HHS Public Access
Author manuscript
Pain. Author manuscript; available in PMC 2020 June 08.

Published in final edited form as:
Pain. 2019 September ; 160(9): 1909–1919. doi:10.1097/j.pain.0000000000001539.

Virtual reality, music, and pain: developing the premise for an interdisciplinary approach to pain management

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1. Introduction

Research in pain management seeks to offer new approaches to pain treatments that present severe side effects. This endeavor is of increasing importance as opioid misuse and deaths in the United States rise,[66] and as health care practitioners and patients are advised to move away from opioid-based pain management.

Virtual reality (VR) and music therapy (MT) have been separately explored as interventions for alleviating pain with relatively consistent levels of success.[9,69,85] In this article, we refer to VR as immersive computer-generated environments designed to make a user experience them as real. Music therapy refers to the use of music to promote healing.[9] An approach to

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Conflict of interest statement
E. Honzel reports personal fees from University of Maryland outside the submitted work. A. Varshney reports grants from National Science Foundation, grants from State of Maryland's MPower Initiative during the conduct of the study; L. Colloca reports grants from NIDCR (R01DE025946), PCORI, MPower the State, UM Grants, personal fees from Elsevier during the conduct of the study. The remaining authors have no conflicts of interest to declare.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

pain management that combines MT and VR may present novel opportunities for reducing patient pain suffering by presenting a focused aesthetic multisensory stimulation. This might in turn regulate mood, emotions, attention demands, memory, and patients' engagement. Although many nonpharmacological methods of pain control have been explored (eg, hypnosis and meditation), we have chosen to focus on VR and MT as 2 highly compatible methods, with the intent of addressing our concepts and perspectives as basic scientists, musicians, physicians, and educators.

We conducted a PubMed literature search using the terms: VR and pain; MT and pain. We found 288 and 243 articles, respectively, and reviewed them (E.H. and L.C.). Manually, we also found 37 additional published data-based articles and comprehensive reviews. We presented a total of 53 selected data-based articles (Table 1). Studies were selected that directly investigated the relationship between music or virtual reality and pain in both healthy and pain-afflicted populations using objective and subjective measures of pain as the primary outcome. Studies that assessed multiple interventions beyond virtual reality or music were excluded.

2. Virtual reality and pain

2.1 Neurobiological bases of immersive virtual reality and their relationship with pain

There are several proposed mechanisms for how VR experiences may alleviate pain.[30,49,74,87] It has been suggested that VR engages pathways that would otherwise be devoted to pain signaling through distraction.[49,86] In this theory, VR creates a positive effect on cognitive variables to both enhance pain control[50] and moderate pain signaling pathways through memory, emotions, and other senses including haptic, aural, and visual.[20] It is also possible that VR distances patients from their current state through immersion. For example, patients with walking pain may be able to enter a reality where they are not physically moving their limbs but are able to virtually experience walking.[16] Efforts are under way to understand the mechanism through which VR functions have clinical relevance.[43] Researchers must discover whether the underlying mechanism is distraction,[23] in which case, salience is key; whether it acts through fundamentally regulating mood, emotions, and altering how we see and perceive the world around us, in which case, total immersion is paramount; or whether it requires active cognitive engagement, in which case, guided experiences may need to be explored.[43]

Despite the current paucity of VR equipment that is compatible with functional magnetic resonance imaging (fMRI) techniques, a few studies have reported that VR as compared to a no-VR condition decreases the neural activity in regions of interest (ROI) such as the anterior cingulate cortex, primary and secondary somatosensory cortices, insula, and thalamus in healthy participants when thermal painful stimulations are given.[30] A follow-up study indicated that the aforementioned ROIs are differently modulated by VR and pharmacological treatments. Healthy participants underwent a thermal painful stimulation in a within-subject design that included (1) control (no analgesia), (2) opioid (4 ng/mL hydromorphone administration), (3) immersive VR, and (4) combined opioid and VR.[31] The opioid alone reduced pain unpleasantness (Hedges' $g = -0.367$) and blood oxygen level-dependent activity in the insula and thalamus. Virtual reality alone reduced both worst pain intensity (Hedges' g = −0.367) along with neural activity in the insula, thalamus, and secondary somatosensory cortices. Interestingly, combining opioid and VR interventions resulted in a larger reduction of pain reports compared with opioid alone on all subjective pain measures (Hedges' g = −2.46). This finding supports the concept that multimodal combined pain therapeutics can be clinically relevant. As MRI-compatible technology improves, future studies with combined VR-MT should explore the mechanisms through which multimodal approaches modulate pain-related and other processes in patients suffering from pain.[31]

2.2 Acute pain

Virtual reality pain management for acute pain has been frequently studied and reviewed in both healthy subjects[11,25,80,81] and pain patients, especially burn victims[26,37,44,53,75,79] and patients with phantom limb pain.[1,68,73] One pioneering study was conducted on 2 adolescents, showing that they were able to better tolerate painful procedures during burn dressing changes during a VR experience.[27] In the years since this study, Hoffman et al. have performed numerous studies with larger sample sizes examining VR interventions as an adjunctive treatment for burn pain.[5,52,53,78] For example, adult patients showed both improvement of pain function (eg, motion exercise ranges during physical therapy)[28] and pain reduction during wound care.[29] All patients reported significantly better outcomes with the immersive VR as compared to no VR.[28] Although the study was unblinded, the order of the condition was randomized and counterbalanced. Research that explores different VR features (eg, high-tech VR helmets,[32]) is aiming to further determine VR's impact on experimental pain.

A systematic review that assessed studies comparing VR with a control condition or an alternative intervention indicated that VR reduces experimental pain and acute clinical pain associated with burn injury care.[55] The review showed that VR works less with needle-related pain, and fully immersive VR-based tools were more likely to provide pain relief. Indovina et al.[35] analyzed VR interventions during painful medical procedures, including studies that looked at acute pain and other measures of distress, in varied patient populations. The authors, while confirming the validity of the VR interventions, called for the establishment of predictive factors that would encourage the development of personalized VR experiences.

2.3 Chronic pain

As Indovina et al.[35] noted, studies considering VR interventions to treat chronic pain are "in (their) infancy." However, the numbers of such studies are increasing in recent years. Jones et al.[41] explored the efficacy of a 5-minute immersive VR environment (*Cool!*) as a pain intervention in 30 study participants with moderate chronic pain conditions (ie, cervical spine, lumbar spine, hip, shoulder, abdominal, thoracic pain, and diffuse pain from myalgia or connective tissue disease and neuropathy). During the VR treatment session, participants reported lowered pain by 60% and, after the session, lowered pain by 33% (Hedges' g = −0.741) as compared to their presession self-report of moderate pain.[41] In another chronic pain study, Jin et al. designed and tested the VR game *Cryoslide* in a randomized, controlled crossover study as an intervention to relieve "spikes" of pain and found a reduction of clinical pain compared with baseline and controls.[39] Keefe et al.[43] posited several ways in which VR could be used to treat specific chronic pain conditions, including altering pain-related movement patterns and integrating VR with behavioral interventions (eg, hypnosis, meditation, and exposure therapy). Future studies using immersive VR tools that are tailored to the etiology of pain disorders (eg, phantom pain[1]) are needed.

2.4 Technical applications and audio-based interventions

A wide range of VR interventions have been developed. Well-established applications such as *Cool!* (DeepStream VR Inc, Seattle, WA, 2014) and *Snow World* (MultiGen-Paradigm.com, 2001) have provided a sense of immersion through visual and aural components. Other interventions are beginning to explore olfactory[19] and tactile[21] stimuli. The effectiveness of these interventions has been explored using a variety of subjective measures, including pain scales,[44] as well as objective measures such as blood-oxygen–dependent measurements of brain activity,[31] vital signs,[86] and measures of skin conductance.[84] While early VR interventional studies primarily used expensive equipment, commoditization has made lower-cost VR interventions more feasible.[15] Virtual reality hardware and software are evolving rapidly, and the viewing systems are becoming less expensive and more portable. At the same time, the library of digital content is rapidly increasing. This might facilitate the use of VR as an adjunct or alternative therapy for the treatment of distinct aspects of pain (sensory and affective components) across pain disorders.

Virtual reality interventions that are considered "higher tech" have been shown to increase the therapeutic effects of VR due to the increase of "presence," or the illusion of entering and being in the virtual world.[33] These higher tech interventions used sound effects, which indicate that incorporating auditory input for interventions may increase the sense of presence and therefore increase efficacy. A recent study directly examined the effect of adding aural input to a VR intervention in healthy subjects participating in a cold-pressor pain study.[40] Virtual reality including audio elicited higher pain tolerance as compared to an aural-only condition, a VR-only condition, and a control group (Hedges' $g = 0.43$). This suggests that the addition of sound may increase the attention-demanding nature of the experience, providing greater reduction of the perception of pain. The authors note that determining which kind of sounds is most effective in combination with the VR (context-relevant or distracting) may help describe the mechanisms through which VR therapies work.[40]

3. Music and pain

Music-based therapies have been used to mitigate acute[34] and chronic pain[9] as observed using subjective measures (eg, pain rating scales) and objective methods (eg, fMRI).[13]

3.1 Neurobiological bases of music and their relationship with pain

Several studies have sought to explain the neural underpinnings of the human experience of music in general.[47] Neural responses to music are centered in the nucleus accumbens, a major reward brain center, and its dopaminergic stimulator, the ventral tegmental area

[60,71,72] The activation of the mesolimbic reward system and the release of dopamine in response to music has demonstrated its pleasure-giving capability.[45,46] This highlights the unique ability of music to connect and engage with multiple parts of the brain and music-evoked emotions.[45] Reybrouck et al. compiled results from 12 studies that used network science algorithms. They concluded that music activates the auditory cortex, the brain reward system, and areas associated with the mind wandering, with distinct changes associated with perceptual, action-related, cognitive, affective, and evaluative processes.[70] Studies have also shown that this pathway of anatomical substrates is shared with the perception of pain, indicating that the 2 may be more closely linked than once believed.[48]

The quantitative understanding of MT treatments as they relate with pain has also been explored. Dobek et al.[12] used fMRI to examine neural activity related to painful stimuli in subjects listening to music they enjoyed vs controls who had no music, finding altered neural patterns indicative of decreased pain when music was playing. Garza-Villarreal et al. found that listening to music reduced pain in fibromyalgia through top-down regulation of the modulatory network, with higher connectivity between the left angular gyrus, the right dorsolateral prefrontal cortex and the left caudate (lCau), and decreased connectivity with the right anterior cingulate cortex, the right supplementary motor area, and the precuneus and right precentral gyrus. Pain reduction levels were correlated with the connectivity of the left angular gyrus to the right precentral gyrus.[17] If these results are further confirmed, listening to music to activate the pain modulatory systems could open up new strategies for nonpharmacological treatments of pain.

3.2 Acute pain

Many studies have shown MT to be effective in treating acute pain.[2,42,54,56,58,63,67,76,77,88] For example, preferred music reduced subjective perception of pain in postcardiac surgical patients compared with controls ($P = 0.0001$).[36] Forty-five minutes of MT reduced heart rate, respiratory rate, oxygen saturation, and pain in patients undergoing C-clamp application after percutaneous coronary intervention in comparison with controls receiving uninterrupted rest.[7] However, results regarding MT's efficacy are conflicting.[8,10,59,61] The discrepancy in results may be due to various factors, including inadequate study designs and controls or subjectivity of musical experiences (eg, music anhedonia).

3.3 Chronic pain

Parallel to studies in VR, MT has suggested effectiveness in managing chronic pain.[3,14,18,22,24,57,65] For example, Bradt et al.[3] explored the feasibility of an 8-week vocal MT treatment program on chronic pain disorders in a population of older Afro-American inner-city adults. The study established the feasibility of the intervention and demonstrated large effect sizes for self-efficacy at weeks 8 and 12, a moderate effect size for pain interference at week 8, and no improvements for general activities and emotional functioning, paving the road for further research in MT.

Music-based therapies have also been explored in the context of opioid use disorders. Some studies found that music reduced opioid intake,[64] yet others reported that while the music was enjoyable to the patients, the amount of analgesic used did not differ in music-treated patients vs controls.[82] In a recent preliminary research report, Chai et al.[6] discussed the future of using music as an adjunct to opioid administration by establishing the feasibility of the intervention and determining experimentally key points of relevance for clinical endpoints (eg, music features, patients' preferences, motivation, and engagement).

3.4 Technical applications

The range of music-based interventions offered under the umbrella of "Music therapy" is incredibly wide. Activities range from music listening, to vocal therapy, to music production using instruments. It is worth noting that MT, as strictly defined, requires active participation on behalf of the subjects in the presence of a therapist. Most "MT" studies may be more accurately described as music medicine (MM), which usually involves listening to prerecorded music without the presence of a therapist. However, Bradt et al. examined the impacts of MT vs MM and showed that both interventions resulted in equal decreased pain and improved psychological outcomes in cancer patients.[4]

Overall, these studies bring up the interesting notion that, for music to be an effective aesthetic intervention, listeners must engage with what they are experiencing (eg, vocalization and improvisation). In MT, this is often accomplished by a music therapist acting as a guide. In MM, the unguided nature of the intervention makes this more difficult to control for.

4. Limitations and future directions

Many VR and MT studies miss either the appropriate controls (eg, nonimmersive VR, pink noise vs ambient music, and passive music listening) and/or blinding of both research staff and study participants. Moreover, most of the VR and MT studies focused on pain intensity, when VR and MT may change the nature of affect associated with pain experience (eg, distressing or frightening), pain quality (eg, sharpness of pain) and the effectiveness based on pain location (eg, distinct body representation).[38] Magnitude-based inferences related to clinical relevance are based on the examination of outcomes beyond the statistical significance. Based on the studies we reviewed (Table 1), there is a need for additional systematic meta-analyses[34] that account for heterogeneity of the studies. Only such approach allows for quantifying the efficacy of MT and VR and their potential to implement their uses routinely to optimize clinical outcomes. Future randomized placebo-controlled clinical trials and comparative effectiveness research will also help define the clinical relevance of VR, MT, and combined VR-MT. Finally, it is important to consider whether and how expectancies and contextual placebo effects may influence the effectiveness of VR-MT interventions.[51]

Despite these limitations, recent studies have illustrated increased pain tolerance especially in patients who self-selected their musical experience[62,83] or were immersed in VR contexts.[43] The hypoalgesic properties of both MT and VR could be further explored in the context of combined VR-MT applications. Virtual reality brings the unique opportunity to reach a high level of engagement on multiple sensory and cognitive levels, as well as the specialization necessary for creating MT-based clinically meaningful experiences that lead to pain reduction. This may help bridge the gap between MT and MM. The possibilities of

VR-MT interventions range from minimal contact, using speakers or mobile phones, to use of spatial sound-enabled VR headsets. Stereo 360° cinematographic rendering of virtual scenes could transport patients to the stage of a rock concert, where they are able to change positions and alter which instruments they hear best, or place them in the middle of an operatic finale. Although studies have examined the effects of adding sensory components to VR interventions, exploring multiple VR-MT contents may elucidate the differential effects unique to certain pain disorders and patient predictors of beneficial outcomes.

5. Conclusions

Based on the studies discussed above, both VR and MT might contribute to reducing pain through mechanisms that include distraction and demand on attention, mood and emotion regulation, and immersion and engagement. Virtual reality and MT can act as a multimodal pain intervention by activating in turn, sensory-perceptual, action-related, cognitive, affective, and evaluative processes. Future research is needed to explore the mutual contribution of these processes and their effect sizes. At the time of this publication, no studies have been published that assess music as part of the VR intervention for pain management. We believe that with the relative novelty and ongoing development of VR and MT experiences, it is both feasible and logical to introduce VR-MT environments to promote therapeutic hypoalgesic outcomes. Immersive VR-MT presents a unique and promising approach to pain management and could help further our understanding of the complex relationship between music and VR-driven neurobiological healing mechanisms.

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Table 1

Description the studies discussed in this review.

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Ambron et al. (2018)[1]	VR	Phantom limb pain patients	n = 2	Case study	n/a	Subjective	Intensity	Numerical pain scale (NRS)	Missing data
Carrougher et al. (2009)[5]	VR	Burn injuries patients	n = 39	Within-subjects	One session w/VR, one session w/out VR (order counterbalanced)	Subjective	Intensity (worst pain), time spent thinking about pain, unpleasantness, and opioid equivalents	Graphic rating scale (GRS)	GRS, worst pain: 0.536 Opioid equivalents: −0.171
Demeter et al. (2015)[11]	VR	Healthy participants	n = 62	Within-subjects	Baseline, tonic noxious heat stimulation only	Subjective and objective	Intensity and threshold	NPS, latency of intolerability, temperature at which pain was first perceived, and thermal sensory analyzer (TSA)	NPS heat intensity: −0.671
Ford et al. (2018)[15]	VR	Burn injury patients	n = 10	Observational study	n/a	Subjective	Intensity	Satisfaction questionnaire (no pain ratings)	Missing data/
Gutierrez-Maldonado et al. (2012)[25]	VR	Healthy participants	n = 45	Within-subjects	No VR	Subjective	Threshold, tolerance, intensity, self-efficacy, and catastrophizing	Pain Catastrophizing Scale (PCS) and Visual Analogue Scale (VAS)	Strongest pain intensity: −0.126
Hoffman et al. (2000)[27]	VR	Burn injury patients	n = 2	Within-subjects	Videogame only during wound care	Subjective	Intensity	VAS	Missing data
Hoffman et al. (2000)[28]	VR	Burn injury patients	n = 12	Within-subjects	Control condition: no distraction during physical therapy	Subjective	Intensity	VAS	Average pain: −1.12 Worst pain: −1.11
Hoffman et al. (2004)[30]	VR	Healthy participants	n = 8	Within-subjects	No VR during thermal stimuli	Subjective and objective	Intensity (time spent thinking about pain, unpleasantness, worst pain, amount of fun, amount of nausea, and presence)	GRS and fMRI	Missing data

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Hoffman et al. (2004)[33]	VR	Healthy participants	n = 39	Between-subjects	Low-tech VR	Subjective	Cognitive, sensory, and affective components of pain	Rankings from 0-10	−1.49
Hoffman et al. (2006)[32]	VR	Healthy participants	n = 77	Between-subjects	No distraction	Subjective	Cognitive, affective, and sensory components of pain	Rankings from 0-10	Missing data
Hoffman et al. (2007)[31]	VR	Healthy participants	n = 9	Within-subjects	No analgesia, opioids	Subjective, objective	Intensity	GRS, blood oxygen level–dependent assessments of brain activity (fMRI)	Worst pain intensity VR–/opioid– vs VR +/opioid–: −1.32 VR–/opioid– vs VR–/opioid+: −0.367 VR–/opioid– vs VR +/opioid+: −2.46
Hoffman et al. (2008)[29]	VR	Burn injury patients	n = 11	Within-subjects	No VR during wound care	Subjective	Worst pain, pain unpleasantness, time spent thinking about pain, and fun	GRS	Worst pain: −1.05 Unpleasant: −1.09
Jeffs et al. (2014)[37]	VR	Burn injury patients	n = 30	Between-subjects	Passive distraction and standard care	Subjective	Intensity	Adolescent pediatric pain tool	Missing data
Jin et al. (2016)[39]	VR	Chronic pain patients	n = 20	Within-subjects	Self-mediated session (regular distracting activities)	Subjective	Intensity	VAS	−0.96
Johnson et al. (2016)[40]	VR	Healthy participants	n = 32	Within-subjects	Baseline (no sound, no VR), sound only	Objective	Tolerance	Pain tolerance times	Sound only vs baseline: 0.293†† Head mounted device (HMD) only vs baseline: 1.01†† HMD + sound vs baseline: 1.01†† HMD + sound vs sound only: 0.941†† HMD + sound vs HMD only: 0.430††
Jones et al. (2016)[41]	VR	Chronic pain patients	n = 30	Within-subjects	n/a (pre–post pain scores)	Subjective	Intensity	NRS	−0.741

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Kipping et al. (2012)[44]	VR	Burn injuries patients	n = 41	Between-subjects	Distraction	Subjective, objective	Intensity	VAS, heart rate (HR), oxygen saturation (OS)	Subject VAS, dressing removal: −0.465 Subject VAS, dressing application: −0.420
Loreto-Quijada et al. (2014)[50]	VR	Healthy participants	n = 77	Between-subjects	No VR	Subjective, objective	Intensity, tolerance, threshold, time perception, and pain sensitivity range	VAS, PCS	Missing data
Maani et al. (2011)[52]	VR	Burn injury patients	n = 2	Case study	n/a	Subjective	Intensity/ unpleasantness	GRS	Missing data
Maani et al. (2011)[53]	VR	Burn injury patients	n = 12	Within-subjects	No distraction during wound care	Subjective	Intensity/ unpleasantness	GRS	Worst pain ≥7: Worst pain: −1.331‡‡ Unpleasantness: −2.13‡‡ Time thinking about pain: −2.44‡‡ Worst pain <7: Worst pain: −0.40‡‡ Unpleasantness: −0.75‡‡ Time thinking about pain: −1.79‡‡
Sano et al. (2015)[73]	VR	Phantom limb pain patients	n = 6	Within-subjects	n/a	Subjective	Pain total score (sensory and affective components)	Short Form McGill Pain Questionnaire	−0.230
Schmitt et al. (2011)[75]	VR	Burn injury patients	n = 54	Within-subjects	No VR	Subjective	Sensory, affective, and cognitive components	GRS	−0.516
Smith et al. (2017)[80]	VR	Healthy participants	n = 25	Within-subjects	Neutral, pleasant, threatening, socially positive, and socially negative contexts	Subjective, objective	Intensity (threshold)	Pressure pain thresholds (PPTs) and PCS	Missing data
Sulea et al. (2014)[81]	VR	Healthy participants	n = 6	Within-subjects	No VR	Subjective	Intensity	"Perceived level of pain on a 0-10 scale"	Missing data

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Wiederhold et al. (2014)[86]	VR	Chronic pain patients	n = 40	Within-subjects	Pain focus condition	Subjective and objective	Intensity	HR, skin temperature, "self-report questionnaires… on a scale of 1 to 7"	Mean pain rating: −0.848 (pilot cohort)
Bradt et al. (2015)[4]	Music therapy (MT), music medicine (MM)	Cancer pain patients	n = 31	Between-subjects	n/a	Subjective	Intensity	NRS	MT, pre-therapy to post-therapy: −0.366 MM, pre-therapy to post-therapy: −0.450 MT vs MM: 0
Colwell et al. (2013)[10]	MT, MM	Hospitalized pain children	n = 32	Between-subjects	n/a	Subjective, objective	Pain/anxiety	HR, blood pressure (BP), OS, Wong-Baker FACES Pain Rating Scale	Pain rating score, post-treatment: Music listening vs music composition: 0.21 Music listening vs Orff-based: 0 Music composition vs Orff-based: −0.18
Mondanaro et al. (2017)[63]	MT	Postspine surgery pain patients	n = 60	Between-subjects	Standard care	Subjective	Intensity	VAS	VAS, MT preintervention vs postintervention: −0.44 VAS, after intervention: −0.31
Bradt et al. (2016)[3]	MT	Chronic pain patients	n = 55	Between-subjects	Waitlist (no music received at time of study)	Subjective	Intensity, interference, and self-efficacy	Westhaven-Yale Multidimensional Pain Inventory (MPI), Pain Self-Efficacy Questionnaire (PSEQ), NRS	MPI: −0.08, −0.24‡ NRS: −0.61, −0.27‡
Gutgsell et al. (2013)[24]	MT	Hospital inpatients	n = 200	Between-subjects	Standard care alone	Subjective	Intensity	NRS, Functional Pain Scale	NRS: −0.69 "Change Score" from baseline
Madson et al. (2010)[54]	MT	Solid organ transplant pain patients	n = 58	Within-subjects	Pre-test/post-test design	Subjective	Intensity	10-Point Likert-type scales	−0.30§
Ames et al. (2017)[2]	MM	Postoperative pain patients	n = 41	Between-subjects	Controlled non–music listening	Subjective	Intensity	VAS, NRS, and opiate intake	VAS: −0.12‖ NRS: 0.00‖ Opioid intake, IV: 0.30 Opioid intake, epidural: 0.26

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Chan et al. (2007)[7]	MM	Interventional pain patients (C-clamp procedure)	n = 66	Between-subjects	45-min uninterrupted rest period	Subjective and objective	Intensity	Systolic and diastolic pressure (SBP and DBP), HR, respiratory rate (RR), OS, and UCLA Universal Pain Assessment Tool	UCLA Universal Pain Assessment, MT vs control at 45-min timepoint: −1.37
Chantawong et al. (2017)[8]	MM	Patients undergoing loop electrosurgical excision procedure (LEEP)	n = 150	Between-subjects	No music listening during procedure	Subjective	Intensity (pain, anxiety, and satisfaction)	VAS	VAS, pain score difference from baseline: −0.26
Dobek et al. (2014)[12]	MM	Healthy participants	n = 12	Within-subjects	No music during painful stimulus	Subjective and objective	Intensity	fMRI, State-Trait Anxiety Inventory (STAI), Crowne-Marlowe Social Desirability Scale, PCS, TSA	Average pain rating: −2.21 Maximum pain rating: −2.57
Garza-Villarreal et al. (2015)[17]	MM	Fibromyalgia patients	n = 22	Within-subjects	Pink noise	Subjective, objective	Intensity	PCS, fMRI	Missing data
Guetin et al. (2012)[22]	MM	Lumbar pain, fibromyalgia, inflammatory disease, and neurological disease patients	n = 87	Between-subjects	Standard treatment only	Subjective	Intensity	VAS	VAS at day 60: −0.79
Jafari et al. (2012)[36]	MM	Post–cardiac surgery patients	n = 60	Between-subjects	No music	Subjective	Intensity	NRS	Intensity directly after intervention: −0.64 Intensity 30 minutes after intervention: −0.91 Intensity 1 h after intervention: −0.96
Karalar et al. (2016)[42]	MM	Renal calculi pain patients	n = 89	Between-subjects	No headphones or music or music without noise canceling headphones	Subjective	Intensity	VAS	Music+/headphones+vs music–/headphones–: −1.23 music+/headphones+vs music+/headphones–: −0.63
McCaffrey et al. (2003)[57]	MM	Chronic osteoarthritis pain patients	n = 66	Between-subjects	No music listening (quiet sitting)	Subjective	Intensity	Short Form McGill Pain Questionnaire (Pain Rating Index, VAS)	PRI: 1.64¶ VAS: 2.05¶

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for ***Pain* intensity outcome (Hedges' g)**†
McCaffrey et al. (2006)[58]	MM	After hip or knee surgery	n = 124	Between-subjects	Standard postoperative care	Subjective, objective	Intensity	Pain medication intake, NRS	Pain rating, average of days 1-3: −1.12 Pain medications administered: −0.31
Meeuse et al. (2010)[59]	MM	Interventional pain (sigmoidoscopy)	n = 307	Between-subjects	Standard of care	Subjective	Intensity	VAS	−0.122
Mercadie et al. (2015)[61]	MM	Fibromyalgia patients	n = 81	Between-subjects	Environmental sounds	Subjective	Intensity	VAS	Active situations, music vs sound: −0.02# Passive situations, music vs sound: 0#
Mitchell et al. (2006)[62]	MM	Healthy participants	n = 54	Within-subjects	White noise	Subjective and objective	Intensity, tolerance, and perceived control	VAS, pain rating index of the McGill Pain Questionnaire	Pain intensity (VAS): Relaxing music vs white noise: −0.340; preferred music vs white noise: −0.760; relaxing music vs preferred music: −0.431
Nilsson et al. (2005)[64]	MM	Open hernia repair pain patients	n = 75	Between-subjects	Silence	Subjective, objective	Intensity	Cortisol, blood glucose, immunoglobin A levels, BP, HR, OS, and NRS	Pain NRS; intraoperative MT vs control: −0.74; postoperative MT vs control: −0.97
Onieva-Zafra et al. (2013)[65]	MM	Fibromyalgia patients	n = 55	Between-subjects	No music listening	Subjective	Sensory, affective, evaluative, and intensity	McGill Pain Questionnaire Long Form, VAS	VAS after 4 wk: −1.67
Özer et al. (2013)[67]	MM	Open heart surgery pain patients	n = 87	Between-subjects	Standard of care	Subjective and objective	Intensity	BP, HR, OS, RR, and unidimensional verbal pain intensity scale	Post-test pain (verbal pain intensity scale): −2.16
Schneider et al. (2018)[76]	MM	Postoperative (orthopedic) pain	n = 42 (n = 65 for pain logs collected, as several patients completed the exercise multiple times)	Within-subjects	Pre–post intervention pain scores	Subjective	Intensity	NRS	−0.69

Reference	Intervention	Participants	Sample size	Study design	Control group(s)	Measurement type*	Pain	Measurement outcomes	Effect size for *Pain* intensity outcome (Hedges' g)†
Shabandokht-Zarmi et al. (2017)[77]	MM	Hemodialysis patients, during fistula puncture	n = 114	Between-subjects	Headphone (no music) or control (no intervention)	Subjective	Intensity	VAS	Music vs control: 1.87**; Music vs headphone-only: 1.96**
Vaajoki et al. (2012)[82]	MM	Laparotomy recovery	n = 168	Between-subjects	No music listening	Objective	n/a	Analgesic use, length of hospital stay, and adverse events	Missing data
Villarreal et al. (2012)[83]	MM	LHealthy participants	n = 48	Between-subjects	Environmental sounds, noise	Subjective	Intensity	VAS	Missing data
Yeo et al. (2013)[88]	MM	Cystoscopy related pain patients	n = 70	Between-subjects	No music during procedure	Subjective	Intensity	VAS, physiological functions (hemodynamic values; mean arterial pressure; heart and respiration rates)	VAS: −1.16

Negative values for Hedges' g indicate a higher value in the control group than in the treatment group. For measures evaluating pain, a negative Hedges' g reflects a decrease in the treatment compared with the control group. For measures evaluating measures such as threshold, a negative Hedges' g value indicates a higher pain threshold in controls compared with the treatment group. Hedges' g: |0.2| = small effect size; |0.5| = medium effect size; |0.8| = large effect size.

* "subjective" indicating measurements based on subjects' self-reported perceptions of their experience; "objective" indicating measurements independent of subject bias. Missing data = case studies or studies in which mean and/or SD were not reported.

† Hedges' g: (mean [tx grp] – mean [control grp])/(combined SD).

‡ (Week 8, follow-up)—data taken from "Change Score" from baseline.

§ Comparison between pre-MT and post-MT.

‖ Average of 4 time-points.

¶ Average of 3 time-points, reflecting change in pain level (D1, D7, and D14).

Average of 3 time-points.

** Calculated using pain score difference before and after intervention.

†† Using log10-transformed times.

‡‡ subjects stratified based on "worst pain" in the no VR condition.

fMRI, functional magnetic resonance imaging; VR, virtual reality.