical genres, a significant drop in Cort concentrations was observed ($p < 0.001$). ML showed a significant change in biomarkers among the participants during the ML period compared with the silence period: Silence versus ABBA ($p = 0.037$); Silence Vs Mozart ($p = 0.005$); silence Vs Strauss ($p = 0.003$).	RCT, biomarkers measured pre and post intervention, scores reported with appropriate statistical analysis
Beck, <i>et al.</i> [14], Denmark	Adult Danish workers With diagnosis of work-related stress	20	GIM	GIM sessions and standard care	Wait-list control group receiving only standard care.	6 GIM sessions in a period of 9 weeks	PSS, POMS-37, 12-item self-rating scale KSQ, 16-item scale WHO-5 Well-Being Index, GAD-7, MDI, ISS	Cort, T, and melatonin.	After 9 weeks of intervention, the review evidenced a significant decrease in sCortl and psychological stress symptoms in the GIM group	A significant difference regarding sCort levels was evident when comparing results among the GIM group and the wait-list control group $p = 0.04$, medium ES (0.43) No significant differences were found regarding T levels, the study showed a small EF for the biomarker (ES=0.22) GIM's group demonstrated significant improvement in their scores for well-being ($p = 0.03$)	RCT double-blinded, data from all participants included, biomarkers measured pre and post intervention, scores reported with appropriate statistical analysis.

Jacobs and Friedman [15], United States	Healthy adults	36 (Final sample 33)	MM	Relaxation Techniques tape	Music audiotapes	6-week intervention period	None	EEG (alpha and theta frequency bands)	The findings suggest that MM represent a hypoactive central nervous system state that may be similar to Stage 1 sleep and that MM may exert their therapeutic effects, in part, through cerebral energy conservation/restoration. Increased theta EEG activity during the practice of MM.	Compared with the ML group, the MM intervention group showed a significant increase in central, parietal and occipital theta power from begin to end of the relaxation period ($p < 0.0043$, $p < 0.0127$, $p < 0.0246$), respectively. MM group demonstrated a significant within-group increase in central theta power from BEGIN to END of the relaxation period whereas the music group did not, $p < 0.0001$.	RCT, biomarkers measured pre and post intervention, scores reported with appropriate statistical analysis
Kreutz, et al. [16], Germany	Healthy Individuals	31	Singing	Choir Singing	Listening	2 sessions conducted 1 week apart (60 min each).	PANAS	Ig-A, albumin, and Cort.	Singing condition led to a significant increase of S-IgA/albumin and positive mood. This condition did not significantly affect Cort responses. Listening condition led to a significant decrease in Cort levels and increase in negative mood. No significant changes were seen in regards of S-IgA levels for the listening condition.	Highly significant increase of S-IgA/albumin and positive affect for the singing condition ($p < 0.005$, $p < 0.05$), respectively. Cort levels showed a significant decrease from baseline after intervention in the listening condition ($p < 0.001$). Changes of positive mood during listening condition correlated significantly with changes of cortisol levels, $r = 0.40$, ($p < 0.05$).	Pre-post study design, biomarkers measured pre and post interventions, PANAS measured pre and post interventions, scores reported with appropriate statistical analysis.
McKinney, et al. [17], United States	Healthy individuals	28	GIM	GIM	Wait list control group	6 individual GIM sessions, (1- 1/2 to 2 hours).	Marlowe-Crowne Social Desirability Scale (MCSDS), Creative Imagination Scale (CIS), POMS (TDM) and Depression/Dejection and Fatigue/Inertia)	Cort	A significant change in Cort levels was seen in the GIM intervention group. Changes in Cort were associated with Depression/Dejection during the pretest to posttest and posttest to follow-up periods GIM intervention group showed a significant decrease in TDM scores between pre and post sessions	Cort levels in the GIM intervention group experienced significant change overtime $P < 0.025$	RCT, data from all participants included, biomarkers measured pre and post intervention, MCSDS, POMS (TDM, Depression / Dejection and Fatigue/Inertia) measured pre and post intervention scores reported with appropriate statistical

Gingras, <i>et al.</i> [18], Austria	Healthy Individuals	39	MM	Repetitive drumming/instructions shamanic journeying	Instrumental meditation music/instructions to use the music for relaxation	15-minute music excerpt repetitive drumming or instrumental (MM)	Multidimensional mood questionnaire, Experience questionnaire	Scort	Review showed a significant effect of the overall MM intervention on sCort concentration. Evidenced lower Cort concentrations post-exposure but not significant interactions with music style.	Significant main effect of MM exposure in sCort concentration (p = 0.023)	RCT, data from all participants included, power analysis conducted beforehand, biomarkers and instruments measured pre and post interventions, results and scores reported with appropriate statistical analysis.
Ooishi, <i>et al.</i> [19], Japan	Healthy males.	26	ML	Listening to slow- and fast-tempo music sequences	Rest period	Two listening sessions a day. On each day they listened to one of the experimental music sequences	Self-reported emotions (Arousal and valence)	Oxy, Cort, HR and HRV	ML intervention showed a significant decrease in sOxy concentration and HR component of the HVR when a slow-tempo music sequence was presented. On the contrary, the HF showed an increasing trend. On the other hand, when fast-tempo music sequence was presented Scort level decreased and the LF of the HRV to HF ratio (LF/HF) increased. A significant correlation was found among the ratio of the change in the Oxy level and the change in HF, LF/HF and HR, whereas, in the Cort level no correlation was found with indices of autonomic nerve activity.	Salivary oxytocin level was significantly greater than the baseline, after listening to the slow-tempo music sequence. (p = 0.0007) Review showed significant lower levels of sCort than the baseline after the participants listened to the fast-tempo music sequence (p = 0.022). A decrease in heart rate was shown in the review, participants experienced a lower heart rate while receiving ML compared to control groups (p=0.017)	2 x 2 within-subjects design, order of the music sequences, the order of the pieces of music in each sequence and the assignment to the earlier or later listening session were randomized, biomarkers and self-reported emotions measured pre and post intervention, results and scores reported with appropriate statistical analysis.
Koelsch, <i>et al.</i> [20], Germany	Healthy volunteers	143	ML	Instrumental music	Computer-generated pieces	41 minutes per set of stimuli	POMS	oxy, Cort, HR and HRV	ML was associated with a stronger Cort response to the acute stressor in the music group.	ML stimuli had a significant impact on the recovery of Cort levels when comparing music and control groups directly (p< 0.02). ML showed a significant increasing trend in positive mood in the music group (p= 0.001).	Double-blinded RCT, data from all participants included, biomarkers and instruments measured pre and post interventions, scores reported with appropriate statistical analysis
Fukui and Toyoshima [21], Japan	Musically talented healthy individuals.	21	ML	Two stimulus category (Preferred music and disliked music)	Two stimulus category presented to control group	Two stimulus categories were each presented for 5 min.	None	T, Estrogen, and Cort. (AR) and arginine vasopressin receptor 1A genotypes.	Cort levels decreased significantly with both types of ML stimulus. T levels in women increased	ML to either chill-inducing or disliked music showed significant decrease in Cort Levels in both sexes (P	Between-subject design, randomized, biomarkers measured pre and post-

									with chill-inducing music and decreased with music they disliked, whereas T levels decreased in men with both types.	= 0.0029 Significant change in Estrogen levels before and after stimuli (Bonferroni P < 0.0001) No significant differences found regarding the relationship between the receptors and changes in each hormone.	intervention, scores reported with appropriate statistical analysis
Fukui and Yamashita [6], Japan	Healthy individuals	88	ML	ML, ML with visual stress, visual stress without ML, silence.	Between - subject comparison	30 minutes	POMS	T and Cort	Review showed a significant difference in the way T was affected by music between the sexes. ML intervention decreased T in males and increased its levels in females. ML impacted Cort concentration. Significantly decreased with ML intervention and increased under other interventions. No sex-related differences were found under any of the conditions studied for Cort.	ML intervention decreased testosterone in males (p=.0460) and increased its levels in females (p=.0012) Cort levels showed a significant decrease with ML intervention compared with any other intervention. (p=0.0035).	Between - subject design, randomized, biomarkers measured pre and post-intervention, scores reported with appropriate statistical analysis
Hirokawa and Ohira [22], Japan	Healthy individuals	24	ML	High- uplifting music, low- uplifting music, and silence after a stressful task.	Within- subject comparison	20 minutes	MMS	(S-IgA), (NK) cell level, T lymphocyte CD4+, CD8+, CD16+, dopamine, NE, and EPI levels	Review showed an increasing trend for NE level when subjects were exposed to High- uplifting music. After 20 minutes of silence intervention, active NK cells showed a significant decreasing trend. Results of the study were inconclusive, changes in biomarkers like NE influenced by exposure to a stress task	ML intervention significantly increased IgA ($p = 0.019$.) Statistically significant increase in NE level from the baseline to the post-Stroop test (p=0.019). confidence level, p = 0.054 .	Within- subject study, order of the experimental conditions was counterbalanced. Biomarkers and MMS measured pre and post-interventions, scores reported with appropriate statistical analysis
Lai and Li [23], China	Healthy individuals	54	ML	Alternating music and chair rest	Chair rest and music sequence.	30 minutes	Self- perceived stress was measured by means of a 0–10 cm VAS	HR, BP, finger temperature and Cort.	Review evidenced that ML intervention had a significant impact in autonomic responses when listening to preferred music for 30 minutes. ML was correlated with lower perceived stress level, Cort, HR, MAP and higher finger temperature	ML intervention had significant decrease in Cort levels, HR, MAP and perceived stress level when compared with chair rest intervention (P < 0.05). When comparing the two interventions, significant differences were found in terms of post- test HR, Cort levels, finger temperature and MAP (P	Randomized Controlled Crossover Clinical Trial, data from all participants included, biomarkers and instruments measured pre and post interventions, scores reported with appropriate statistical analysis

Karageorghis, <i>et al.</i> [24], United Kingdom	Healthy participants	42	ML	Slow, sedative music; fast, stimulative music	No music	33 min	Affect Grid	sCort, HR, and BP	Slow sedative music was correlated with lower levels of sCort and with more positive affective responses when compared with the fast stimulative and no music condition. The review evidenced that fast stimulative music, tend to inhibit the return of HR toward resting levels.	Study showed a statistically significant decrease in SCort in ML intervention when compared to control group p=0.003 . A decrease in HR was shown, participants experienced a lower HR while receiving ML compared to control group (p<0.05)	Randomized, counterbalanced, crossover design, a priori power analysis. Biomarkers and self-rating scales measured pre and post-interventions, scores reported with appropriate statistical analysis
Tan, <i>et al.</i> [25], Brunei	Healthy Individuals	23	ML	Relaxing music	Silence	15 min	None	HR, BP, Scor, Salivary total protein	Review did not find differences in regard to HR recovery, resting pulse rate, and SCort between ML and non-music interventions. Review concluded there is no significant difference in biomarkers' measures among ML and Silence intervention	No significant difference observed between the median HR when participants were exposed to ML as compared to silence intervention.	Within-subject study, randomized. Biomarkers measured pre and post-interventions, scores reported with appropriate statistical analysis
Duchemin, <i>et al.</i> [26], United States	Healthy Individuals.	32	MM	MBI	Wait-list group	8-week, All sessions last 1 hour except for week 5 session that lasts 2 hours and includes mindful eating.	Perceived Stress Scale (PSS) and the Depression Anxiety Stress Scale (DASS-21). Maslach's burnout inventory.	S α -amyl	S α -amyl levels positive correlated with burnout scores. Review showed a significant decrease in S-Amyl levels in MM intervention group compared with Wait-list group.	Significant decrease in S-Amyl in the intervention group compared to the waiting list control group (p=0.026)	RCT, data from all participants included, "Intention to treat" analyses which included all subjects randomized were performed, biomarkers and instruments measured pre and post interventions, scores reported with appropriate statistical analysis
Thoma, <i>et al.</i> [27], Germani	Healthy participants	60	ML	Relaxing music listening and water sound condition	Control condition (non-acoustic control condition including resting without acoustic stimulation)	10 min	Trier Inventory for the Assessment of Chronic Stress, STAI	sCort and S α -amyl, HR, respiratory sinus arrhythmia (RSA).	SCort response to the stressor differed significantly between the 3 conditions. There were not significant differences in regard to HR between groups	The 3 interventions significantly differed regarding sCort response to the stressor (p = 0.025) S α -amylase reached baseline values faster in the ML intervention group compared to the rest control group (p=0.026)	Between-Subject design, participants were randomly assigned to one of the groups., a priori power analysis was conducted to estimate the optimal sample size. Biomarkers and instruments measured pre and post

3. Results

3.1. Overview

All study designs were randomized controlled trials (RCTs). Study samples sizes ranged from 21 to 143 subjects with intervention duration ranging from 5 minutes to 2 hours and an outcome follow-up spanning from 1 day to 12 weeks.

3.1.1. Music Interventions

Reviewed studies included 4 main music interventions:

- A) Music Listening (ML, 10 studies) is the active or passive action of listening to vocal and/or instrumental sounds combined and organized by using rhythm, melody or harmony [6, 13, 19-25, 27].
- B) Meditational Music (MM, 3 studies) combines elements of mindfulness meditation, yoga movements and relaxation with music, using repetitive rhythmic sequences [15, 18, 26].
- C) Guided Imagery and Music (GIM, 2 studies) includes relaxation, music listening and imagery where music serves as a catalyst to evoke spontaneous images to come to conscious awareness, while therapist through dialogue provides grounding and focus to the client [14, 17].
- D) Singing (one study) is initiated by a warm-up phase, which include breathing, stretching, and vocalization exercises, then, sections and pieces are rehearsed by an amateur choir [16].

3.1.2. Biomarkers of Stress Associated with Music

Reviewed studies showed that music mainly affected the following specific biomarkers: cortisol (11 studies), heart rate (5 studies), blood pressure (4 studies), salivary α -amylase (2 studies), testosterone (2 studies), IgA (2 studies), oxytocin (1 study), and EEG theta wave (1 study).

Cortisol: Three studies showed a statistically significant decrease in cortisol (salivary cortisol) in the Music Listening (ML) intervention when compared to Meditational Music (MM) $p=0.022$ [19], $p=0.003$, [24], and $p=0.025$ [27]. Four additional controlled studies involving the ML intervention also showed a significant decrease in Cortisol levels, with $p<0.02$, $p=0.0029$, $p=0.0035$, and $p<0.05$ respectively [6, 20, 21, 23]. One study comparing singing and ML [16] found that ML, led to a decrease in Cortisol ($p<0.001$). Two studies involving comparing Guided Imagery and Music (GIM) to wait-list control group [14, 17] revealed a significant decrease in cortisol ($p=0.04$ and $p<0.025$ respectively). Lastly, one study involving intervention of MM [18] demonstrated a significant effect of MM on salivary cortisol concentration, with lower post-exposure cortisol concentrations ($p=0.023$).

Heart Rate: A decrease in heart rate was shown in four studies where participants experienced a lower heart rate while receiving ML compared to control groups ($p<0.001$, $p=0.017$, $p<0.05$, $p=0.023$, and $p<0.05$, respectively) [13, 19, 23, 24]. Trappe et al. showed that different types of music all lead to a decrease in heart rate [13], whereas Karageorghis et al. found that faster tempo music actually had the opposite effect with fast, stimulative music inhibiting the return of heart rate toward resting levels [24]. One study found no significant difference in heart rate between the ML group and the control silence group [25]. Thoma et al. showed that heart rate measures did not significantly differ between the ML group, and the MM groups [27].

Blood Pressure: Three ML intervention studies demonstrated a significant decrease in systolic blood pressure [13, 23, 25] ($p<0.001$, $p<0.05$, and $p<0.05$, respectively). Lai et al. showed a significant decrease in self-perceived stress, which correlated to a decrease in systolic and diastolic blood pressure, ($p<0.05$) [23]. Trappe et al. also found a decrease in diastolic blood pressure in subjects receiving ML in the form of instrumental Romantic-era music ($p=0.003$) [13]. One study found no significant effects on systolic or diastolic blood pressure in participants during the recovery process, immediately after strenuous exercise [24].

Salivary α -Amylase: One study involving mindfulness-based intervention (a form of MM) showed a significant decrease in salivary α -amylase in the intervention group compared to the waiting list control group ($p=0.026$) [26]. One study showed that salivary α -amylase reached baseline values faster in the ML intervention group compared to the rest control group ($p=0.026$) [27].

Testosterone: Three studies investigated how listening to music affected Testosterone plasma levels [6, 14, 21]. Sex-related differences in Testosterone secretion when listening to music were shown in two studies [6, 21]. In 2003, Fukui et al. found that ML intervention decreased testosterone in males ($p=.0460$) and increased its levels in females ($p=.0012$) [6]. In 2013, Fukui et al. examined the difference in testosterone levels in men and women during ML. Testosterone levels in women increased with chill-inducing music and decreased with music they disliked, whereas testosterone levels decreased in men with both types [21]. However, one study examining the effects of Guided Imagery and Music (GIM) on biopsychosocial measures of work-related stress, found no significant difference when comparing testosterone levels in the GIM group and the wait list control group ($p=0.93$) [14].

Immunoglobulin A (IgA): Two studies [16, 22] showed an increase in Immunoglobulin A (IgA) in response to music. Kreutz et al. demonstrated that singing significantly increased IgA, along with positive mood ($p < 0.05$) [16]. Hirokawa et al. revealed that ML intervention significantly increased IgA ($p = 0.019$) [22].

Oxytocin: Ooshi et al. found that listening to slow-tempo music is accompanied by an increase in oxytocin [19] with a significant Tempo x Time interaction for the oxytocin level ($p=0.0014$). After the participants listened to the slow-tempo sequence, the study showed that oxytocin level was significantly higher compared to baseline ($p=0.0007$) [19].

EEG theta wave: One study [15] involving MM intervention found increased central, parietal and occipital theta EEG activity ($p<0.0043$, $p<0.0127$, $p<0.0246$, respectively).

Additional Biomarkers: Studies of other biomarkers, such as androgen receptor (AR) [6], melatonin [14], dopamine, norepinephrine, and epinephrine levels, T-lymphocyte CD4+, CD8+, CD16+ [22] showed inconclusive results, and therefore were not included in this review. Other biomarkers were not covered due to the fact that they were examined in the context of medical illness.

4. Discussion

In this review of 16 randomized controlled trials that met pre-defined selection criteria and quality check, we identified four music interventions: Music Listening (ML), Meditational Music (MM), 'Guided Imagery and Music' (GIM), and singing. The reviewed studies showed music was associated with the following specific biomarkers: cortisol, heart rate, blood pressure, salivary α -amylase, testosterone, IgA, oxytocin, and EEG theta wave. We observed a decreasing trend in cortisol, salivary α -amylase, heart rate, and blood pressure, as well as an increasing trend in Immunoglobulin A (IgA), oxytocin, and EEG theta wave, while testosterone revealed sex-related differences. Music interventions are correlated with changes in biomarkers of stress, suggesting that it could be utilized for the development of stress reduction tools.

The human body's response to stress involves a significant increase in cortisol levels, heart rate, and blood pressure. Interestingly, the body's response to stress demonstrates opposite biological trends to those witnessed under musical interventions. In addition to cortisol, biomarkers of chronic stress include high levels of α -amylase, which showed a decrease in response to music. The biological response to music, then, mimics the body's return to homeostasis after undergoing stress. The increases in Oxytocin, IgA, and EEG theta wave come into play as an anti-stress markers, consistent with prior data. In particular, the increasing trend in IgA levels, strengthens the hypothesis that music could be used as a potential immune system booster. Thus, music serves as a catalyst to stress relief and could lead to potential uses in treating immediate and chronic stress in healthy adults.

Chronic stress many times leads to a sustained increase in the biomarkers aforementioned, resulting in chronic medical conditions, such as anxiety disorders. Acknowledging the inner workings of music in healthy adults and the changes in biomarker's responses could guide us in applying music, not only as a therapeutic tool but also as a preventative and health-promoting intervention.

The results of the current review were compared to previous reviews. A recent review by Chanda and Levitin [28] showed similar results pertaining to the biomarkers cortisol and oxytocin using similar interventions; however, it did not include information on salivary α -amylase, heart rate, blood pressure, or testosterone. The review included medical patients (surgical and lung infection patients), creating a significant challenge in confidently attributing biomarker changes to music intervention alone, without the confounding effect of medical illness. Finn and Fancourt [29] also demonstrated similar results, specifically in cortisol, among other stress hormones [29]; however, the review did not focus on specific musical interventions and included patients with medical illness [29]. Another recent review by de Witte, *et al.* [30], although focusing on stress response in relation to music interventions, lacked data on specific biomarkers released in response to those interventions and included clinical settings [30]. Fu, *et al.* [31], reviewed the effect of perioperative music on stress response to surgery. Despite including a sample of medically ill subjects, the study showed similar results, finding that music attenuated the neuroendocrine cortisol stress response [31]. Mojtavavi, *et al.* [32] demonstrated similar results in music's effect on cardiac autonomic function but focused almost exclusively on heart rate [32]. A review by Fancourt, *et al.* [33] cited Cortisol as the most common biomarker investigated. The review did not utilize strict inclusion criteria for the inclusion of healthy adults [33].

The strengths and limitations of this review are highlighted here. A notable strength is the fact that this review focused primarily on randomized controlled trials (RCTs). Excluding patients with medical illness added the advantage of preventing misinterpretation of biomarkers which are usually influenced by medical illness. Excluding small sample and poorly designed studies ensured the integrity of this systematic review. Thus, our review adds to the literature by covering biomarkers of stress specifically shown in healthy adults and describing each biomarker influenced by music interventions. Limitations include that the majority of the reviewed studies report stress-reducing effect with slow tempo or instrumental music, yet the reverse effect with fast tempo music is not consistently observed. In addition to the differences in experimental approaches, individuals' subjective preference for different genres of music might be a complicating factor. In many studies, the type of music selected are slow-tempo, instrumental music, which are considered 'relaxing' or 'comfortable' by the experimenters, whereas in a real-life context, people utilize a variety of genres (some with faster tempos) when they seek stress-reducing or relaxing effects from music. As such, the extent of pleasure derived from listening to the 'relaxing' music selected by the researchers may greatly vary. An interesting question to address in this context is whether there is a correlation between the extent of pleasure derived from music intervention and the extent of stress mediation.

5. Conclusions and Future Directions

Music is associated with significant changes in biomarkers of stress, suggesting that it could be utilized for the development of stress reduction tools. Future work could benefit from distinguishing music's neurochemical effects from its common use as a simple means of distraction. The Human Computer Interface (HCI) research community has been looking into several potential means including visual, auditory and olfactory stimuli. Current wearable devices that promote well-being, such as Fitbit and Apple Watch, which are mostly designed for monitoring, could present exciting opportunities for the HCI community to implement music interventions. Recently, there has been a surge of research and development on hassle-free wearable stress monitoring platforms which continuously detect users' vital signs and/or stress-related biomarkers. New technology to measure cortisol levels using a wireless sweat sensor would expand the use of monitoring biomarkers of stress in response to music in everyday settings [34]. The delivery of music through digital gadgets could be conveniently coupled with these stress monitoring devices without the introduction of additional burdensome tests. The synergistic effect of stress-monitoring devices and automated music intervention in the foreseeable future will also allow the investigation of music interventions on stress management.

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