

Music-induced analgesia: An adjunct to pain management

Psychology of Music

1–14

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DOI: 10.1177/0305735620928585

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Abstract

Increasing evidence shows that music can regulate emotional states and lead to pain reduction, a phenomenon called music-induced analgesia. However, knowledge about which neural circuitry is involved in this effect is still limited. To better understand the efficacy and neural mechanisms of music-induced analgesia, this review highlighted the growing body of literature suggesting music can be considered as an adjunct to pain management. We first conducted a meta-analysis of studies investigating the analgesic effect of music on experimentally induced pain among healthy participants. The meta-analysis result suggests a medium analgesic effect of music on experimentally induced pain, $g=0.52$, 95% confidence interval [0.41, 0.63], $p<.0001$. We then reviewed neuropsychological and neurochemical substrates associated with music-induced analgesia with an emphasis on experimental studies with healthy individuals. We argue that music can modulate pain as a distractor, a mood regulator, a stress reliever, and a reward by briefly summarizing evidence revealing the power of music on pain suppression in a variety of pain conditions. In conclusion, music can be considered as an adjunct to pain management. Pitfalls and promise of music intervention in pain management are discussed in view of current understandings of music-induced analgesia.

Keywords

music, analgesia, pain management, cognitive modulation, affective modulation

As a universal language, music shows tremendous promise in pain relief, especially when considering its non-pharmacological nature. Unlike pharmacological interventions, such as opioids that may come along with undesired side effects and adverse consequences (Dhalla, Persaud, & Juurlink, 2011; Kolodny et al., 2015), music is safe, effective, and nonaddictive. Indeed, increasing empirical evidence shows that music listening can result in the reduction of pain-related perception and emotion regulation, a phenomenon called *music-induced analgesia*.

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However, the knowledge about which neural circuitry is involved in this analgesic effect is still limited. One challenge to address this issue is that music intervention typically involves the coexistence of multiple therapeutic factors and environmental conditions in clinical practice. For this reason, studies applied to healthy volunteers with strict experimental designs and easily controlled painful stimulations are necessary for a better understanding of the efficacy and neural mechanisms of music-induced analgesia.

Therefore, we first conducted a meta-analysis of studies investigating the analgesic effect of music on experimentally induced pain to assess the efficacy of music-induced analgesia at the behavioral level. Then, the neuropsychological and neurochemical substrates associated with music-induced analgesia were reviewed with an emphasis on experimental studies with healthy individuals to reveal the possible neural mechanisms underlying this analgesic effect. Based on the understanding of the efficacy and neural mechanisms of music-induced analgesia, we also discussed whether the analgesic effect induced by music gains a specific advantage over other non-pharmacological sensory-based interventions and summarized the pitfalls and promise of music intervention in pain management in real situations.

A meta-analysis of music-induced analgesic effect on experimental pain

Due to the complexity of music and the individual differences in music taste, the effectiveness of the music-induced analgesic effect is rarely demonstrated with rigorous experimental designs. In this section, therefore, we reviewed experimental studies including comparisons on the analgesic effect induced by music and by other non-pharmacological interventions, regardless of pain stimulus types. This review was conducted in accordance with the PRISMA statement for systematic reviews and meta-analyses (Moher et al., 2015).

Search strategy and selection criteria

Searches were performed using *PubMed*, *ProQuest*, and *Web of Science* for studies written in English and published before the end of April 2019 that investigated the analgesic effect induced by music in experimentally induced pain conditions. Additional papers were identified from published reviews and the reference lists of selected papers. To include as many studies as possible, the inclusion criteria were studies with healthy participants at any age, in which any form of music was initiated at any stage of the experimental procedure. There was no restriction placed on the control group, but studies that lack a control group or involve clinical trials were excluded. The flowchart of the meta-analysis is displayed in Figure 1.

Data extraction and quality assessment

Two authors checked study eligibility and extracted data from studies using a standardized, pre-designed template independently. The following study characteristics were recorded: author, year of publication, sample size (including sex ratio), age, music conditions, non-music comparisons, pain stimulus types, when the music was played, and outcomes.

Statistical analysis

Data were analyzed using the Comprehensive Meta-Analysis Software (CMA, Version 2, Biostat Inc., United States). Outcome measures were pooled using the “fixed effect model”

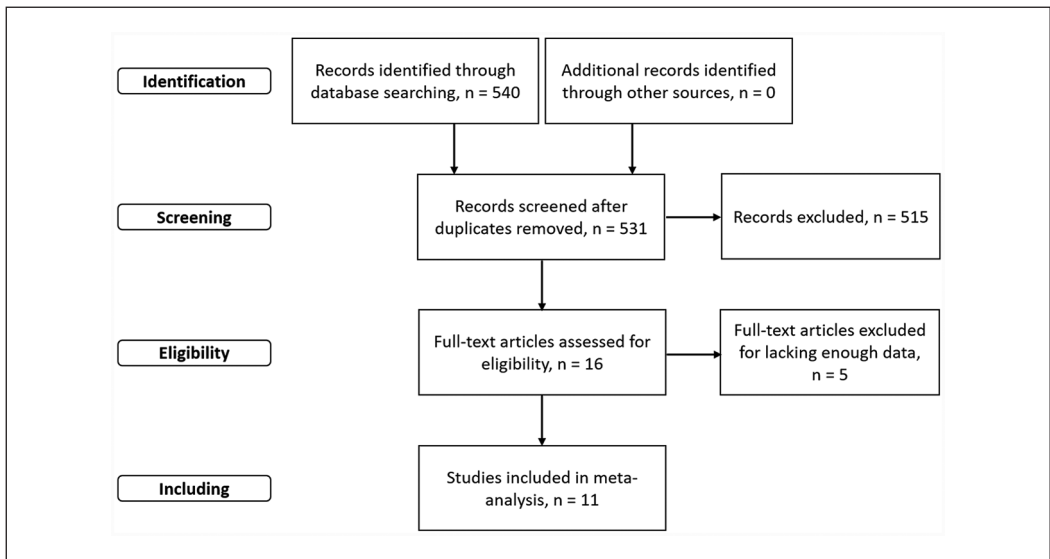


Figure 1. Flowchart showing the procedure to select eligible studies for the meta-analysis.

because all studies in the analysis shared a common true effect size, as suggested by the heterogeneity of participants and interventions (heterogeneity $Q=10.52$; $p_{\text{heterogeneity}}=.40$, $I^2=4.98$, indicating a lack of inter-study heterogeneity). All outcomes were continuous measures. We used bias-corrected standardized mean differences (Hedges' g) when outcomes had different measurement scales. Hedges' g provides a more conservative estimate of the effect size with a correction for bias in small samples (Hedges & Olkin, 1985). The standard formula in CMA for Hedges' g was as follows

$$\text{Hedges' } g = \text{Cohen's } d \left(1 - \frac{3}{(4N-9)} \right)$$

Effect sizes were calculated using F , t , p , and Cohen's d values for within-group and mixed designs (Rosenthal, 1994). Subgroup analyses were not performed due to the small number of studies. In addition, risk of publication bias was assessed using the funnel plots and Egger's bias test.

Results

We identified 540 titles and abstracts, of which we assessed 16 full-text articles for inclusion. We excluded five studies for lacking enough data, and finally included 11 studies (Basinski, Zdun-Ryzewska, & Majkowicz, 2018; Choi, Park, & Lee, 2018; Dobek, Beynon, Bosma, & Stroman, 2014; Garcia & Hand, 2015; Garza-Villarreal, Brattico, Vase, Østergaard, & Vuust, 2012; Hekmat & Hertel, 1993; Mitchell & MacDonald, 2006; Mitchell, MacDonald, & Brodie, 2006; Roy, Lebus, Hugueville, Peretz, & Rainville, 2012; Roy, Peretz, & Rainville, 2008; Ruscheweyh, Kreusch, Albers, Sommer, & Marziniak, 2011) in the meta-analysis. Characteristics of the included studies are summarized in Table 1. The sample size of the studies

Table 1. Study characteristics.

Study	Sample size (females)	Age	Music stimuli	Non-music comparisons	Pain stimuli	When the music was played	Outcomes
Basinski, Zdun- Ryzewska, and Majkiewicz (2018)	30 (15)	Range = 20–69 Mean = 37.1 ± 15.7	Arousing music, positive valence music, and deep music	White noise	Cold-pressor stimuli	During	Pain threshold, pain tolerance, maximal/average pain intensity, and pain controllability
Choi et al. (2018)	50 (26)	Mean = 25.7 ± 2.9	Researcher-chosen music	Weather news, silence	Cold-pressor stimuli	During	Pain tolerance, pain intensity, and pain unpleasantness
Dobek, Beynon, Bosma, and Stroman (2014)	12 (12)	Range = 18–40	Self-selected preferred music	Silence	Thermal stimuli (heat pulse)	During	Average pain rating and maximum pain rating
Garcia and Hand (2015)	30 (16)	Range = 18–50 Mean = 27.77 ± 9.87	Self-chosen relaxing music and self-chosen motivating music	Silence	Cold-pressor stimuli	Before + during	Pulse rate, systolic blood pressure, diastolic blood pressure, pain intensity, pain unpleasantness, and Profile of Mood States score
Garza-Villarreal, Brattico, Vase, Østergaard, and Vuust (2012)	48 (24)	Range = 19–39 Mean = 24 ± 4	Researcher-selected unfamiliar Mozart music	Unfamiliar environmental sounds, pink noise, the paced auditory serial addition task	Thermal stimuli (20 ms duration each)	Before + during	Pain intensity and pain unpleasantness
Hekmat and Hertel (1993)	80	Median = 19	Preferred music and non-preferred music	Silence	Cold-pressor stimuli	During	Pain tolerance and pain intensity
Mitchell and MacDonald (2006)	54 (34)	Range = 18–51 Mean = 22	Self-selected preferred music and researcher- selected relaxing music	White noise	Cold-pressor stimuli	During	Pain tolerance, pain intensity, McGill pain rating index, and perceived control
Mitchell, MacDonald, and Brodie (2006)	44 (24)	Range = 18–45 Mean = 25	Self-selected preferred music	The paced auditory serial addition task; audiotaped comedy	Cold-pressor stimuli	During	Pain tolerance, pain intensity, McGill pain rating index, and perceived control
Roy, Peretz, and Rainville (2008)	18 (9)	Range = 19–39 Mean = 27 ± 6	Researcher-selected pleasant music and researcher-selected unpleasant music	Silence	Thermal stimuli (10 ms duration each)	Before + during	Warmth intensity, pain intensity, pain unpleasantness, and Profile of Mood States score
Roy, Lebeus, Hugueville, Peretz, and Rainville (2012)	30 (16)	Mean = 24.26 ± 7.67	Pleasant-stimulating music, pleasant-relaxing music, and unpleasant- stimulating music	Silence	Transcutaneous electrical stimuli (a 30 ms train of 10×1 ms pulses)	Before + during	Pain rating, RIII reflex, and skin conductance response
Ruscheweyh, Kreusch, Albers, Sommer, and Marziniak (2011)	27 (14)	Range = 18–40 Mean = 24.4 ± 3.4	Self-selected preferred music	Mental imagery task, brush task, concentration-on-pain task	Electrical constant current stimuli (a 21 ms train of 5×1 ms pulses)	Before + during	RIII reflex, pain intensity, and heart rate

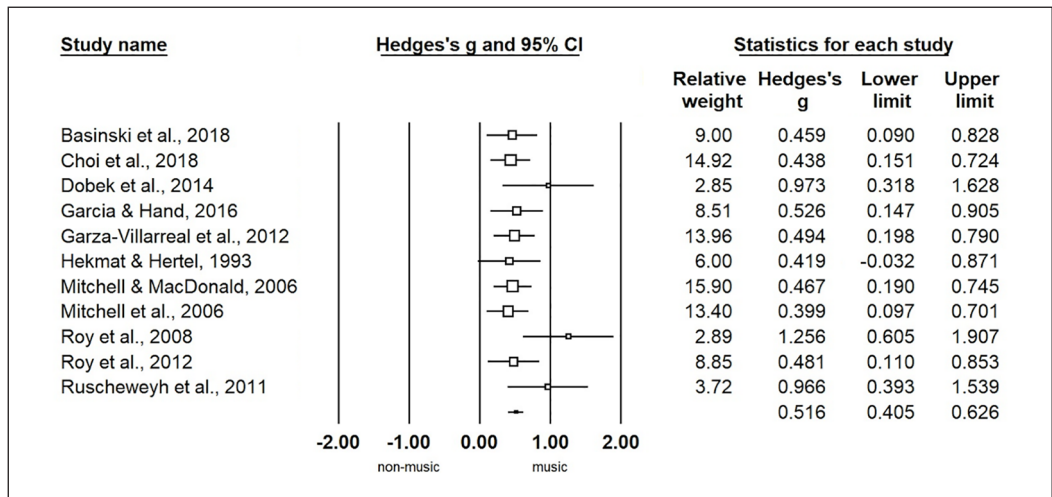


Figure 2. Summarized forest plot for the analgesic effect induced by music. Mean differences between music and non-music are shown with 95% CI. The size of the squares varies according to the relative weight of each study in the meta-analysis.

varied between 12 and 80 participants, and participants received various pain stimuli, including cold-pressor, thermal, and electrical stimuli. The non-music conditions could be noise, environmental sounds, comedy, or other auditory stimuli, and most studies included a comparison of silence condition. Choice of music could be made by participants or researchers. Included studies measured various outcomes, such as pain tolerance, pain intensity, pain unpleasantness, and perceived control. Ratings of pain intensity and unpleasantness were usually measured using the visual analogue scale or the number rating scale.

Meta-analysis results indicated an overall analgesic effect of music as compared to the non-music conditions, as reflected by a significant decrease of pain perception (intensity and unpleasantness) and increase of pain tolerance in the music group, $g = 0.52$, 95% confidence interval (CI) [0.41 0.63], $p < .0001$, representing a medium analgesic effect size (see Figure 2). For publication bias, which arises when studies with null findings were not published, we plotted effect sizes against the number of participants in a funnel plot (see Figure 3). The clear asymmetry in the funnel plot, with a gap in the left bottom side of the plot confirmed by the Egger's test ($p = .0004$), suggests a potential publication bias. Thus, we implemented the trim-and-fill method and failsafe- N calculation, which quantitatively assessed whether such asymmetries would change inferences about the significance of the weighted mean effect size (Duval & Tweedie, 2000), and determined the number of non-significant missing studies needed to nullify significant results (Rosenthal, 1979), respectively. No studies being added during the trim-and-fill procedure, and a failsafe- N calculation of 251 studies would be needed to nullify a significant α -level ($p < .05$). That is, even after trim-and-fill, the overall effect size for the analgesic effect induced by music is positive with the CI that does not span zero.

In short, the meta-analysis results provided an overall estimate of the effectiveness of the music-induced analgesia on experimentally induced pain. Significant decreases of pain perception and increases of pain tolerance were observed in healthy participants when they were listening to music before and/or during experimental pain stimulation. It should be noted that only a limited number of studies were included in this meta-analysis. Thus, subgroup analyses

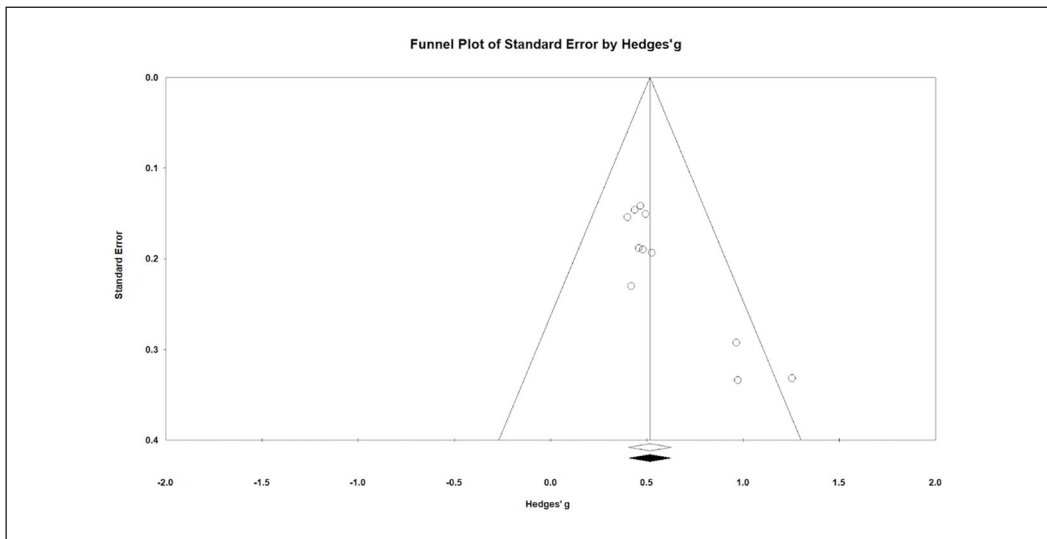


Figure 3. Funnel plot with 95% CI of the estimated effect sizes and their standard errors in individual studies in the meta-analysis.

(e.g., results related to different types of painful stimulation) were not be performed. In addition, there is a potential publication bias, even though the analgesic effect of music survives after trim-and-fill. Nevertheless, the generalization of our results should be taken cautiously.

Neuropsychological and neurochemical substrates underlying music-induced analgesia

As suggested by the behavioral results of meta-analysis, music listening is an effective approach for pain modulation under laboratory settings with rigorous experimental designs and control conditions. However, the underlying mechanism of music-induced analgesia remains unclear. It should be noted that a better understanding of the underlying mechanisms of music-induced analgesia is important to enhance the analgesic effects of music in a variety of pain conditions.

Pain is a subjective and complex phenomenon, and pain perception can be easily influenced by genetic, environmental, pathological, cognitive, and emotional factors (Su, Song, Zhao, & Liang, 2020; Tracey, 2011; Zhou et al., 2019). Among these factors, cognitive (e.g., distraction; Birnie, Chambers, & Spellman, 2017; Wiech, 2016) and emotional modulations (Rhudy & Meagher, 2001) are the two key candidates contributing to music-induced analgesia. Individuals' sensitivities to noxious stimuli and their anxiety levels would decrease, when they are distracted by other stimuli, such as visual lights or distraction cards (Aydin & Sahiner, 2017; Miron, Duncan, & Bushnell, 1989). Such effects become more significant when the distractive stimuli become more cognitively demanding (Bantick et al., 2002). Similarly, when listening to music, as a meaningful auditory distractor, individuals displace their focus of attention away from the pain stimulus, which subsequently leads to pain reduction (Hauck, Metzner, Rohlfs, Lorenz, & Engel, 2013).

Some researchers suggest that music is more effective in modulating the affective dimension of pain (i.e., pain unpleasantness) than the sensory dimension of pain (i.e., pain intensity; Lu, Thompson, Zhang, & Hu, 2019; Meeuse, Koornstra, & Reyners, 2010; Soo et al., 2016). Given

the fact that the positive effect of distraction is often accompanied by emotional arousal associated with the affective significance of the distractor (Vuilleumier, 2005), it is reasonable to consider music as a mood regulator rather than a simple distractor. Individuals prefer consonant (pleasant) sounds to dissonant (unpleasant) sounds (McDermott, Lehr, & Oxenham, 2010; Sammler, Grigutsch, Fritz, & Koelsch, 2007). As combinations of pleasant sounds, music can evoke feelings of intense pleasure, sometimes experienced by listeners as “thrills” or “goose bumps” (Goldstein, 1980). Indeed, pleasant music could induce a stronger analgesic effect as compared to unpleasant music (Roy et al., 2008), regardless of whether the pleasant music conveys happy or sad emotion (Kenntner-Mabiala, Gorges, Alpers, Lehmann, & Pauli, 2007; Zhao & Chen, 2009). Moreover, when individuals listen to unpleasant music, their RIII reflex and pain ratings increase, compared to when they listen to pleasant music, suggesting that the descending pain inhibitory mechanisms are involved in the emotional regulation of music on pain (Roy et al., 2012). Please note that this explanation is in line with the idea that emotions could modulate the ascending nociceptive signals through the descending pain inhibitory mechanisms (Bushnell, Ceko, & Low, 2013; Villemure & Bushnell, 2009).

In addition, one of the potential therapeutic effects of music listening can be attributed to its ability to reduce stress and modulate arousal level. Listening to “relaxing music” has been shown to be effective in reducing stress and anxiety for both healthy individuals and chronic pain patients (Knight & Rickard, 2001). Changes in the hypothalamic-pituitary-adrenal (HPA) axis are responsible for the relaxing music modulation, as two HPA activation markers, that is, cortisol and β -endorphin, decreased during music listening with guided imagery (McKinney, Antoni, Kumar, Tims, & McCabe, 1997; McKinney, Tims, Kumar, & Kumar, 1997). Therefore, reduced pain unpleasantness while listening to relaxing music (Garcia & Hand, 2015) could be explained by the fact that music listening reduces stress via the suppressed activations of the HPA axis (Li & Hu, 2016).

Moreover, listening to music can activate the reward circuitry, including the nucleus accumbens, amygdala, ventral tegmental area, periaqueductal gray, anterior cingulate cortex, orbitofrontal cortex, medial prefrontal cortex, and cerebellum (Blood & Zatorre, 2001; Koelsch & Siebel, 2005; Menon & Levitin, 2005; Salimpoor et al., 2013; Salimpoor, Zald, Zatorre, Dagher, & McIntosh, 2015; Zatorre, 2015). Dopamine cells originating from the ventral tegmental area with strong projection to the nucleus accumbens and forebrain regions are important for the motivational function (Wise, 2004). During the experience of peak emotional response to music, the evoked pleasure can lead to the release of dopamine in the striatal system (Salimpoor, Benovoy, Larcher, Dagher, & Zatorre, 2011). The activation of reward circuitry could modulate the processing of nociceptive information in the manner of learning and valuation (Lee et al., 2015; Schwartz, Miller, & Fields, 2017; Tu, Bi, Zhang, Wei, & Hu, 2020).

Advantages of music in pain modulation

The processing of noxious information is easily influenced by inputs from other sensory modalities (Lu, Yao, Thompson, & Hu, 2020; Peng et al., 2019; Senkowski, Hofle, & Engel, 2014). These inputs could either enhance the salience of the noxious information, leading to an increased pain experience, or distract individuals from pain and regulate their emotions, causing pain reduction (Birnie et al., 2017). In addition to music, the analgesic effects could be induced by other sensory-based interventions, such as positive pictures (Kenntner-Mabiala, Andreatta, Wieser, Muhlberger, & Pauli, 2008; Kenntner-Mabiala & Pauli, 2005), humorous films (Weisenberg, Tepper, & Schwarzwald, 1995), video games (Jameson, Trevena, & Swain, 2011), pleasant odors (Villemure, Slotnick, & Bushnell, 2003), touch (Mancini, Beaumont, Hu, Haggard, & Iannetti, 2015), and handholding (Goldstein, Weissman-Fogel,

Dumas, & Shamay-Tsoory, 2018). For instance, individuals' pain thresholds or pain tolerance increased, when were presented with positive pictures (e.g., erotic pictures) before or during a cold-pressor test (de Wied & Verbaten, 2001; Meagher, Arnau, & Rhudy, 2001).

When different types of interventions attract similar levels of interest, does music have significant advantage in pain modulation as compared to other sensory-based interventions? Since individuals can listen to music with little or no cost to the processing of the concurrent sensory information (Lloyd, Merat, Mcglone, & Spence, 2003; Pud & Sapir, 2006), music is effective in reducing pain in a passive fashion (Mitchell et al., 2006; Roy et al., 2008). Therefore, unlike vision-based interventions, such as playing video games, individuals can easily become involved in music listening without requiring high levels of attention and muscle tension. Music could relax the body, resulting in anxiety reduction, stress relief, and pain attenuation. In addition, the music-induced analgesia can be persistent while music is ongoing, as the physiological effects elicited by the emotional music pieces tend to increase over time (Krumhansl, 1997). In contrast, pleasant odors, although it can be processed passively, are easily to be adapted after a long period of exposure, leading to the reduction of the analgesic effects. However, music may not be as effective as active distractions (e.g., the paced auditory serial addition task) in pain reduction, even though music reduced pain significantly when compared to noise (Garza-Villarreal et al., 2012). Therefore, music-induced analgesia is generally considered as an adjunct to pain management, but not as a replacement for pain-relieving drugs or standard pain treatments.

Music as an adjunct to pain management in clinical conditions

Although the effectiveness of music in clinical applications is questioned (Mak et al., 2017; Shim et al., 2017), an emerging body of literature investigated this issue using evidence-based music interventions through peer-reviewed randomized controlled trials (RCTs). To demonstrate the analgesic effect of music on pain in clinical practice, clinicians usually look for evidence showing that patients require less sedation or analgesics (objectively) or report less pain (subjectively) after listening to music, compared to patients in standard care or under other control conditions (e.g., noise).

Despite individual differences in pain perception and music taste, the analgesic effect of music can be observed in a variety of pain conditions (Gardner, Licklider, & Weisz, 1960; Good, Anderson, Ahn, Cong, & Stanton-Hicks, 2005; Good et al., 1999; Guetin et al., 2012), such as labor pain (Hosseini, Bagheri, & Honarparvaran, 2013; Phumdoung & Good, 2003) and post-operative pain (Voss et al., 2004). Moreover, the analgesic effect induced by music is not only reported by adult patients but also observed in children (Klassen, Liang, Tjosvold, Klassen, & Hartling, 2008; Sundar et al., 2016) and infants (Kurdahi Badr et al., 2017), suggesting that music could be considered as an adjunct to pain management for patients in various age groups.

However, existing clinical studies with different procedures for selecting patients, various experimental designs, and different statistical analysis methods yielded mixed and inconsistent results. To estimate the effects of music on clinical pain in different studies, numerous comprehensive meta-analyses of RCTs have been conducted in the past years (Cepeda, Carr, Lau, & Alvarez, 2006; Hole, Hirsch, Ball, & Meads, 2015; Lee, 2016; Standley, 2002; Tsai et al., 2014). These studies examined the effectiveness of music compared to the standard care or control conditions using different pain-related measures (e.g., pain reduction, pain tolerance, analgesic use, vital signs, and mood regulation). In addition, these studies also investigated potential moderators that appear to affect the outcomes (e.g., pain subtypes, choice of music, timing of delivery, age, gender, and methodological rigor). For instance, Hole et al. (2015) included 73

RCTs of adult patients undergoing surgical procedure, in which music was played before, during, or after the surgery, compared to standard routine care or other non-drug interventions, such as white noise, salience, or undisturbed bed rest. The results suggested that music played at any stage can effectively reduce postoperative pain, anxiety, and analgesia use, as well as increase satisfaction, even when patients took general anesthetics. However, it seems that music choice and delivery timing make little difference to the analgesic outcome (see Kuhlmann et al., 2018, for a similar but more recent meta-analysis study). In general, previous studies demonstrated the additional effectiveness of music in the management of clinical pain compared to the standard care.

Pitfalls and promise in music intervention

To better understand the essence of music-induced analgesia, future studies could be conducted in four directions. First, neuroimaging studies with rigorous experimental designs can be conducted to find the neurological pathways and neurochemical systems responsible for the analgesic effect evoked by different types of music. For instance, high arousal or energetic music makes people excited, in which the limbic system becomes more involved, while low arousal or calming music puts people in a relaxing mood, which decreases the cortisol level. Second, individuals have different music preferences, so it can be difficult to deliver a generalized music intervention to all individuals. Therefore, personalized music intervention should be developed, in which music is played based on the personal preferences of each individual. Third, the analgesic effect induced by music is usually short term (Finlay, 2013). Therefore, it is beneficial to develop multimodal pain management programs that would have greater impacts on overall mood, body functioning, and pain. Studies have demonstrated that delivering music in combination with other cost-effective methods, such as massage (Najafi Ghezeli, Mohades Ardebili, & Raffi, 2017) and vibroacoustic stimulation (Sandler et al., 2017), can be quite effective in relieving pain. Finally, when studying music-induced analgesia, it is important to compare the experimental findings with clinical outcomes, and to investigate whether the analgesic effect involves the same neural mechanisms under laboratory settings and in real clinical conditions.

In conclusion, this review conducted a meta-analysis showing a medium analgesic effect of music on experimentally induced pain and discussed the possible psychological and neurophysiological mechanisms underlying this analgesic effect. We argue that music can modulate pain as a distractor, a mood regulator, a stress reliever, and a reward. With this knowledge, the therapeutic uses of music in pain management can be significantly improved.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (31701000, 31822025, 31671141), the Informatization Special Project of Chinese Academy of Sciences (XXH13506-306), and CAS Key Laboratory of Mental Health, Institute of Psychology (KLMH2018ZG02). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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